



## Original Article

## Prenatal diagnosis of Down syndrome: A 13-year retrospective study



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## ABSTRACT

**Objective:** The aim of this study is to summarize the experience on prenatal diagnosis of Down syndrome.

**Materials and methods:** The study includes a retrospective data analysis of 157 prenatally detected cases of Down syndrome, routinely diagnosed among 6448 prenatal investigations performed during a 13-year period (2002–2014) in a single tertiary center.

**Results:** The prevalence of diagnosed Down syndrome cases was 2.4%. Maternal age alone was indication for prenatal diagnosis in 47 cases (45.2%), increased first-/second-trimester biochemical screening test in 34 cases (21.7%), abnormal ultrasound examination in 69 cases (43.9%), positive familial history for chromosomal abnormalities in four cases, and high risk for trisomy 21 revealed by cell-free DNA testing in three cases. Ultrasound anomalies were present in total of 94 fetuses (59.8%). The most common abnormality was cystic hygroma found in 46 cases (29.3%). A regular form of Down syndrome (trisomy 21) was found in 147 cases (93.6%), Robertsonian translocation in six cases (3.8%), and mosaic form in four cases (2.6%).

**Conclusion:** In prenatal diagnosis of Down syndrome noninvasive screening methods are important for estimation of individual risks, in both, young population of woman and older mothers, while conventional and molecular cytogenetic methods are essential for definite diagnosis and proper genetic counseling.

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## Introduction

With the incidence estimated between one in 1000 to one in 700 live births, Down syndrome is the most common chromosomal abnormality, and considered one of the major congenital causes of intellectual disability in human population. Moreover, if we take into account pregnancies ending up with medically induced abortions and stillborn, the incidence of Down syndrome increases to approximately one in 450 births [1]. During the last 20 years, the increase of 10% in number of pregnancies with Down syndrome has been noticed in Europe, mainly due to increasing maternal age at the time of conception. However, development and the increasingly widespread practice of prenatal screening followed by

terminations of pregnancies have resulted in stable live birth prevalence [2].

Prenatal diagnosis of Down syndrome comprises noninvasive screening methods which provide the risk estimation of having affected pregnancy, while the definite diagnosis is made by karyotyping of cultured fetal cells obtained by one of invasive procedures, mainly chorionic villus sampling (CVS) or amniocentesis. As the most common chromosomal aberration trisomy 21 is detected in approximately 1.6–3.2% of all prenatal karyotyping investigations performed [3,4] Over the years several screening strategies have been applied, and the methods used are maternal age assessment, first- and/or second-trimester ultrasound examinations, and maternal serum biochemical testing at the first and/or second trimester of pregnancy. Furthermore, in the last few years a noninvasive prenatal testing (NIPT) using analysis of cell-free fetal DNA from maternal plasma has been widely introduced [5]. In order to give parents better informed counseling and to minimize the risk of miscarriage associated with invasive procedures, the present

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guidelines and studies are directed toward calculation of individual risks for every pregnant woman and improvements in sensitivity ratios and reduction of false-positive results.

The aim of this study is to summarize the experience on prenatal diagnosis of Down syndrome, presenting a 13-year data collected in a single tertiary center.

## Materials and methods

A retrospective survey covering a 13-year period from January 2002 to December 2014 at our Department included 157 prenatally detected cases of Down syndrome, routinely diagnosed after CVS, amniocentesis, cordocentesis or analysis of materials collected after termination of pregnancy (TOP). Throughout observed period, a total of 6448 fetal karyotyping analyses were performed. Indications for prenatal diagnosis are given in Table 1. Advanced maternal age was defined as 35 years or older at expected date of delivery. Abnormal ultrasound findings detected at first-trimester examination (11–13 + 6 weeks gestation) included nuchal lesions defined as increased nuchal translucency (NT) thickness or cystic hygroma (CH), abnormal ductus venosus (DV) flow and the absence of nasal bone. NT measurements were performed at mid-sagittal plane and compared to NT nomograms at a given gestational age. Increased NT thickness was considered  $\geq 2.5$  mm. CH was defined as a bilateral, mostly symmetric septated cystic structure located mainly in the occipital region of the neck, with or without associated anasarca. Ultrasound findings discovered during second-trimester examination included various major abnormalities and minor/soft markers associated with aneuploidies (Table 2).

Cytogenetic analysis was performed on cultured amniocytes, fetal blood cells, skin fibroblasts, or on short-term cytotrophoblast/mesenchymal stroma cultures, following European Cytogeneticists Association guidelines [6]. Fluorescence *in situ* hybridization (FISH) was carried out with commercially available 21q22.1 specific region probe (Kreatech Diagnostics, Netherlands), according to manufacturer's protocols.

Descriptive statistics were used for the analysis of collected data. Comparisons for categorical variables were made using Pearson  $\chi^2$  test, and for comparison of continuous variables between two groups, due to violation of normality assumption, nonparametric Mann–Whitney *U*-test was used.  $P < 0.05$  was considered statistically significant.

## Results

During a 13-year period (2002–2014) a total of 6448 prenatal investigations were performed, and Down syndrome was diagnosed in 157 cases (2.4%). In 91 cases (58.0%) the diagnosis was made after amniocentesis, in 54 (34.4%) after CVS, in eight (5.1%) after analysis of materials collected after TOP, and in four cases (2.5%) after cordocentesis. Indications for prenatal diagnosis are presented in Table 1. The mean maternal age was 35.9 years (SD 5.2

years, range 20–46 years). The diagnosis was made in 49 cases (31.2%) during the first trimester, in 107 cases (68.2%) during the second, and in one case (0.6%) in the third trimester of pregnancy. However, in a period from 2002 till 2007 in only 13.1% of cases karyotyping was performed in the first trimester, in comparison with the higher rate of early diagnosis assessment in 2008–2014 (42.7% cases) ( $P < 0.0001$ ). The mean gestational age at the time of diagnosis in a period 2002–2007 was 17 weeks, and in 2008–2014 was 14 weeks and 6 days. Furthermore, during a period 2002–2007 61 cases with Down syndrome was detected among 3610 diagnostic procedures performed (1.7%), in comparison with detection rate of 3.3% in 2008–2014 (96 cases within 2838 investigations).

There was a statistically significant difference in gestational age when the diagnosis was performed between a group of women older than 35 and younger mothers (median gestation of 16.4 weeks vs. 15 weeks) ( $P = 0.006$ ). In a group of mothers aged less than 35 ( $n = 53$ ), the most common indication for prenatal diagnosis was abnormal ultrasound examination (60.4%), while in 30.2% of cases positive first- or second-trimester biochemical screenings (with or without ultrasound abnormalities) indicated fetal karyotyping (Table 1). In this group, ultrasound anomalies were found much more often (in 81.1% of fetuses) than in group of women aged 35 or older (53.8% of fetuses) ( $P < 0.0001$ , Pearson  $\chi^2$  test). Among all diagnosed Down syndrome cases, an abnormal first-/second-trimester ultrasound scan was observed in 94 fetuses (59.8%).

The most common ultrasound finding was CH ( $n = 46$ ), in 12 cases associated with anasarca. Increased NT thickness was observed in 33 cases. As an additional finding, abnormal DV flow was found in 10 and absent nasal bone in six cases. Soft markers and major structural malformations diagnosed at second-trimester scan are summarized in Table 2. Furthermore, in five cases polyhydramnios was present, in two starfish amnion, and in one case amniotic band syndrome. Isolated soft markers were found in three fetuses, while in cases with echogenic intracardiac focus (EIF) and bilateral choroid plexus cysts (CPC) patients underwent amniocentesis due to positive maternal serum screening test, and in a case of pyelectasis because of positive familial history for chromosomal abnormalities.

Amniocentesis was performed in three dichorionic diamniotic (DCDA) twin pregnancies. The indication for prenatal diagnosis in two cases was ultrasound finding of CH present in a single twin, while cytogenetic analyses in both cases revealed trisomy 21 in affected twin, and normal karyotype in other fetus. In the third case amniocentesis was performed solely due to advanced maternal age, and the trisomy 21 was observed in one twin.

A regular form of Down syndrome (trisomy 21) was found in 147 cases (93.6%), Robertsonian translocation (RT) in six (3.8%), and mosaic form in four (2.6%), with the percentage of trisomic cells ranging from 5% to 33%. Male to female ratio (sex ratio, SR) was 1.9. Robertsonian translocation was of parental origin in two cases and *de novo* in four cases. In a 35-year-old patient, amniocentesis was performed at 17 weeks gestation after results of high risk for

**Table 1**  
Indications for prenatal diagnosis in a group of women younger than 35, and in older mothers.

Maternal age	Indication No. of cases (%)					Total No. of cases (%)
	Maternal age alone	Combined screening <sup>a</sup>	Second-trimester maternal serum screening <sup>a</sup>	Ultrasound anomaly	Other <sup>a</sup>	
<35 years	0	10 (18.9)	6 (11.3)	32 (60.4)	5 (9.4) <sup>b</sup>	53 (100)
$\geq 35$ years	47 (45.2)	10 (9.6)	8 (7.7)	37 (35.6)	2 (1.9) <sup>c</sup>	104 (100)

<sup>a</sup> With or without abnormal ultrasound findings.

<sup>b</sup> Positive familial history for chromosomal abnormalities in three cases; high risk for trisomy 21 revealed by non-invasive prenatal test (NIPT) from maternal plasma in two cases.

<sup>c</sup> Positive familial history for chromosomal abnormalities in one case; high risk for trisomy 21 revealed by NIPT in one case.

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