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Original Article

Antenatal screening for chromosomal and genetic abnormalities: Cost effectiveness and outcome

Simin Taghavi[1], Hossein Alikhah[2], Sharareh Barband[3], Fereshteh Farhadi[4], Mohammad Naghavi-Behzad*[3], Saeed Jodi-Khajeh[5], Sahar Mohammadi[6], Reza Piri[7]

[1] *Women' s Reproductive Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*
[2] *Department of Emergency Medicine, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran*
[3] *Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran*
[4] *Research Center for Evidence Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran*
[5] *School of Traditional Medicine, Tabriz University of Medical Sciences, Tabriz, Iran*
[6] *Department of Emergency Medicine, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran*
[7] *Medical Philosophy and History Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*

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Abstract

Introduction: As an essential part of antenatal care, pregnant women of all ages should be offered screening for chromosomal abnormalities before 20 weeks of gestation. This study was aimed to evaluate the type and frequency of chromosomal abnormalities following pregnancy screening tests, so that we can compare the actual pregnancy outcomes with test results, helping us in practical decision making.

Methods: A cross-sectional study was conducted on 557 pregnant patients, presenting for prenatal diagnostic amniocentesis for chromosomal abnormalities, to Al-Zahra hospital, Tabriz, Iran, since 2012 to 2015. Amniocentesis was conducted by an expert obstetrician at second trimester between 16 and 22 weeks of gestation. An interview was set for pregnancy outcomes to assess the test results.

Results: Of 557 cases, the mean maternal age in amniocentesis was 31.84 ± 6.92 years (range: 15-47 years). Amniocentesis revealed the presence of chromosomal abnormalities in 32 cases (5.7%). The most common diagnosed chromosomal abnormality was Down syndrome (50.0%) followed by other chromosomal abnormalities. Following up the patients, 92.4% of newborns did not have any congenital abnormality, but the remaining (7.6%) had both chromosomal and non-chromosomal abnormalities. No fetal loss was reported in this study. Assessment of total costs revealed that $US100 had been spent for hospitalization, and about $US500 for genetic tests.

Conclusion: There is still no consensus on the most cost-effective strategy that should be implemented to diagnose chromosomal anomalies. Therefore, we did not have an actual gold standard to compare with amniocentesis. More studies analyzing natural outcome after prenatal diagnosis of these chromosomal abnormalities are needed.

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Introduction

As an essential part of antenatal care, pregnant women before 20 weeks' gestation should undergo invasive diagnostic testing and screening for chromosomal abnormalities.[1] Prenatal diagnosis suggestions provide important information about the pregnancy and fetal health. Such information is valuable

* **Corresponding Author:** Mohammad Naghavi-Behzad, Email: dr.naghavii@gmail.com

to the family that wants to know more about the pregnancy and also to the families considering termination of a pregnancy with a chromosomal or congenital abnormality.[2]

In spite of being an invasive method, amniocentesis remains as a widely used prenatal diagnostic examination for screening fetal karyotype abnormalities early in the second trimester of pregnancy.[3,4] However, although amniocentesis is known as a simple, low-risk, and reliable method,[4-6] it is still an invasive procedure with the risk of procedure-related complications, including miscarriage.[2,4,5]

Amniocentesis as a prenatal diagnostic test for chromosomal abnormalities always comes to comparison between the risk of giving birth to a child with chromosomal abnormality and the risk of amniocentesis-related complication.[5,7] Studies have showen that modification in the initial costs of the diagnosis procedure has a prominent effect on parents' decision making.[5] Some have found that reduction in payments and costs increases the probability of taking part in amniocentesis procedure.[5]

The examples of complications of second trimester amniocentesis are leakage of pregnancy loss, amniotic fluid, fetal injury, and infection.[8] Fetal loss is the most severe complication of amniocentesis and might depend on operator's skill, technical methods, maternal age and gestational age (GA) at the time of amniocentesis, previous history of miscarriage, previous bleeding, and concomitant fetal anomalies.[4,9,10] The total pregnancy loss rate following amniocentesis is composed of the spontaneous loss and the procedure-related loss.[4]

The rate of procedure-related pregnancy loss recommended by the CDC and ACOG for amniocentesis counseling is 0.5%.[11] The only available randomized trial is associated with 1% extra risk of fetal losses, with a total loss rate of 1.7%.[4,12]

In current study, it was aimed to evaluate the frequency and type of chromosomal abnormalities following pregnancy screening tests, so the results of current study will be compared with normal pregnancies. This issue will help us to decide if these tests are reliable to use in the future. This study also evaluated the cost effectiveness of these tests in order to assess the current use of these tests and its affordability for Iranian families.

Methods

This cross-sectional study was conducted in Tabriz University of Medical Sciences, Tabriz, Iran, on 557 pregnant women attending for amniocentesis as a prenatal diagnostic method for chromosomal abnormalities at Al-Zahra educational-clinical center, Tabriz City, which is the main referral center in northwest of Iran, since 2012 to 2015.

Inclusion criteria for case group included pregnant women with a high risk for trisomy syndromes according to nuchal translucency and pregnancy-associated plasma protein A and free β-human chorionic gonadotropin (β-hCG) in first trimester and triple test or quad test in second trimester. Women with the history of having newborn or fetus with known congenital single gene disorders or chromosomal abnormality with more than 40 years of age and structural chromosomal abnormalities also were included in the study.

In case of rejecting to participate in the study, rejecting to undergo procedure after giving information about sampling methods, fetal risks of invasive intervention, or financial issues, patients were excluded from the study.

The information was collected from patients and their first-degree families' members and medical records using prepared questionnaires. For all pregnant women, demographic data, GA at amniocentesis, and pregnancy outcome were recorded.

The study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences, which was in compliance with Helsinki Declaration, and all patients signed informed written consent before the inclusion in the study.

Amniocentesis was performed between 16 and 22 weeks of gestation by an expert obstetrician. The fetal anatomy and fetal conditions were evaluated by ultrasonography

before the procedure. All procedures regarding amniocentesis were conducted using an aseptic technique and continuous ultrasound guidance and the free-hand technique without any anesthesia by the maternal-fetal medicine team. A 22-gauge spinal needle was inserted into the free space of amniotic cavity without any umbilical cord or fetal parts; also it was tried to avoid transplacental insertion as much as possible. Then 15-20 ml of amniotic fluid (1 ml per week) was aspirated for chromosomal study, while discarding the first 1 ml of aspirated fluid. All the patients were asked to rest for 10–20 minutes after procedure completion. Then, patients undergoing amniocentesis without any complications were scheduled for the next visit about 2 to 4 weeks later.

To assess the tests results an interview was set for pregnancy outcomes. Pregnancy outcomes were normal offspring without abnormalities, offspring with abnormalities, and fetal losses.

SPSS software (version 16, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Descriptive data were presented as frequency and percentage (%). After determining the distribution of continuous variables by Kolmogorov-Smirnov test (K-S test), data were analyzed using t-test and Fisher's exact test. The P value less than 0.05 was considered statistically significant.

Results

Finally, 557 pregnant women with singleton pregnancies were included as study group, of which 58.7% presented before 18th week and 41.3% presented after 18th week of GA for evaluation of fetal genetic status. The mean maternal age was 31.83 ± 6.93 years (range: 15-47 years). Offspring of mothers was male in 279 cases (50%) and female in 278 cases (50%). Amniocentesis successfully detected presence of chromosomal abnormalities in 32 pregnant women (5.74%) including 18 females (56.25%) and 16 males (43.75%) fetuses.

Table 1 shows the type of chromosomal abnormalities in studied patients presenting for evaluation of fetal chromosomal status.

As showed in table 1, the most common diagnosed chromosomal abnormality in studied cases was Down syndrome (50%), followed by Turner syndrome (18.75%), structural chromosomal abnormality (18.75%), Trisomy 18 (3.12%), Trisomy 13 (3.12%), Klinefelter syndrome (3.12%), and mosaism chromosomal abnormality (3.12%).

Follow up of outcome of pregnancies and offspring in studied cases showed that in total, 92.4% of newborns did not have any congenital abnormality. No fetal loss was reported in this study.

According to the total costs, patients spent about $US 100 for admission process, and about $US 500 for genetic evaluations. In addition, three days hospitalization for pregnancy termination was assessed as about $US 1000 for each pregnant woman.

It must be mentioned that the cost of providing care for a child with chromosomal abnormality is about $US 400 monthly in this region.

Discussion

The current study evaluated characteristics of

Table 1. Final screening results of all patients (n = 557), referred to Al-Zahra hospital of Tabriz university of Medical Sciences

Indication		Frequency in studied cases [n (%)]	Percent of diagnosis
Normal child	Female	260 (46.67)	0
	Male	265 (47.57)	0
Down Syndrome	Female	9 (1.61)	28.12
	Male	7 (1.26)	21.87
Trisomy 18 (female)		1 (0.18)	3.12
Trisomy 13 (female)		1 (0.18)	3.12
Turner syndrome		6 (1.08)	18.75
Structural chromosomal abnormality	Female	1 (0.18)	3.12
	Male	5 (0.90)	15.62
Klinefelter Syndrome (male)		1 (0.18)	3.12
Mosaic chromosomal abnormality (male)		1 (0.18)	3.12

chromosomal abnormalities in pregnancy screening tests. We also evaluated the cost effectiveness of these tests in a total of 557 pregnant women presenting before or after 18th week of GA for evaluation of fetal chromosomal status.

Amniocentesis is known as a reliable and safe method conducted by experienced personnel for prenatal diagnosis of chromosomal abnormalities.[8] However, although screening and diagnostic methods have changed recently, and with current well-established medical surveillance there are few high-risk pregnancies with do not cause increased rate of caesarean sections.[13]

In Kowalczyk et al. study, of all patients undergoing amniocentesis, 39 karyotypes (9.8%) were found.[9] The most prevalent age at which our patients presented was 15 up to 26 weeks of GA. In our country, the abortion with medical indications is legal only before 18 weeks of GA. Amniocentesis was performed according to the screening test results. According to the previous reports, quad test and triple test must be performed up to 20 weeks of GA. The most common indication for amniocentesis in most studies was advanced maternal age,[12,14,15] followed by abnormal triple test results.[14] These measures are compatible with findings of the present study.

Mothers with trisomy 13, trisomy 18, and triploid neonates are more prone to develop spontaneous abortion, a short life span, and intrauterine death.[10] In a study by Lakovschek et al., all cases with fetal diagnosis of triploidy, trisomy 13, and trisomy 18 were studied. None of the cases with triploidy was born alive. The live birth rate for trisomy 18 and trisomy 13 were 13% and 33%, respectively. They also had short life span.[10]

In regard to amniocentesis indications, advanced maternal age was the most common.[16] Based on the new guidelines, women with a high combined risk for Down syndrome in the first trimester of pregnancy should undergo prenatal diagnosis such as amniocentesis.[17]

In a study, Balkan et al. performed second-trimester amniocentesis on 1068 cases. The age group of 35-39 years old was the most common age group (34.5%). The most common indication for amniocentesis was abnormal maternal screening results. Of all patients, 4.9% had chromosomal aberrations including 39 numerical: 27 trisomies, 10 sex chromosome aberrations, and 2 triploidies, and 10 were structural including 6 inversions, 2 Robertsonian translocations (ROBs), and 2 reciprocal translocations. The chromosomal aberrations were mostly detected among cases undergoing amniocentesis because of abnormal ultrasound findings with abnormal maternal serum screening combined (8.0%). Therefore, it was suggested that routine antenatal ultra-sonographic studies and maternal serum screening should be added to increase the efficiency of genetic amniocentesis complementary measures.[11]

Grether-Gonzalez et al. analyzed 1500 consecutive patients undergoing genetic amniocentesis. They reported 4.5% chromosomal abnormality. The most frequent abnormalities were trisomy 21 (47.0%), trisomy 18 (14.7%), trisomy 13 (8.8%), 45X (8.8%), and 47XXY (5.8%). Pregnancy outcome was known in 32%. Of the cases with chromosomal abnormality, 64% decided to undergo a pregnancy termination, while 35% decided to go on with the pregnancy, of which 37.5% had a perinatal death or spontaneous abortion. Among fetuses with normal or balanced karyotype and normal ultrasound, 2.6% had congenital anomalies. Most patients with fetal disease decided to have an abortion.[6] Our study on 557 cases resulted in 7.6% chromosomal and non-chromosomal abnormalities as pregnancy outcomes. Regarding chromosomal abnormality rate of 5.74% in screening tests, we detected more chromosomal abnormalities than this study. However, compatible in details, the most prevalent abnormality in our study was Down syndrome with a similar ratio of 50%. As mentioned, our study detected a total rate of 7.6% chromosomal and non-chromosomal

abnormalities which is higher than what we expected considering the test results. The point is that screening tests demonstrate only chromosomal abnormalities but our interview detected both chromosomal and non-chromosomal abnormalities.

In a study by Leroy et al., 114 pregnant women underwent chorionic villus sampling (CVS), of which a definitive diagnosis was given in 98.25% of cases. In 1.75% of cases, a secondary amniocentesis was administered. A medical termination of the pregnancy was done in 18.42% of cases.[17]

A combined test performed at the 12th week of gestation enables us to classify the pregnancy as low risk (risk < 1:300) or as high risk (risk > 1:300) for fetal trisomy.[18] Loncar et al. in a study concluded that the combined test if used at late first-trimester and for embryonic crown-rump length (CRL) of 45 to 84 mm, performs as a great diagnostic test of congenital fetal anomalies.[18]

A prospective study of all singleton pregnant women who had an amniocentesis showed that the miscarriage rates (i.e. procedure-related loss and spontaneous loss) after CVS and amniocentesis were 1.9% and 1.4%, respectively. This difference in rates might be due to the difference in GA at the time of the diagnostic tests. The total number of procedures performed in a department was inversely correlated with the miscarriage rate.[19] In our study, there was not a single pregnancy resulted in fetal loss; this may disclose the high quality of procedure, but this is not something to be proud of, because our sample size was about 557 pregnant women and the odds of miscarriage increase with number.

The cost-effectiveness of diagnostic tests for detecting chromosomal abnormalities has been studied by many studies.[20-27] Nevertheless, there is no consensus on the most cost-effective strategy that should be implemented to diagnose chromosomal anomalies. According to the many screening methods to compare, no clinical or single empirical study is likely to assess all available aspects.[20] In some countries, lowering maternal age limit for access to free-of-charge amniocentesis (up to 35 years) would have been cost-beneficial.[28]

Gekas et al. in a study assessing screening costs concluded that approximate amniocentesis cost with diagnostic karyotyping was 500 Canadian dollars.[20] Based on another cohort study, testing women more than 30 years old would cost $103,329 per abnormal birth averted for amniocentesis.[29] In an attempt to estimate the most cost-effective and clinically scanning strategies of screening for fetal anomalies in early pregnancy, Ritchie et al. concluded that strategies including a second trimester ultrasound scan result in a higher rate of detecting abnormalities.[27]

Nadel et al. in a study evaluating the cost-effectiveness of each diagnostic test concluded that ultrasound detected about 80% of fetuses with abnormal structure, with no fetal losses, at a cost of $US 5700 per abnormal fetus; while amniocentesis and karyotyping detected 15 extra anomalous fetuses with nine iatrogenic fetal losses, at an incremental cost of $46100 per anomalous fetus. Thus, it was concluded that the increased diagnostic yield of amniocentesis, as compared with ultrasound, cannot be justified by the cost and iatrogenic fetal loss rate.[30] We agree that invasive procedures such as amniocentesis are less cost-effective than other diagnostic procedures, but they surely increase the detection rate of abnormal fetuses in general.

Considering the burden imposed on the health care system and family, especially when affected people reach adulthood and the fact that they do not have an appropriate level of function in community, isolation, therapeutic abortion, and limitation is an appreciated method to relieve parents from the stress of caring for severely mentally retarded offspring.[31,32] Considering the fact that in our country the abortion with medical indications is legal only before 18 weeks of GA, we should consider the procedure right after 15 weeks until 18 weeks of GA in order not to be late for the legal procedure of

therapeutic abortion. The main reason for efficacy of prenatal diagnosis is the fact that the average cost of one "prevented" case of Down syndrome is lower than the lifelong costs of care for such an offspring.[33,34]

Conclusion

Although many studies have examined the cost-effectiveness of different diagnostic tests to detect chromosomal anomalies, there is no consensus on the most cost-effective strategy yet. Therefore, there is no actual gold standard to compare with amniocentesis.

Prenatal diagnostic testing procedures are effective at any risk level or age. Some modifications in current guidelines should be made in a way that offers testing to all pregnant women (not just high-risk patients), because the average cost of a prevented case of chromosomal defective individual is lower than the lifelong expenses of care for these population. Further studies are encouraged to analyze natural outcomes following prenatal diagnosis of these chromosomal abnormalities.

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Authors' Contribution

All of the authors contributed equally.

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Conflict of Interest

Authors have no conflict of interest.

Ethical Approval

This study was approved by the Regional Medical Ethics Committee of Tabriz University of Medical Sciences under the number 5/4/10631.

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