Outcome of Pregnancies Presenting for Diagnostic Evaluation of Fetal Trisomy

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Abstract: Prenatal diagnostic amniocentesis offers an opportunity to obtain important information about the pregnancy. This study was aimed to evaluate the outcome of pregnancy in pregnant women presenting for diagnostic amniocentesis of fetal trisomy. Also, the methods of termination of pregnancy in patients with positive results were evaluated. A "cross- sectional" study was conducted on consecutive pregnant patients at risk for trisomy syndromes according to NT or NF and double marker, triple marker or Quad test. The prepared questionnaires were used for collecting the required information from patients and their medical records. All amniocenteses were performed by one expert obstetrician. The fetal conditions and anatomy were evaluated by ultrasound scan before the procedure. The collected data underwent the statistical analysis by SPSS-17 software. Of total of 557 studied pregnant women, 522 (90%) had normal result of amniocentesis, but 35 (6%) had abnormal result and had need for pregnancy termination. The justifications for pregnancy termination were issued for 17 women according, but 18 cases could not achieve the justification and terminated illegally. In total, 482 women (92%) delivered their newborn (by cesarean or NVD), of which 442 (84%) were at term and 40 (8%) were preterm. Also, babies outcomes were as following: Healthy live baby (467(50.8%)), not-Healthy live baby (16(1.7%)), Stillborn (8(0.9%)), Live born but neonatal death (16(1.7%)), Live born with death during the first year (3(0.3%)), Termination (34(3.7%)), Spontaneous abortion (9(1.0%)). It seems that second trimester amniocentesis is a relatively safe and reliable method for prenatal diagnosis. However, it is recommended to be done by well trained and experienced hands. It could find six chromosomally abnormal fetuses in every 100 cases of procedure.
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1. Introduction

Amniocentesis is the most common invasive prenatal diagnostic examination to screen fetal karyotypic abnormalities early in second trimester (Pitukkijronnakorn et al., 2011; Mazza et al., 2011). Although prenatal diagnosis by amniocentesis has been accepted as a reliable and low risk method (Grether-González et al., 2010), it is still an invasive diagnostic procedure and is associated with risks of complications, including miscarriage (Grether-González et al., 2010). Although the technique is simple, it may result in the pregnancy loss (Pitukkijronnakorn et al., 2011; Garrouste et al., 2011). However, prenatal diagnosis also offers the opportunity to obtain important information about a pregnancy. This information is valuable to the parents that want to know as much as possible about the fetal health and to the parents that is considering terminating a pregnancy with an abnormality (Seth et al., 2011).

The number of late pregnancies, at 40 years or more has dramatically increased recently resulting in higher risks of first trimester miscarriages. Screening and diagnostic conditions have changed recently with lower than expected diagnostic ratio. Although with present medical surveillance these pregnancies are not considered at high risk for the child, but are at higher risk for the mothers, associated with increased rate of caesarean sections, hemorrhages, thromboembolic accidents, and hypertensive disorders (Tournaire, 2010).

Making decision for prenatal diagnostic amniocentesis for trisomy syndromes requires comparing the risk of giving birth to an affected child and the risk of amniocentesis-related miscarriage (Garrouste et al., 2011; Minna et al., 2011).

This study was aimed to evaluate the outcome of pregnancy in pregnant women presenting for diagnostic amniocentesis of fetal trisomy. Also, the methods of termination of pregnancy in patients with positive results were evaluated.

2. Material and Methods

A "cross- sectional" study was conducted on consecutive pregnant patients presenting to Tabriz Al-Zahra Hospital since 2008 till 2011.

The enrolment was according the inclusion criteria including: 1) pregnant women at high risk for trisomy syndromes according to NT or NF and double marker, triple marker or Quad test; 2) the history of having fetus or newborn with Down syndrome or known congenital single gene disorders; 3) mothers with age 40y or higher (when they had personal request); 4) parents with structural chromosomal abnormalities.

Also, the exclusion criteria were: 1) rejecting the participation in study; or 2) rejecting the procedure after giving information about sampling method, fetal risks of invasive intervention, or financial problems.

The prepared questionnaires were used for collecting the required information from patients and their medical records. For all participants, demographic data, gestational age at amniocentesis, and pregnancy outcome were recorded.

This study was approved by the Regional Ethics Committee, and all patients signed the informed consent before inclusion in the study.

All amniocenteses were performed by one expert obstetrician (one of authors) at second trimester between 16 and 22 weeks of gestation. The fetal conditions and anatomy were evaluated by ultrasound scan before the procedure. All procedures were performed in the maternal- fetal medicine unit under an aseptic technique and continuous ultrasound guidance. The spinal needle no. 22G was inserted into the free space of amniotic cavity without any fetal parts or umbilical cord, while being care to prevent transplacental insertion as much as possible. Then, 15 to 20 ml of amniotic fluid (1 ml per week) was aspirated, while discarding the first 1 ml. The patients were ordered to take rest for 10–20 min after completion of amniocentesis. Then uncomplicated patients were scheduled for the next visits in 2 and 4 weeks later.

Finally, the collected data underwent the statistical analysis by SPSS-17 software, using t-test and Fisher's exact test. Statistical significance was defined at $p<0.05$.

3. Results

A total of 557 pregnant women were enrolled in the study, of which 522 had normal result of amniocentesis without the need for pregnancy termination, but 35 had abnormal result and had need for pregnancy termination.

So, 35 patients presented to province Legal Medicine Organization (LMO) for requesting justification for pregnancy termination. Also, a woman who presented to an adjacent province LMO for requesting justification were included in the study (n=36).

Table 1: Pregnancy termination in patients with abnormal test results (n=35)

	Status		Frequency	Valid (%)
Need for termination	Not needed		522(56.7%)	93.9%
	Needed		35 (43.3%)	6.1%
Legal Permission to termination	Given		17(1.8%)	3.1%
	Not given		18(2.0%)	3.2%
Method of Termination	Legal termination	Spontaneous abortion	1(0.1%)	0.2%
		Medical	14(1.5%)	2.5%
		Surgical	1(0.1%)	0.2%
	Illegal termination*	Medical	17(1.8%)	3.1%
		Surgical	2(0.2%)	0.4%
*One of women, who achieved the justification for pregnancy termination, tried to termination after expiration of the justification.				

The justifications were issued for 18 women according to medical, local, and religious (Islamic) laws. However, the remaining 18 cases could not achieve justifications for pregnancy termination, mostly because of late presentation (after 18th week, according to LMP or GA), for requesting the justification.

One of women, who achieved the justification for pregnancy termination, emigrated and excluded from the study (n=35).

Table 1 presents the status of pregnancy termination in patients with abnormal test results.

Table 2 shows the outcome of pregnancy and delivery methods in studied patients. It must be mentioned that the information about the labor method,and children health was mostly collected by phone contact (according to their phone numbers recorded in medical records); and regarding the industrial nature of the study region, Tabriz, and multiplicity of emigrations and immigrations during the study period, we could not achieve information about the labor method in 32 cases, although we could achieve information about the children health of 28 of them from their friends or neighbors.

Table 2: Outcome of pregnancy in studied patients with known outcome (n=525)

Labor method	Full term- Vaginal (NVD)	79(8.6%)	15%
	Full term- Cesarean	363(39.5%)	69.1%
	Preterm-Vaginal (NVD)	11(1.2%)	2.1%
	Preterm- Cesarean	29(3.2%)	5.5%
	Termination	34(3.7%)	6.5%
	Spontaneous abortion	9(1.0%)	1.7%

As showed in table 2, 482 women (92%) delivered their newborn (by cesarean or NVD), of which 442 (84%) were at term and 40 (8%) were preterm.

Table 3 presents the outcome of pregnancy and offsprings in studied cases. The "Healthy live babies" were normal regarding growth, walking, speaking, and cognitive reactions of 1-3 years old child, but the "not-Healthy live babies" were abnormal in one or more of these criteria. As mentioned above, we could not achieve any information about the children's health in 4 cases.

Table 3: Outcome of pregnancy from fetus- neonate viewpoint (n=553)

Baby outcome	Healthy live baby	467(50.8%)	84.4%
	not-Healthy live baby	16(1.7%)	2.9%
	Stillborn	8(0.9%)	1.4%
	Live born but neonatal death	16(1.7%)	2.9%
	Live born with death during the first year	3(0.3%)	0.5%
	Termination	34(3.7%)	6.5%
	Spontaneous abortion	9(1.0%)	1.7%

4. Discussions

We studied the outcome of pregnancy in 557 pregnant women presenting for diagnostic amniocentesis of fetal trisomy. Also, the methods used for termination of pregnancy in patients with positive results were evaluated.

Comparison of 106 patients who underwent amniocentesis with 138 patients, who did not consent to having the invasive test (Kowalczyk, 2011), showed that apart from a small difference in average birth weight, there were not any significant differences in infant condition and their postpartum biophysical parameters. Other than gestational diabetes which was more often in patients who did not undergo amniocentesis, no statistically significant differences in the frequency of other pregnancy complications have been found (Kowalczyk et al., 2011).

Neonates with trisomy 13, trisomy 18, and triploidy could be born alive or associated with a high rate of spontaneous abortion, intrauterine death, and a short life span (Lakovschek et al., 2011). The studies about natural fetal and neonatal outcome for pregnancies with prenatal diagnosis of fetal trisomy provide reliable information for parental counseling pertaining to risk of intrauterine death. These findings suggest that long-term survival implications for trisomy are different when it is diagnosed prenatally (Burke et al., 2012).

One study on 1500 genetic amniocentesis revealed chromosomopathy in 4.5%. There were five fetal losses (1%). Of cases with chromosomopathy, 64.4% decided to have an abortion while 16 (35.6%) continued the pregnancy, of which 37.5% had a spontaneous abortion or perinatal death and 62.5% had an alive new born (Grether-González et al., 2010).

In our series, all patients with abnormal result of amniocentesis suggesting chromosomal abnormality chose the pregnancy termination.

The definition of "fetal loss associated with amniocentesis" used in each study can be varied quite widely, The fetal loss can either occur less than 2 weeks after procedure, at 24 and 28 week gestation or as long as early neonatal deaths (Pitukkijronnakorn et al., 2011; Nanal et al., 2003; Nassar et al., 2004; Kong et al., 2006). We defined it as less than one week after the process. We had the fetal loss in 9 (1.7%) of patients.

Tabor et al. did not find statistically significant relation between amniocentesis and fetal loss rate and premature delivery (Mazza et al., 2011; Mungen et al., 2006).

Lo et al. conducted a retrospective study on 120 cases undergoing second-trimester pregnancy termination for the fetal diagnoses of trisomy. The pregnancies were terminated by vaginal misoprostol. Fetal diagnosis affected the outcome of pregnancy termination (Lo et al., 2008).

Corrado et al. compared the pregnancy outcome in patients underwent amniocentesis (n=2990) with patients who declined to undergo amniocentesis (n=487). A total of 30 fetal losses occurred within 24 weeks' gestation (1%), while in the control group, there were four losses (0.8%). Previous vaginal bleeding increased the risk of fetal

loss after amniocentesis, but a history of two or more miscarriages is not associated with a greater loss rate, while the increased percentage in patients affected by uterine myoma appears connected (Corrado et al., 2012).

Balkan et al. performed 1,068 second-trimester amniocentesis of which 52 cases (4.9%) were known to have chromosomal aberrations (Balkan et al., 2011). This rate in our series was 6% which is comparable with their results.

In a review of 1000 amniocenteses, there were 21 fetal loss before 28 weeks of gestation (2.2%), three loss after 28 weeks (0.3%) and six stillbirths (0.6%) resulting in a total post procedural loss rate of 3.1% (Giorlandino and Cignini, 2009). Miscarriage within two weeks of amniocentesis occurred in six patients (0.62%). These results suggest that amniocentesis is a relatively safe and reliable method for prenatal diagnosis, but it has been recommended to be done by experienced personnel (Ajayi, 2011). However, Balkan et al. suggested that complementary measures, such as routine antenatal US and maternal serum screening, should be added to increase the efficiency of genetic amniocentesis (Balkan et al., 2011).

In Hanprasertpong et al. study, the fetal loss within 14 days after the amniocentesis was 0.12%. Leakage of amniotic fluid occurred 0.1% but only one case aborted (Hanprasertpong et al., 2011). Intrauterine infection could be responsible for 25-40% of preterm births (Petit et al., 2012). Intraamniotic infection is a major risk factor for spontaneous rupture of membranes, clinical chorioamnionitis, preterm delivery (PTD) and poor perinatal outcome (Okyay et al., 2011; Bodner et al., 2011; Daskalakis et al., 2009; Vigliani, 2009). The risk for abortion and preterm premature rupture of membranes (PPROM) does not increase in women who have undergone amniocentesis (Cignini et al., 2011).

A principal factor affecting safety and effectiveness of amniocentesis is the volume of procedures performed by the operator. Perinatologists undertaking more than 50 amniocenteses per year are considered as high-volume performers (Alfirevic, 2009; Kalogiannidis et al., 2011; Jenkins and Wapner, 2000). High-volume experience is reported to have decisive impact on rates of procedure-related adverse outcomes (Blackwell et al., 2002). In one study (Kalogiannidis et al., 2011), more than 6000 amniocenteses have been performed over the last 15 years by the same operator, a number comparable or even superior to those of other analyses (Kalogiannidis et al., 2011; Jenkins and Wapner, 2000; Blackwell et al., 2002). In our institution, more than 2000 amniocenteses have been performed over the last 5 years.

The miscarriage rate in singleton pregnancies has been reported as 0.2% to 3% in literatures (Horger et al., 2001; Sirivatanapa et al., 2000; Chaabouni et al., 2001; Kong et al., 2006; Seeds, 2004). In one study, no miscarriages occurred in the group of twins (Kalogiannidis et al., 2011). Yukobowich et al. (Yukobowich et al., 2001) reported a miscarriage rate of 2.73% up to four weeks after the procedure while Cahill et al. report 3.2% up to 24th gestational week (Cahill et al., 2009). We had 1.3% of abortion during a week after the process.

Pitukkijronnakorn et al. studied all pregnant women ≥35 years old (2,990 cases) scheduled for second trimester genetic amniocentesis. The procedure-related fetal loss before 24 and 28 weeks were 0.17 and 0.50%, respectively. The most common symptom reported before fetal loss was abdominal pain. All abortion had symptoms initiated after 48 h post procedure. The abortion rate was significantly higher in pregnant women ≥41 years old. They suggested that some factors influencing the risk of fetal loss might be independent of the amniocentesis procedure (Pitukkijronnakorn et al., 2011).

Uludag et al. compared short- and long-term complications of amniocentesis performed with 20G, 21G, and 22G needles on 793 pregnant women in Turkey, and showed that the rates of fetal loss, vaginal bleeding, bloody amniotic fluid and amniotic fluid leakage were similar among the three groups (Uludag et al., 2010). We used the spinal needle no. 22G for all cases.

Buyukkurt et al. evaluated the effect of genetic amniocentesis on the preterm delivery rate in 14,579 pregnant women. They concluded that second trimester genetic amniocentesis does not seem to have any additional adverse effect on the preterm delivery rate (Buyukkurt et al., 2010).

Borrelli studied the complications of diagnostic amniocentesis on1580 patients. Late complications included abortions (in the week following amniocentesis) (0.78%), and preterm labor (6%).They concluded that a good performance and careful selection of patients are necessary to decrease complications due to amniocentesis (Borrelli et al., 2006).

Nassar et al. in a study on complications of 1347 second-trimester amniocenteses found 22 complications (1.6%): fetal loss (0.22%), bleeding (0.59%), and rupture of membranes (0.82%). Complications were significantly increased with gestational age, number of punctures, and ultrasound anomalies. They concluded that genetic amniocentesis performed at a tertiary care center is safe with the fetal loss rate of 0.22% (Nassar et al.,

2004).

A study, including all singleton pregnant women who had an amniocentesis (n=32852) or CVS (n=31355), showed that the miscarriage rates (i.e. spontaneous loss and procedure-related loss) after amniocentesis and CVS were 1.4% and 1.9%, respectively. This difference may be explained by the difference in gestational age at the time of the procedures. The miscarriage rate was inversely correlated with the number of procedures performed in a department (Alfirevic, 2009).

One study compared 4877 amniocenteses versus non-exposed controls to assess the risk of very low birth weight (VLBW) and extremely low birth weight (ELBW) attributable to second trimester amniocentesis. In the study population, the VLBW were 0.71% and the ELBW were 0.41%. In the control group, the VLBW were 0.67% and the ELBW were 0.34% ($p>0.05$). No effect of the second trimester amniocentesis was noted on VLBW and ELBW (Mazza et al., 2011).

Conclusions:

It seems that second trimester amniocentesis is a relatively safe and reliable method for prenatal diagnosis. However, it is recommended to be done by well trained and experienced hands. It could find six chromosomally abnormal fetuses in every 100 cases of procedure.

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