

# Detection Rate and Sonographic Signs of Trisomy 21 Fetuses at 14–17 Weeks of Gestation

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**ABSTRACT:** **Background:** Early prenatal ultrasound is an important part of prenatal screening in Israel. No studies have described the rate of trisomy 21 [T21] identification at 14–17 weeks gestation.

**Objectives:** To describe the rate of T21 identification by transvaginal sonograms (TVS) at 14–17 weeks gestation.

**Methods:** We conducted a historical prospective study. Since 1986, early TVS of 72,000 fetuses at 14–17 weeks gestation have been prospectively recorded together with prenatal screening data at a private ultrasound center (AL-KOL, Haifa). We calculated the fraction of T21 cases by dividing the total number of cases with abnormal sonographic findings by the total number of diagnosed T21 cases. We also examined the percentage of verified T21 cases that had completely normal prenatal screening tests prior to the early prenatal TVS, thus revealing the contribution of this examination to the existing prenatal screening. Fisher's exact test was used to calculate odds ratios for each sonographic marker.

**Results:** Of 137 T21 fetuses, 123 had sonographic markers on early TVS, yielding a prediction capability of at least 89.87%. Of all T21 cases, 14% had completely normal nuchal translucency/first-trimester screening prior to the abnormal 14–17 week TVS findings. Isolated abnormal sonographic findings, which were found to increase the risk for T21, were common atrioventricular septal canal (odds ratio 88.88), duodenal atresia (OR 88.23), nuchal edema (OR 39.14), and hydrocephalus (OR 15.78). Fetal hydronephrosis/pyelectasis was non-significant when isolated (OR 1), and cardiac echogenic focus was associated with a decreased risk (OR 0.13).

**Conclusions:** Early prenatal TVS at 14–17 weeks may identify almost 90% of T21 and adds 14% to the identification rate at the first-trimester screening.

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**KEY WORDS:** Down syndrome, trisomy 21 (T21), ultrasound, nuchal translucency (NT), nuchal edema, nuchal thickness, transvaginal ultrasound, prenatal diagnosis

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Trisomy 21 (T21), the most common fetal trisomy, occurs in 1:690 pregnancies [1] and is associated with structural and cognitive abnormalities. Screening for fetal T21 is typically based on four main components: maternal age, biochemical screening of placental markers, sonographic screening of fetal nuchal translucency (NT), and systematic anatomic screening in the second trimester. Recently, non-invasive prenatal testing (NIPT) of fetal DNA in maternal circulation was also introduced. This method is sensitive but expensive and thus may be of limited use for the general population.

The second-trimester sonographic systematic screening in search of anatomic abnormalities can be performed at 14–17 weeks by transvaginal sonography (TVS) or later by transabdominal sonogram (TAS) [1-8]. In Israel, an early TVS examination at 14–17 gestational weeks has become the standard of care. Thus, most pregnant women undergo two sonographic anatomic surveys: an early TVS extensive anatomic screening at 14–17 gestational weeks, and a late abdominal sonographic screening at 22–24 weeks [9]. In this time period of 14–17 weeks gestation, 96% of fetal malformations are detectable, including over 99% of the cardiac anomalies, leading to termination of pregnancy in 1:50 accordingly screened pregnancies [9].

Several sonographic abnormalities have been suggested as markers associated with fetal T21: cardiac anomalies, duodenal atresia, elevated nuchal translucency and several other “soft signs” [2-9]. The most common sonographic marker of T21 is an elevated NT in the first trimester, which itself has a detection rate of about 70% (without biochemical markers) [3]. NT appears in the first trimester and usually disappears by 17–19 weeks. This finding has also been described as nuchal thickening, nuchal fold/thickness, cystic hygroma, webbed neck, nuchal edema, non-septated cystic hygroma, antero-lateral cervical cyst, jugular lymphatic distension, pterigium coli [7], etc., and is associated with fetal dyskaryosis, although it may also be a transient finding in normal fetuses [3]. The pathophysiology beyond an elevated NT has

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not been completely elucidated. In addition to NT, several other fetal sonographic signs have been examined as possible markers of T21, so-called soft markers, since they may be transient and disappear later in pregnancy. These include absent nasal bone, pyelectasis or hydronephrosis, echogenic bowel, cardiac echogenic chorda tendineae (“golf ball”), and choroid plexus cysts (CPC) which is related more to trisomy 18. Most of these signs have not been validated as significant markers of T21, although most studies did not examine them separately. Almost 25 years ago, Nyberg et al. [4] looked at the detection rate of T21 at 18–22 weeks by TAS and found common atrioventricular septal canal (CAVC) and duodenal atresia to be specific markers of T21 [4].

However, these anomalies appear in only a minority of T21 fetuses, and since NT would have already been absorbed and disappeared at 18–22 weeks, in our experience only 20% of the T21 cases are detectable at this gestational age. More recently, Agathokleous and team [5] published a meta-analysis of 48 publications on the “soft markers” of T21. Despite the importance of the soft markers, there are some limitations, such as the wide range of gestational ages at which the sonography was performed (14–24 gestational weeks), multiple investigators, various sonographic devices and variable sonographic skills. This meta-analysis concluded that isolated absence of the fetal nasal bone, aberrant right subclavian artery, elevated NT, and hydrocephalus are reliable and significant markers of T21.

The early mid-trimester TVS examination necessitates skill and experience and is not accepted worldwide as a screening method. Conversely, in Israel, TVS has been embraced by most obstetric sonographers since 1987 and is common practice [6,9]. TVS at 14–17 weeks may be viewed as a window of opportunity since NT is still detectable and has not yet been absorbed, and most of the second-trimester anomalies are already detectable at this gestational age [9]. Another advantage of TVS screening at 14–17 weeks is the possibility of offering and performing early termination of pregnancy (TOP), thus minimizing emotional stress and the risks of the procedure [10].

Regarding the detection of T21 by later mid-trimester abdominal ultrasound, Offerdal et al. [11] concluded: “Our data can be considered as a reference standard for population screening for trisomy 21 based solely on maternal age and second-trimester ultrasound imaging. The prenatal detection rate of trisomy 21 cases was poor and remained unchanged throughout the 18-year study period. If improvement in detection rates is desired, additional programs are necessary.”

Since the detection rate of fetal T21 by the early second trimester (weeks 14–17) using TVS has not been reported, this was the objective of this study. In addition, we looked at the importance of each sonographic marker at this gestational age.

## SUBJECTS AND METHODS

Between 1986 and 2012, 72,000 TVS examinations were performed by a single experienced sonographer (M.B.) in our center (AL-KOL, Haifa). Starting in 1986, every examination was recorded including patient’s age and the detected fetal anomalies. From 1997 biochemical markers were prospectively added to every recorded patient’s chart, in addition to age and detected anomalies. In 2012, the prospectively gathered 72,000 examinations were summarized retrospectively. TVS was performed using a Philips IU22 MHz probe (USA) and Elscint 6.5 and 7.5 MHz probes (Israel) [5–9]. All were private patients either self-referred or referred by their attending physician for a systematic screening for the detection of fetal anomalies. Patients signed an informed consent and the institutional review board on human experimentation approved the study.

## STATISTICAL ANALYSIS

The study population consisted of 137 fetuses diagnosed with T21 by chromosomal analysis during pregnancy. The control group comprised the other 71,863 fetuses examined at 14–17 weeks gestation. In this study we examined the fraction of T21 cases identified by dividing the number of cases with abnormal sonographic findings by the total number of verified T21 cases. Furthermore, Fisher’s exact test was used to calculate odds ratios (OR) for the accurate detection of T21 for each sonographic abnormality separately in order to assess its specific significance. In addition, we examined the percentage of verified T21 cases that had completely normal prenatal screening tests prior to the TVS exam at 14–17 weeks gestation, thus revealing the contribution of the TVS examination to the existing prenatal screening.

## DEFINITIONS FOR SONOGRAPHIC ABNORMALITIES

- **Nuchal thickening/edema:** In the TVS examination, the sonographic beam is directed to the nuchal area and not through the fetal face, as in cases of TAS at 11–13 weeks when the fetus is looking upwards. Therefore, there is almost no nuchal thickening at all, normally. Every NT  $\geq 3$  mm at 11–17 weeks was considered abnormal, as were lateral nuchal cysts larger than 5 mm. Whenever the nuchal edema was  $> 5$  mm or septated, we considered it as septated cystic hygroma. Axillary cysts and fetal hydrops were also included in the category of fetal edema.
- **Hydronephrosis/pyelectasis:** This anomaly was defined as a  $> 3$  mm enlargement of fetal kidney pelvises on anterior-posterior [AP] section.
- **Fetal nasal bone:** We previously reported that absence of fetal nasal bone is not a reliable sign of T21 at 14–16 weeks; therefore, we did not include this “marker” in our results [12].

- **Hydrocephalus:** Hydrocephalus was defined as lateral ventricles wider than 12 mm each, floating or atretic/contracted choroid plexus.

## RESULTS

Since it is impractical to summarize and follow 72,000 patients, in order to verify the accuracy of T21 in our population we used two different methodologies. In the first we calculated the expected rate of T21. According to Snijders et al. [2], the probability of T21 based on the patients' ages (by different age groups) was 189 in the cohort of 72,000 patients. We detected only 137 cases documented by karyotype. However, there were 54 cases in our cohort that had undergone TOP due to the finding of common atrioventricular septal canal (CAVC) and NT without karyotype assessment. We calculated that over 90% of these 54 cases had T21, which explains the difference between the 189 expected and 137 observed T21 fetuses.

In 90% of the patients who had undergone amniocentesis due to increased nuchal edema and CAVC at 14–17 weeks, the karyotype was T21. Several other cases of CAVC without nuchal edema but with multiple fetal malformations had fetal trisomy 18. One case of CAVC without nuchal edema and with no other fetal anomalies had normal karyotype.

Furthermore, we examined the central registry of the Ministry of Health's Genetic Institute (where all cases of T21, either born or diagnosed by amniocentesis or CVS, are registered). We were able to check the 47,000 patients examined in our center from 1986 to 2005. Our records matched the registry in all cases except for one, a 38 year old woman who delivered a T21 neonate which was missing from our records. This patient was offered amniocentesis but refused.

Of 72,000 TVS examinations at 14–17 weeks of gestation, T21 was identified in 137 fetuses. As mentioned, in 54 women the detection of NT with a common atrioventricular septal canal led to TOP without fetal karyotyping. The median maternal age in the group of identified T21 was 36 years, compared to 31 years in the control group.

Of the 137 fetuses with documented T21, sonographic anomalies were detected in 123 (89.87%), leading to amniocentesis and correct diagnosis. Of these, in 33 fetuses the sonographic abnormality was isolated whereas in 90 there was more than one anomaly. In the other 14 cases of T21, the sonographic screening at 14–17 weeks failed to find any clue or abnormality suggesting fetal dyskaryosis.

Nineteen of the T21 fetuses (14%) had normal first-trimester nuchal translucency and biochemical screening. However, TVS at 14–17 weeks detected sonographic markers leading to amniocentesis and correct diagnosis. In most of these cases, fetal nuchal edema or cystic hygroma was in fact detected at 14–17 weeks, despite previously normal

first-trimester nuchal translucency [Figure 1] [9]. Some of them had additional sonographic markers such as common atrioventricular septal canal [2].

We evaluated the sonographic anomalies as possible "markers" of Down syndrome. Four fetal sonographic markers were found to be significantly associated with T21: common atrioventricular septal canal (OR 88.88), duodenal atresia (OR 88.23), nuchal edema (OR 39.14), and hydrocephalus (OR 15.78) [Table 1]. However, fetal hydronephrosis/pyelectasis and single umbilical artery were not significantly associated with trisomy 21, whereas echogenic focus in the fetal heart was associated with a decreased risk of trisomy 21 [3-5].

**Figure 1.** Classic nuchal edema of 6 mm width (between stars) in a 15 week trisomy 21 fetus (between arrows), on transvaginal sonography, transverse section. This fetus had a normal first-trimester nuchal translucency examination



**Table 1.** Sonographic markers

Sonographic marker (isolated)	No. of cases in trisomy 21 group (N=137)	No. of cases in control group (N=72,000)	Confidence interval (%)	Odds ratio	P value
Nuchal edema	23	369	22.248–48.190	39.148	< 0.001
Hydronephrosis	2	1044	0.249–4.075	1	1
CAVC (common atrioventricular septal canal)	2	12	19.793–387.758	88.88	< 0.001
Duodenal atresia	1	6	10.61–722.792	88.235	0.013
Hydrocephalus	3	102	4.964–48.130	15.781	0.001
Echogenic focus	1	3790	0.02–0.975	0.132	0.011
Hydronephrosis in the presence of echogenic focus	1	138	0.536–27.034	3.82	0.232

The solitary isolated findings that were associated with trisomy 21 were nuchal edema, hydronephrosis, common atrioventricular septal canal (CAVC), duodenal atresia, and echogenic focus

## DISCUSSION

In our study, early mid-trimester TVS screening at 14–17 weeks detected 90% of trisomy 21 fetuses. Thus, a normal TVS examination decreased the risk of trisomy 21 by tenfold, in keeping with Agathokleous et al. [5] who reported a 7.7-fold decreased risk with a normal sonographic examination in the second trimester. The strengths of our study include the utilization of a reliable database with a large number of patients, and the fact that all examinations were performed by a single experienced sonographer, thus eliminating inter-observer variability which is a common confounder in ultrasound research.

We feel that the high detection rate at 14–17 gestational weeks, in addition to other advantages previously mentioned and elaborated in another publication [9], justifies performing early mid-trimester ultrasound for prenatal screening of T21. More recently, Gupta and co-authors [13] also described the advantages of early second-trimester sonography (at 14–16 weeks) to improve the fetal anatomic survey in obese patients. The main difficulty with this approach is that TVS examination at 14–17 weeks necessitates a high level of experience, capability and training in the detection of fetal anomalies.

As we previously specified [14], in 23,439 cases the incidence of newborns with anomalies decreased from 1.95% to 1.34% ( $P < 0.01$ ). The incidence of termination of pregnancy because of fetal anomalies increased from 0.35% to 0.83% ( $P < 0.003$ ), and the detection rate of malformations increased from 53.94% to 79.60% ( $P < 0.001$ ) [13]. It was concluded [13] that termination of pregnancy after TVS detection of fetal anomalies had an impact on the prevalence of anomalies in newborns.

In conclusion, a targeted sonographic detailed scan during gestational weeks 14–17 is the optimal ‘time window’ for the sonographic prenatal detection of T21. Of all the prenatal screening tests for T21, NIPT is the most sensitive. However, since NIPT is costly and does not preclude the need for a detailed ultrasound exam, it may not be cost-effective [13]. Furthermore, in cases of “precious pregnancies,” i.e., pregnancies conceived by in vitro fertilization/assisted reproduction technologies after longstanding infertility when there is no satisfactory or non-reportable results of NIPT [15,16], the sonographic detailed scan may aid in the decision flowchart before invasive testing/amniocentesis. As previously stated [17], maternal screening for T21 is developing and has undergone significant changes in the last two decades. According to our findings, the 14–17 weeks TVS may add significantly to the detection rate of the first-trimester screening, with a higher yield and detection rate than the later mid-trimester adnominal ultrasound [11]. In summary, TVS screening at 14–17 weeks

can detect almost 90% of fetal T21 cases and adds 14% to the sensitivity of first-trimester NT and biochemical screening.

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“Everyone is entitled to his own opinion, but not his own facts”

Daniel Patrick Moynihan (1927-2003), American politician and sociologist