

## An Overview of Prenatal Screening/Diagnosis Programs for Down Syndrome in Turkey

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**ABSTRACT** The aim of this paper is to demonstrate the prenatal screening variables and risk factors of pregnancies with Down syndrome (DS) babies, and to explicate invasive prenatal testing strategies. This study consists of 21 "trisomy-21" fetuses, diagnosed prenatally within the framework of prenatal screening and diagnosis programs at the Division of Perinatology, Hacettepe University. It also consists of a review of the prenatal screening variables and gestational risk factors for invasive prenatal testings. Researchers observed that advanced maternal age is the main risk factor for having an invasive prenatal testing. The other important factor associated with DS is ultrasonographic findings. Increased "double/combined test" risk (n=12), and increased "triple test" risk (n=3) were noted in 21DS cases. Among all the DS cases; 18 of them were terminated, the rest rejected the termination option. Prenatal diagnosis of DS is important in clinical practice, but physicians often come under the pressure of social and legal issues.

### INTRODUCTION

Down syndrome (DS) is the most frequently demonstrable genetic cause of intellectual disability (Weijerman et al. 2010). In addition to intellectual disability, individuals with DS have typical facial appearance and a variety of other clinical findings which include: heart defects, gastrointestinal malformations, developmental delay, vision and hearing problems, dermatological abnormalities, decreased thyroid function, increased risk for infections, hematological disorders and other clinical problems (Roizen 2003). DS involves trisomy of chromosome 21, in about 95 percent of all cases. Translocation between chromosome 21 and the long arm of the acrocentric chromosomes or translocation consist of two chromosome 21 long arms and mosaicism with a mixture of normal and trisomy 21 cells are responsible for the pathogenesis in the remaining 5 percent of all cases (Faas et al. 2011). Prenatal screening and diagnosis of DS are widely accepted and applied within the framework of

antenatal care programs. Down syndrome (in all living births) incidence has decreased due to pregnancy terminations after 1980s, when prenatal diagnosis programs started (Maxwell et al. 2015). However, heterogeneity of social (mainly economical and religious) environment of different communities affects the decision-making, and practice of physicians in the field of prenatal screening and diagnosis programs (Hill et al. 2012). On the other hand, undiagnosed babies with DS create legal problems in some countries and this reality gives form to routine clinical practice. Legal climate in Turkey enforces physicians to have prenatal screening routinely and offer prenatal diagnosis in necessary cases. Gil et al. (1995), reported that for double/combined test, triple test (sometimes quadruple test), cell free DNA testing and ultrasonographic examinations are the main tools of prenatal screening for aneuploidies. Physicians are free to choose the convenient method for their patients. On the contrary, offering prenatal diagnosis of DS is compulsory for pregnancies with advanced maternal age due to legal pressure. Advanced maternal age, presence of ultrasonographic soft markers associated with aneuploidies, screen-positive results on prenatal screening tests (double/combined, triple, cell free DNA testing and others), fetal trisomy history in previous pregnancies, parenteral translocations with increased risk of trisomy 21 or others and consanguinity

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are the main indications of diagnostic tests for DS (Huang et al. 2015). Moreover, ACOG published a recommendation in 2007, that an invasive method (amniocentesis, chorionic villus sampling or cordocentesis), is required for prenatal diagnosis if prenatal screening program predict an increased risk for having a child with DS or some other trisomies (ACOG Practice Bulletin No. 88, December 2007).

### Objectives

The aim of this study is to evaluate the relation between prenatal screening and diagnosis programs for DS in Turkey. To that effect, researchers analyzed clinical features and characteristics of 21 pregnancies with DS fetuses diagnosed prenatally at the Division of Perinatology, Hacettepe University, between January 2014 and April 2015.

### MATERIAL AND METHODS

This study comprises of 21 “trisomy-21” fetuses/babies diagnosed prenatally within the framework of prenatal screening and diagnosis programs at the Division of Perinatology, *Hacettepe University, Ankara, Turkey*, between “January 2014- April 2015”. Total live birth number was 2720 during the same period.

Prenatal diagnosis is obligatory for  $\geq 35$ -years old pregnancies in Turkey, just because of medical issues and court decisions although there is no written governmental recommendation and/or regulation. Thus, prenatal screening program (biochemical tests and ultrasound examinations) is essential for under 35-year of age due to the same reason described above. Prenatal screening program covers routine antenatal ultrasound scan as a part of combined test, and also independently. Echogenic intracardiac focus (EIF), choroid plexus cyst (CPC), pyelectasis, thickened nuchal fold (ThNF), hyperechogenic bowel (HEB), absent nasal bone (ANB), single umbilical artery (SUA), short femur and humerus are accepted as ultrasonographic fetal soft markers for fetal aneuploidy (Ahman et al. 2014). Physicians are free to have obstetric ultrasound examination whenever they want, and as much as it is necessary (there is no governmental limitation). Our departmental preference is to have ultrasonographic examination for at least, 4 times during pregnancy. First one is performed to show

fetal viability, between the 11<sup>th</sup> to 14<sup>th</sup> gestational weeks, mostly as a part of combined test, at the 20<sup>th</sup> gestational week for anomaly scan and at the 28<sup>th</sup> gestational weeks to see fetal growth curve.

The general policy of governmental and civil institutions (although some attempts have been made by some civil medical associations), do not have medical recommendations and regulations to prevent misuse of this material in court decision-makings. Besides, there is still no written consensus between governmental and non-governmental medical societies involved in prenatal screening/diagnosis services. Most of the Turkish physicians prefer to follow-up text book and literature knowledge in their clinical practice as well as the advices of various international medical societies/associations. In this report, all pregnancies had an increased risk for having a child with DS and also, had an at least, one indication for prenatal diagnosis (the invasive diagnostic tests such as amniocentesis, chorionic villus sampling and cordocentesis) (Table 1).

Two diagnostic methods (conventional cytogenetic analysis (karyotyping) and quantitative fluorescence PCR (QF-PCR)), were performed on all specimens to detect fetal aneuploidies. Specimens were both prepared immediately (direct preparation) for QF-PCR and cultured for 3 days (cordocentesis), 12 to 15 days (amniocentesis) and 15 to 20 days (chorionic villus sampling) for conventional cytogenetic analysis (karyotyping). Using uncultured cells with QF-PCR allowed for rapid diagnosis of aneuploidies. Fetal echocardiography is performed in necessary cases. Medical and individual histories were questioned in detail, and consultations were made to related departments when necessary.

### RESULTS

Clinical features and demographic characteristics of the cases are shown in Table 1. Among all pregnant women, advanced maternal age (n=14), increased “double/combined test” risk (n=12), increased “triple test” risk (n=3), ultrasonographic soft markers and congenital abnormalities (n=12) were the main indications to perform an invasive procedure. Fourteen pregnant women had more than one indication for prenatal diagnosis. Major congenital abnormality has

**Table 1: Variables of 21 Down Syndrome cases**

<i>Number of individuals</i>	<i>Maternal age</i>	<i>Systemic diseases</i>	<i>Karyo type</i>	<i>Ultrasound scan</i>	<i>Indication</i>	<i>Performed test</i>
1	31	-	+	NT: 2.44 mm	AUS, DTR	CVS
2	32	-	+	Hyperechogenic bowel, polyhydroamnios	AUS	AC
3	37	Heterozygous Factor-V Leiden mutation	+	NT:2.6 mm	AMA AUS	AC
4	38	-	+	-	AMA, DTR, TTR	AC/KS
5	44	-	+	-	AMA, DTR	AC
6	39	-	+	NT:4.5 mm	AMA, AUS	CVS
7	43	-	+	NT:4.95mm, common subcutaneous edema	AUS, DTR	CVS
8	35	Hypothyroidism	+	Cystic hygroma	AMA, AUS, DTR	AC
9	42	-	+	-	AMA, DTR	KS
10	39	Hypothyroidism	-	Absence of nasal bone, AV canal defect, hypoplastic left heart, NT:4.5 mm	AMA, AUS	-
11	30	-	+	-	DTR	CVS
12	32	-	+	-	DTR	AC
13	44	Asthma	+	Common subcutaneous edema, hydrops fetalis, multiple skeletal anomaly	AMA, AUS	AC
14	39	-	+	-	AMA	CVS
15	36	-	+	NT:3.2 mm	AMA, AUS, DTR	CVS
16	41	Hypothyroidism, thrombophilia defect	+	Pelviectasis	AMA, DTR, TTR	AC
17	30	-	+	Three lymphatic Cystic hygroma	AUS	AC
18	41	Goiter	-	AVSD	AMA,	-
19	24	-	+	Bilateral Pelviectasis	AUS AUS AVSD	CVS
20	30	FMF	+	-	DTR, TTR	AC
21	39	-	+	-	AMA, DTR	CVS

*Abbreviations:* **AMA:** advanced maternal age, **AUS:** abnormal ultrasonographic findings, **DTR:** increased double/combined test risk, **TTR:** increased triple test, **AC:** amniocentesis, **CVS:** chorionic villus sampling, **KS:** cordocentesis **NT:** nuchal translucency

been observed only in 4 cases (19 %), and that is less than what we have expected to observe (with congenital cardiac abnormalities and others).

The results of the present study demonstrate that two-third of the cases belonged to “over 35-year” old pregnancies. In Turkey, legal climate together with scientific findings enforce physicians to offer prenatal diagnosis for  $\geq 35$ -years of maternal age routinely in clinical practice. Prenatal screening programs are mainly performed for women under 35-year of age and an obligation due to medico-legal issues. In this paper, the researchers have demonstrated that prenatal screening tests (six double/combined tests and two triple tests) are additionally applied to six (both screening tests together in two)  $\geq 35$ -years old patients that is unnecessary due to the defaults of medical system (probably due to exaggerated expectations of patients and income/salary policies of physicians).

In the present study, patients’ ultrasonographic signs which consist of increased nuchal translucency, hyperechogenic bowel, absent of nasal bone, cardiac defects, renal pyelectasis, subcutaneous edema, hydrops fetalis, cystic hygroma and multiple skeletal anomaly were noted (n=13) (13/21; 61.9 %). Two or more systemic ultrasonographic signs of the same individual were detected in five of the 13 cases (38.5 %), otherwise, increased nuchal translucency was detected in 8/13 individuals (61.5%). In Turkey, there is no numerical limitation for ultrasound examinations within the framework of national antenatal care and prenatal diagnosis programs. Payers are “Social Security Council (SGK)” which is a governmental institution and private insurance companies for regular citizens. Patients pay for their medical services themselves in private medical system. For this reason, ultrasound examinations are applied generously together with double test as a part of combined test (nuchal translucency measurement) and independently in all patients.

Invasive procedures such as amniocentesis (n=12), chorionic villus sampling (n=8) and cordocentesis (n=2) were performed within the framework of prenatal diagnosis program according to the gestational week on admittance. Consent forms were signed by the patients before having the invasive procedure. In one individual who has underwent amniocentesis at a different center, and has been diagnosed with DS, cordocentesis was also performed at our center

on the family’s request. In one individual, amniocentesis was planned after the “induced abortion decision” due to ultrasonographic findings and it was reported as DS. In a total of 21 cases (all regular DS), 18 of them were terminated, 3 of the rest individuals reject termination of their pregnancies. Hypothyroidism was noted in three individuals and 2 of them were accompanied by hereditary thrombophilia (MTHFR 1298 polymorphism and Factor V Leiden mutation). Nodular goiter, Familial Mediterranean Fever and bronchial asthma were noted respectively in 3 individuals. None of the present individuals had consanguinity (which is something unexpected in Turkish population).

## DISCUSSION

Maternal and fetal risk factors that may influence the presence of trisomy-21 fetuses within the framework of prenatal screening and diagnosis programs have been analyzed in this paper. The researchers have also studied the clinical features, characteristics and chromosomal findings of the DS babies. Advanced maternal age ( $\geq 35$  in Turkey), presence of ultrasonographic soft markers associated with aneuploidy, screen-positive results for aneuploidy on prenatal screening tests (double/combined, triple, cell free DNA testing and others), fetal trisomy history in previous pregnancies, parental translocations with increased risk of trisomy 21 or others and consanguinity are the main indications for prenatal diagnosis of DS (David et al. 2000; Hui et al. 2015).

It is a well-known fact that maternal age is directly related to the risk for having a child with fetal aneuploidy (Hook 1981; Donner 2015). In the present study, advanced maternal age ( $\geq 35$ ), was the main factor for prenatal diagnosis of DS (n=14). The risk of DS as a result of advanced maternal age increases in a non-linear fashion. Incidence ranges from approximately 1 in 1300 in young women to 1 in 30 in 45-year-old pregnancies (Morris et al. 2002). The risk of having a baby with DS and risk of pregnancy loss because of invasive diagnostic procedures are approximately same at age 35. Consequently, age 35 has been used as a cut-off value for offering an invasive testing as a result of the study of Morris et al. (2005).

The miscarriage risk associated with invasive procedures has been reported to be under 1

percent for both amniocentesis and CVS (Mazza et al. 2007).

In women under 35-years of age, ultrasonographic evaluations and maternal serum biochemical markers are used for calculating the risk for having a baby with fetal aneuploidy (Ahman et al. 2014). Among all 21 DS cases; 13 cases had ultrasonographic soft markers, 12 cases had increased double test and 3 cases had increased triple test. Thickened nuchal fold was the most common ultrasonographical finding (n=8) in our study. The others are; hyperechogenic bowel in one, echogenic intracardiac focus in one, nasal bone absence in one and multiple anomalies with hydrops fetalis in one. It has been reported that soft markers were detected in 5.9 percent of fetuses (5.1% were isolated, 0.7% were multiple and only 0.1% were combined) with aneuploidies by Ahman et al. (2014).

Different prenatal screening tests can be used as a part of antenatal care programs as reported previously (Akolekar 2015). In these series, 12 of 21 DS cases had an increased double/combined test risk while three individuals had an increased triple test risk. The fuzzy part of this research's clinical finding is the application of biochemical screening tests for women e"35 years-age to whom we always offer prenatal diagnosis (invasive tests).

Analysis of cell-free DNA in maternal blood as a part of prenatal screening is used commonly in private practice (Pan et al. 2013) Aneuploidy screening programs is probably going to be different in the future with the improvement of technology, but, 'NIPT' is still not a routine clinical practice in most countries (Cuckle et al. 2015). However, its application in government hospitals is limited due to its cost and we do not have this screening methodology in our series.

In this study, 8 pregnant women of 21 DS underwent chorionic villus sampling and 9 individuals underwent amniocentesis for definitive diagnosis. Both amniocentesis and cordosentesis were performed for one individual because of family request and anxiety, and one cordocentesis due to late admittance. Surprisingly, two cases (both with additional congenital abnormalities) refused termination option and gave living birth at term. There were no significant complications (such as pregnancy loss, infection, vaginal bleeding) noted after performing invasive prenatal tests.

## CONCLUSION

Prenatal diagnosis of DS is very important and physicians are under the pressure of social and legal issues. Court decisions, legal atmosphere and social issues (economic and religious), influences decision making in prenatal screening and diagnosis programs.

## RECOMMENDATIONS

Prenatal screening and genetic counseling is compulsory even though there is no written regulation or recommendation related to the methodologies. Clinicians should offer appropriate diagnostic test to women with increased risk for aneuploidy at screening.

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