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By how much does increased nuchal translucency increase the risk of adverse pregnancy outcome in chromosomally normal fetuses? A study in 16 260 fetuses derived from an unselected pregnant population

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Abstract

Objective: To estimate the magnitude of a possible increase in risk of adverse outcome in fetuses with normal karyotype and increased nuchal translucency (NT), and to determine how well NT measurements can distinguish between fetuses with normal and adverse outcome.

Study Design: We studied 16 260 consecutive fetuses with normal karyotype derived from an unselected pregnant population. The following cut-offs for increased risk of adverse outcome were chosen à priori: NT ≥ 95th percentile, ≥3mm, ≥3.5 mm, and ≥4.5mm. The positive and negative likelihood ratios (+LR, –LR) of the risk cut-offs with regard to fetal malformation, miscarriage, perinatal death, termination of pregnancy and total adverse outcome were calculated, and receiver operating characteristic (ROC) curves were drawn.

Results: The total rate of adverse outcome was 2.7%. +LR and –LR of NT ≥3.0mm were: for lethal or severe malformation +LR 15.0 (95% CI 7.0-28.6), –LR 0.89 (0.81–0.95); for malformation of at least intermediate severity +LR 8.1 (95% confidence interval, CI, 4.3-14.0), –LR 0.95 (0.92–0.97); for termination of pregnancy +LR 41.6 (95% CI 17.1-86.6), –LR 0.67 (0.41–0.85); for any adverse outcome +LR 6.4 (95% CI 3.4–11), -LR 0.96 (0.94–0.98). The odds for these adverse outcomes increased with increasing NT. NT ≥3mm did not significantly increase the risk of miscarriage or perinatal death. Areas under ROC curves for NT were small with 95% confidence intervals below or only slightly above 0.5.

Conclusion: Our likelihood ratios can be used to calculate the individual risk of unfavorable outcome, but NT screening cannot reliably distinguish between normal and adverse outcome in fetuses with normal karyotype.

Introduction

The association between increased nuchal translucency (NT) in the first trimester and chromosomal aberrations is well documented [1, 2, 3]. However, NT is increased in 4.4% of euploid fetuses [2]. These fetuses have been reported to be at increased risk of adverse pregnancy outcome, e.g., structural abnormalities, particularly cardiac defects, genetic syndromes, and fetal loss [4–18]. Most of the studies reporting on an association between increased NT and adverse outcome had no control group [4, 9–15, 17, 18], which makes it difficult to interpret their results, because the prevalence of adverse outcome among fetuses with increased NT (i.e., the positive predictive value of increased NT) depends entirely on the study population. Accordingly, the reported prevalence of adverse outcome among fetuses with increased NT varies widely [4, 5, 8–18]. Two of the three published studies that did have a control group were performed in high-risk pregnancies [8, 16].

The aim of our study was to estimate the magnitude of a possible increase in risk of adverse outcome in fetuses with normal karyotype and increased NT in an unselected pregnant population, and to determine how well NT measurements can distinguish between fetuses with normal and adverse outcome.

Subjects and methods

Study design

Our population is a subgroup of pregnancies in the Swedish NUPP-trial (NUPP is an abbreviation for NackUPPklarning, which is Swedish for nuchal translucency), which has been described in a previous publication [19]. This national multi-center trial involved eight Swedish hospitals and included 39 572 unselected pregnancies. It was approved by the Ethics Committees at the Karolinska Institute in Stockholm, and those of the Medical Faculties of Lund University and Uppsala University. Those who consented to take part were randomized to a routine ultrasound examination either at 12 – 14 gestational weeks or at 18 weeks. The 12-week scan included NT screening for Down's syndrome. The present study includes those pregnancies that were randomised to a routine ultrasound examination at 12 – 14 weeks with at least one living fetus at the routine scan and information available about the result of the NT measurement. Exclusion criteria are loss to follow-up, chromosomal abnormality verified by karyotyping, or no information on karyotype in a fetal loss. The karyotype was considered normal on the basis of normal results of genetic testing or absence of stigmata of chromosomal aberration at pediatric examination of a living newborn.

All midwives and obstetricians were certified by the Fetal Medicine Foundation (FMF) as being competent to perform NT screening for chromosomal anomalies. The quality of our NT measurements was regularly checked by the FMF. The 12-week routine scan included pregnancy dating, scrutiny of fetal anatomy, and measurement of NT in accordance with the technical guidelines published by the FMF, the risk of fetal aneuploidy being calculated using the FMF software[20]. In clinical practice a risk of trisomy 21 ≥1:250 was regarded as increased. Women at increased risk of fetal chromosomal anomaly because of increased NT, a fetal structural anomaly detected at any scan during pregnancy, or a history suggesting an

increased risk, e.g., a previous pregnancy where the fetus had a chromosomal anomaly, were offered fetal karyotyping. Information on pregnancy outcome was retrieved from delivery records, from departments of neonatology, pediatric cardiology, pediatric surgery, neurosurgery, plastic surgery, genetics and pathology providing services to the hospitals involved, and from the National Registry of Congenital Anomalies.

Classification of congenital malformations

For statistical purposes fetuses and newborns with more than one malformation were assigned one main malformation diagnosis. Congenital heart malformations diagnosed within the first 12 months of life, and other types of malformation diagnosed (or suspected and later confirmed) before the baby was dismissed from postnatal care are included. Malformations were grouped into four categories according to their likely clinical consequences [21]. These groups were modified after a proposal by the Royal College of Obstetrics and Gynecology (RCOG) in 1997 [22]. The categories were 1) lethal malformations 2) severe malformations, i.e., malformations associated with possible survival and severe immediate or long-term morbidity 3) malformations of intermediate severity, i.e., malformations associated with short- or long-term morbidity of moderate severity 4) minor malformations, i.e., malformations or abnormalities with minor morbidity or only occasional long-term morbidity. All heart malformations except isolated atrial and ventricular septal defects, and isolated valve disorders, were regarded as major heart defects and were classified as severe malformations.

Classification of fetal loss

Stillbirth <28 weeks of pregnancy was defined as miscarriage, and stillbirth ≥28 weeks of pregnancy as intrauterine fetal death. Perinatal death included intrauterine death ≥28 weeks of pregnancy, intrapartum death, and death within 7 days of birth. In Sweden, termination of pregnancy is rarely allowed >22 weeks of pregnancy.

Classification of adverse outcome

Adverse outcome was defined as miscarriage, termination of pregnancy, perinatal death, or live birth of a baby with a malformation of at least intermediate severity.

Statistical analysis

Fetuses were defined as being at increased risk of adverse outcome using the following NT cut-offs: NT ≥ 95th percentile, ≥3.0 mm, ≥3.5 mm, or ≥ 4.5 mm. The definition of the 95th percentile was that used by the FMF at the time of the trial [2]. The sensitivity and false-positive rate (1 minus specificity) of these risk cut-offs and their positive and negative predictive values and positive and negative likelihood ratios with regard to adverse outcome (malformation, miscarriage, perinatal death, termination of pregnancy) were calculated. In addition, receiver-operating characteristic (ROC) curves were drawn to determine the diagnostic performance of NT with regard to identifying fetal malformations, miscarriage, perinatal death, and any adverse outcome. The area under the ROC curve and the 95% confidence interval (CI) of this area were calculated. If the lower limit of the CI for the area under the ROC curve was > 0.5, the diagnostic test was considered to have discriminatory potential.

Statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS Inc, Chicago, IL, USA, 2003). The statistical significance of differences in proportions was determined using Fisher's exact test or the Chi-2 testc The 95% confidence interval (CI) of likelihood ratios was calculated using StatXact, version 4 (Cytel Software Corporation, Cambridge, MA, USA, 1999).

Results

Of 19 796 women randomized to a 12 – 14 week scan, 17 973 had at least one living fetus at the scan. The number of fetuses eligible for inclusion was 18 266. Information about NT thickness was available in 16 567 fetuses. Missing information about NT is explained by the woman being too advanced in her pregnancy for NT measurement to be possible (crown rump length >84mm), difficulties with measuring NT, failure to document the NT measurement in the trial database, and obvious lethal malformations, e.g., anencephaly. After exclusion of 80 fetuses with chromosomal abnormality, 104 fetuses lost to follow up, and 123 fetal losses with unknown karyotype, our total study group comprised 16 260 fetuses (Figure 1). These had normal karyotype either according to genetic testing or to normal results of a pediatric examination after birth. Among the 16 260 fetuses, 427 (2.6%) had NT $\geq$ 95th percentile, 133 (0.8%) had NT $\geq$ 3mm, 46 (0.3%) had NT $\geq$ 3.5mm, and 19 (0.1%) had NT $\geq$ 4.5 mm. The mean age (± SD) of the mothers was 30.1 years ± 4.9, 50% were nulli-parous, and 1.8% of the pregnancies were in vitro fertilization pregnancies.

Total adverse outcome (malformation or fetal loss or both)

The rate of adverse outcome was 2.7% (441/16 260). Sensitivity, false positive rate, positive predictive value, and positive and negative likelihood ratios of increased NT with regard to total adverse outcome are presented in Table 1. Increased NT significantly increased the risk of adverse outcome, and the risk increase rose with increasing NT. NT ≥3mm increased the likelihood of adverse outcome approximately six-fold, NT≥ 3.5mm increased it approximately 15-fold, and NT ≥ 4.5mm increased it approximately 30-fold. For all NT cut-offs the negative predictive value was high (≥ 97%).

Fetal malformations

Among 16 260 fetuses we found 772 congenital malformations, 297 of these being minor. The remaining 475 congenital defects were found in 333 fetuses/babies, of which 15 had a

multiple malformations sequence, 18 had a malformed heart consisting of at least two different cardiovascular malformations but no extra-cardiac malformations, and 24 had anomalies in two or three organ systems (Table 2). This corresponds to a prevalence of fetuses with malformation(s) of at least intermediate severity of 2.0% (333/16 260). Of the 333 malformed fetuses, six (0.04% of all fetuses) had a lethal malformation, 110 (0.7% of all fetuses) a serious malformation, and 217 (1.3% of all fetuses) a malformation of intermediate severity.

Sensitivity, false positive rate, positive predictive value and positive and negative likelihood ratios of increased NT with regard to fetal malformation are presented in Table 3. Increased NT increased the risk of fetal malformation, and the risk increase rose with rising NT. NT ≥3mm increased the likelihood of lethal or serious malformation approximately 15-fold, NT ≥3.5mm increased it about 40-fold, and NT ≥ 4.5 mm increased it about 80-fold. In a subgroup comprising only non-malformed fetuses and fetuses with malformations of at most intermediate severity**,** NT ≥ 3mm increased the risk of intermediate malformation approximately 4-fold, and NT ≥4.5mm increased it approximately 15-fold. For all NT cut-offs the negative predictive value was high (≥98%). In 17 of 26 malformed fetuses with NT ≥95th percentile, no anomaly was suspected at the NT scan, whereas an anomaly was seen or suspected in nine fetuses.

Fetal loss

Among fetuses with normal karyotype there were 92 (0.6% of all fetuses) perinatal deaths, 23 miscarriages (0.1% of all fetuses including 17 karyotypings of living fetuses and six karyotypings after fetal demise, i.e., amniocentesis because of missed abortion in two cases and karyotyping of abortion products in four cases), and 24 (0.1% of all fetuses) terminations of pregnancy. Three women terminated their pregnancy because of increased risk of trisomy 21 despite amniocentesis having shown normal karyotype and despite no fetal malformation

having been detected at scanning. The calculated risk of trisomy 21 in these three cases was 1:170 (NT 2.3 mm), 1:249 (NT 2.2 mm) and 1:2 (NT 4.1 mm). Autopsy was not carried out in these three fetuses. The remaining 21 women terminated their pregnancy because of fetal malformation, the malformation having been detected at the NT scan in 17 and in four at a later scan.

For all types of fetal loss, the negative predictive value was > 99% for all cut-offs. There was no association between increased NT and intrauterine death, intrapartum death, postnatal death ≤7 days of birth, or total perinatal death. NT ≥95th percentile increased the odds of miscarriage fivefold (p = 0.02), but there was no statistically significant association between NT ≥3mm, ≥3.5mm or ≥4.5mm and miscarriage. Increased NT significantly increased the risk of termination of pregnancy both among malformed fetuses (NT ≥3mm increasing the likelihood approximately 9-fold and NT ≥3.5 mm or

≥4 .5 mm increasing it approximately 20-fold, p< 0.001 for all comparisons) and among fetuses with no known malformation (NT ≥3mm increasing the likelihood approximately 50-fold, p = 0.021, and NT ≥3.5 mm increasing it more than 150-fold, p = 0.006).

ROC curves

ROC curves are shown in Figure 2. NT had potential to discriminate between fetuses with and without lethal malformations (area under ROC-curve for lethal malformations 0.81, 95% CI 0.66 – 0.96) and between fetuses with and without lethal or serious malformations (area under ROC-curve 0.57, 95% CI 0.52 – 0.63). However, NT measurement could not reliably discriminate between pregnancies ending with any adverse outcome, miscarriage or perinatal death and pregnancies not doing so (areas under ROC curves 0.48 – 0.62, lower limit of the 95% CI for the area under the ROC curve < 0.5 for all these outcomes).

Discussion

We have estimated the magnitude of increase in risk of adverse outcome in fetuses with normal karyotype and increased NT. NT ≥ 3.0mm increased the odds of adverse outcome 6-fold, the odds of lethal or serious malformation 15-fold, the odds of termination of pregnancy in malformed fetuses 9-fold and the odds of termination of pregnancy in normally formed fetuses almost 50-fold. The odds for these adverse outcomes increased with increasing NT. We found no association between increased NT and perinatal death and only a weak association between increased NT and miscarriage. The low sensitivity, the high negative likelihood ratios and the small areas under the ROC curves illustrate that NT cannot reliably discriminate between favorable and unfavorable outcome in fetuses with normal karyotype. Therefore NT measurement is not a good screening method for fetal malformation or other adverse pregnancy outcome in fetuses with normal karyotype. Our results of using NT measurement as a screening method specifically for fetal heart malformations have been reported separately[23, 24].

Our study differs from most other studies that have examined a possible association between increased NT and adverse pregnancy outcome [4, 5, 8–18] in that each adverse outcome studied was clearly defined and in that we had a control group of fetuses with normal NT. Most other studies – also those with a control group – lack a clear definition of which anomalies were classified as malformations [5, 8–15, 18], and/or they lack a clear definition of miscarriage versus intrauterine death versus perinatal, postnatal or neonatal death [4, 5, 8–18], and/or they lack a clear description of the method of ascertainment of fetal karyotype [5, 8, 9, 15, 18] or outcome [5, 8, 12–14]. In some studies it is not clear whether fetuses with unknown karyotype were included [4, 5, 10, 15, 18]. All this makes interpretation of results and comparison between studies difficult.

The magnitude of a possible change in risk with a change in NT can only be calculated if

there is a control group. We believe that it is helpful to know the magnitude of a risk increase/decrease (i.e., positive and negative likelihood ratios) when counselling patients. The likelihood ratio can be used to calculate the individual risk, if the prevalence of the condition sought for in one's own population is known[25, 26]. In the three previously published studies with a control group [5, 8, 16] the authors did not present likelihood ratios, but we have calculated their likelihood ratios using their published data. The results are shown in Table 4. In all studies, increased NT increased the odds of malformation, miscarriage and termination of pregnancy. In none did increased NT change the odds of perinatal/neonatal death. It is interesting to note that the positive likelihood ratios of increased NT with regard to miscarriage are similar in all studies, despite two studies having been performed in high risk populations and two in unselected populations, and that the positive likelihood ratio of NT ≥3 mm with regard to malformation in our study of an unselected population is similar to that in a study of a high-risk population (Table 4). However, it is important to bear in mind that the true association between increased NT and spontaneous fetal loss is almost certainly not reflected in the results of our study or in those cited [5, 8, 16], because in all studies termination of pregnancy interfered with the spontaneous loss rate. Had there been no terminations of pregnancy, the association between increased NT and spontaneous fetal loss might have been completely different. Amniocentesis/chorionic villus sampling may have affected the apparent spontaneous loss rate, too. In no study did normal NT substantially decrease the odds of adverse outcome.

In our study increased NT increased the risk of termination of pregnancy among malformed fetuses, probably as a consequence of the association between increased NT and lethal and severe malformations. It is thought-provoking that increased NT increased the risk of termination of pregnancy also among fetuses with no known malformation. We are aware that three women terminated their pregnancy because they worried about the increased risk of

trisomy 21 that had been calculated on the basis of an NT measurement, despite amniocentesis having shown normal karyotype and despite no malformation having been detected at ultrasound examination. There may have been additional similar cases among the losses excluded, where the reason for termination was not known in every case. This highlights the difficulties with risk information and emphasizes the importance of giving well-balanced information both when women are first offered NT screening for Down's syndrome and when the screening result is communicated to them.

Studies without a control group can report nothing but the prevalence of the outcome studied. This corresponds to the positive predictive value of increased NT [4, 9–15, 17, 18]. It is impossible to know if the reported prevalences are higher than expected, particularly in those studies that seem to have been performed in high-risk pregnancies [10, 11, 14, 17] or where the study population was not clearly described [4, 12, 18]. Nonetheless, with one exception [4], the prevalences of malformations in fetuses with increased NT reported in studies without a control group do seem higher than expected (9.5%–30.3% versus the expected 2–3% in an unselected population [27]). The figures describing fetal loss in studies without a control group [4, 9–15, 17, 18] are very difficult to interpret without any information on the background risk and without a clear definition of the different types of fetal loss (reported miscarriage rates in those studies are 1.8% – 13.2%; reported rates of other types of spontaneous loss than miscarriage, e.g., perinatal death, postnatal death, or neonatal death are 0.5% – 3.8%; and reported rates of termination of pregnancy are 2.3% – 16.9%).

Our study shares with other similar studies the weakness of not all fetuses lost having undergone autopsy for ascertainment of fetal malformations [5, 8–16, 18] and of not all live-borns having undergone karyotyping but normal karyotype having been assumed on the basis of absence of stigmata of chromosomal anomaly at pediatric examination after birth. We are aware that among children that appeared phenotypically normal at birth, there might have

been some with an undetected chromosomal abnormality, e.g., Klinefelter's syndrome or Turner's syndrome. The exclusion of fetal loss with unknown karyotype may also have introduced some bias, because increased NT was less common (even though not statistically significantly so) among the fetal losses excluded than among the fetal losses included (the latter all having normal karyotype confirmed by genetic testing, the former all having unknown karyotype).

To sum up, we have calculated the magnitude of increase in risk of adverse outcome in fetuses with normal karyotype and increased NT using our own data but also using published raw data of other studies. Both in unselected populations and in high-risk populations increased NT ≥3 mm seems to increase the risk of malformation almost 10-fold and the risk of miscarriage about 5-fold. Larger NT increases the risks even more. We believe that this information may be useful when counselling patients, because it allows calculation of individual risks. The clinical consequence of our findings and those of others is that fetuses with increased NT, no signs of malformations at the NT scan, and normal or unknown karyotype should be thoroughly examined with regard to structural anomalies later in pregnancy when structural anomalies are more likely to be detectable than at the time of the NT scan. This is important, because prenatal diagnosis of some malformations – by enabling planning of perinatal management – might reduce postnatal mortality and morbidity [28 – 32]. How to convey the information to parents-to-be of a possible increased risk of spontaneous fetal loss in fetuses with increased NT but normal or unknown karyotype is a delicate matter, because the scientific basis for such information is rather weak (see above). However, it is important to bear in mind, that unless the background risk is very high, the odds of favourable outcome will be higher than those of adverse outcome.

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Legends

Figure 1. Flow of fetuses in the study.

NT, nuchal translucency; TOP, termination of pregnancy

*Missing information about NT is explained by the woman being too advanced in her pregnancy for NT measurement to be possible (crown rump length >84mm), difficulties with measuring NT, failure to document the NT measurement in the trial database, or obvious lethal malformations, e.g, anencephaly.

** These cases are described in the text

Figure 2. Receiver operating characteristic curves describing the diagnostic performance of nuchal translucency measurements (absolute values) with regard to detecting total adverse outcome (green), lethal malformation (blue), lethal or serious malformation (purple), spontaneous abortion (orange), and perinatal death (red) in fetuses with normal karyotype (n = 16 260).

Fig 1.

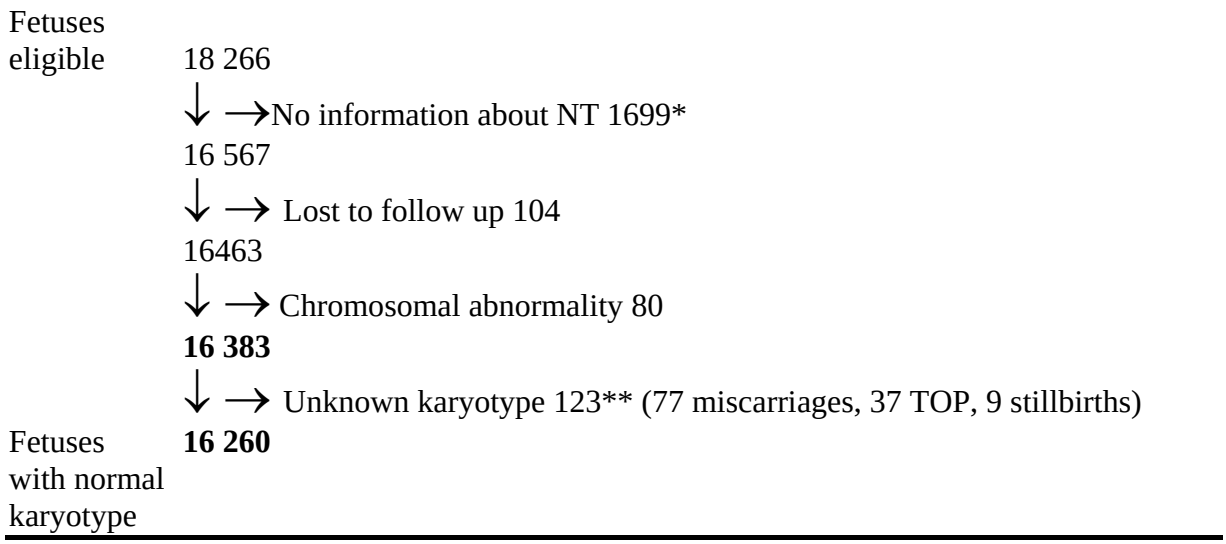
Fetuses eligible
18 266
↓ →No information about NT 1699*
16 567
↓ → Lost to follow up 104
16463
↓ → Chromosomal abnormality 80
16 383
↓ → Unknown karyotype 123** (77 miscarriages, 37 TOP, 9 stillbirths)
Fetuses with normal karyotype
16 260

Fig 2

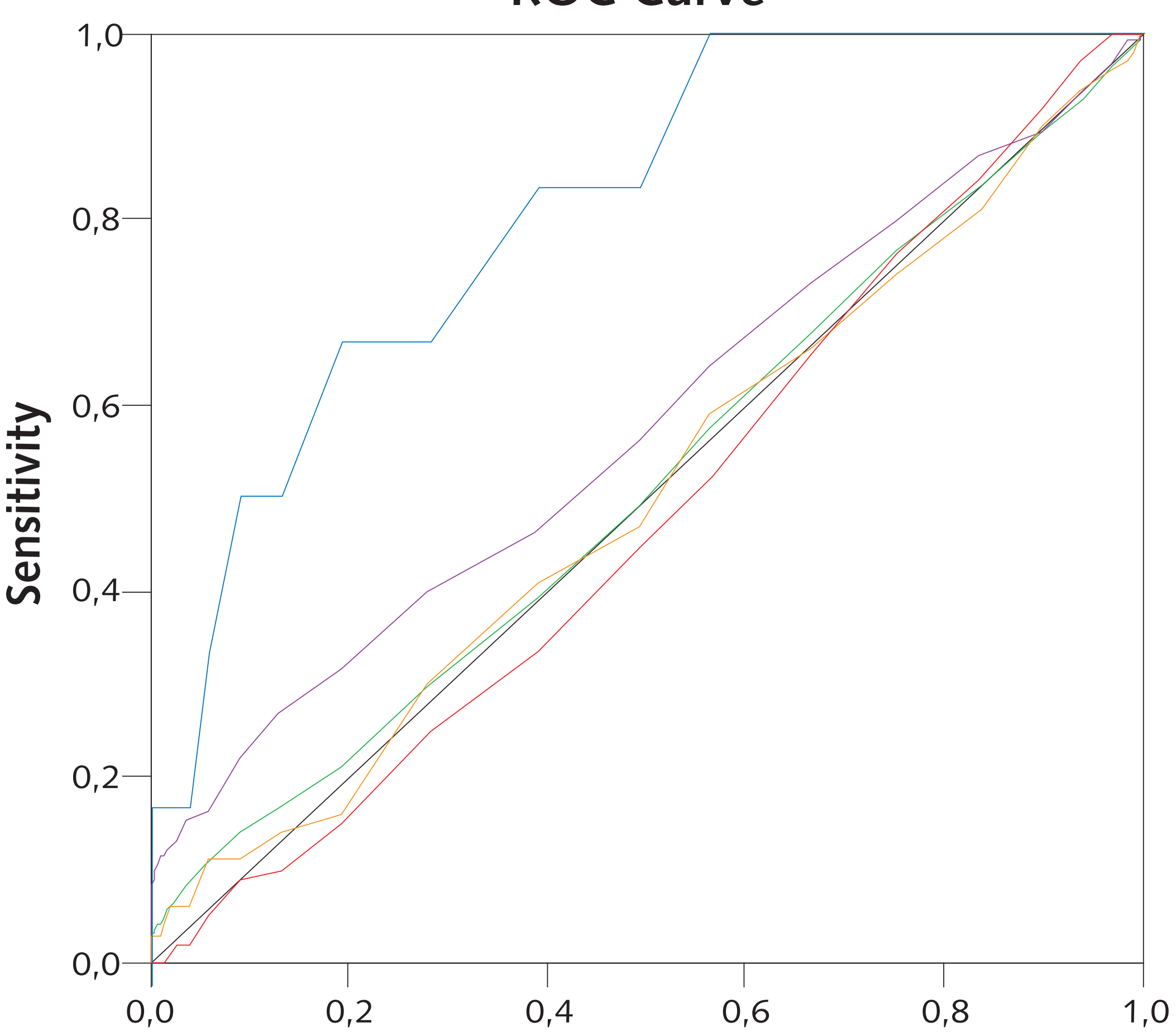
ROC Curve
Sensitivity
1,0
0,8
0,6
0,4
0,2
0,0
0,0
0,2
0,4
0,6
0,8
1,0
1 - Specificity
Total adverse outcome
Lethal or serious malformation
Spontaneous Abortion
Perinathal death
Lethal malformationa known normal karyotype

Table 1. Sensitivity, false positive rate (1 minus specificity), positive predictive value, and positive and negative likelihood ratios of increased nuchal translucency with regard to total adverse outcome in fetuses with normal karyotype (n = 16260)

Nuchal translucency cut-off	Sensitivity, % (95% CI)	False positive rate,% (95% CI)	PPV, %	+LR	-LR	p-value*
≥95th percentile	7.0 (4.6–9.4) (31/441)	2.5 (2.3–2.7) (396/15819)	7.3 (31/427)	2.8 (1.8–4.2)	0.95 (0.92–0.98)	<0.001
≥3.0mm	4.5 (2.6–6.5) (20/441)	0.7 (0.6–0.8) (113/15819)	15.0 (20/133)	6.4 (3.4–11.0)	0.96 (0.94–0.98)	<0.001
≥3.5mm	2.9 (1.4–4.5) (13/441)	0.2 (0.1–0.3) (33/15819)	28.3 (13/46)	14.5 (5.9–32.4)	0.97 (0.95–0.99)	<0.001
≥4.5mm	2.0 (0.9–3.8) (9/441)	0.1 (0.0–0.1) (10/15819)	47.4 (9/19)	32.3 (8.8–131.1)	0.98 (0.96–0.99)	<0.001

PPV, positive predictive value; +LR, positive likelihood ratio; -LR, negative likelihood ratio; CI, confidence interval

*Statistical significance of the difference between sensitivity and false positive rate determined by Fisher´s exact test or the Chi square test

Table 2. Main malformation diagnoses

	Number of fetuses	Number of fetuses with NT ≥ 3 mm
Lethal anomaly	**6**	
Anencephaly	2	
Frontal encephalocele	1	
Bilateral renal agenesis	1	
Infantile polycystic kidney disease	2	1
Serious anomaly	**110**	
Hydrocephalus[1]	7	
Lobar holopresencephaly	1	1
Porencephaly[1]	1	
Spina bifida[1]	10	1
Bilateral iris agenesis	2	
Microphtalmus	1	
Atresia of the ear/external ear tract	3	
Major heart malformation[2]	29	2
Oesophageal atresia	2	
Malformation of the stomach	1	
Atresia of the duodenum, jejunum, or ileum[3]	6	
Malformation of the colon	1	
Anal atresia	3	
Extra-hepatic biliary atresia[1]	1	
Malformation of the liver	1	
Renal dysplasia[3]	2	
Hydronefrosis with megalourether	1	
Arthrogryposis	1	
Osteochondrodysplasia	2	
Osteogenesis imperfecta	2	
Absence of arm/hand or leg/foot[3]	8	1
Diaphragmatic hernia	2	
Other malformation of the diaphragm[1]	2	
Exomphalos	2	1
Gastroschisis	3	
Ectodermal anhidrotic dysplasia	1	
Multiple malformations or syndrome	15	6

Cont.

Table 2 continued.

	Number of fetuses	Number of fetuses with NT ≥ 3.0mm
Anomalies of intermediate severity	**217**	
Coloboma of the lens	1	
Coloboma of the iris	2	
Other malformations of the pupil	1	
Facial cleft[1]	23	
Choanal atresia	2	
Non-major cardiac anomalies		
- Atrial septal defect	7	
- Ventricle septal defect	63	3
- Persistent arterial duct	11	
- Isolated valve anomaly	7	1
Isolated malformation of peripheral vein/artery	1	
Congenital ovarian cyst	3	
Hypospadia	27	
Other malformations of the penis and testis	4	
Isolated hydronephrosis	8	
Single renal cyst	1	
Vesico-uretheral reflux	1	
Other renal malformation	3	1
Malformation of the skeleton of the face	4	1
Craniosynostosis	1	
Clinodactyli	1	
Talipes	25	
Cleft foot	1	
Syndactylia with synostosis	4	
Malformation of the sternocleidomastoid muscle	14	
Other skin malformations	2	

[1]One case with associated anomalies

[2]18 of the 29 cases with major heart malformation had more than one cardio-vascular diagnosis

[3]Two cases with associated anomalies

Table 3. Sensitivity, false positive rate, positive predictive value and positive and negative likelihood ratios of increased nuchal translucency with regard to congenital malformation (n = 16 260).

Outcome, NT cut-off	Sensitivity % (95% CI)	False positive rate % (95% CI)	PPV %	+LR (95% CI)	-LR (95% CI)	p-value*
Lethal malformation *(n=6)*						
NT≥95th percentile	16.7 (0.4–62.1) (1/6)	2.6 (2.4–2.9)(426/16254)	0.2 (1/427)	6.4 (0.2–28.9)	0.86 (0.23–1.0)	0.148
NT≥3.0mm	16.7 (0.4–62.1) (1/6)	0.8 (0.7–1.0) (132/16254)	0.8 (1/133)	19.7 (0.6–107.4)	0.85 (0.23–1.0)	0.048
NT≥3.5mm	16.7 (0.4–62.1) (1/6)	0.3 (0.2–0.4) (45/16254)	2.2 (1/46)	57.8 (1.9–400.2)	0.84 (0.23–1.0)	0.017
NT≥4.5mm	0.0 (0.0–45.9) (0/6)	0.1 (0.0–0.2) (19/16254)	0.0 0/19	0.0 (0.0–961.8)	1.00 (0.54–1.0)	1.000
Lethal or serious malformation *(n=116)*						
NT≥95th percentile	13.8 (6.8–18.6) (16/116)	2.5 (2.3–2.8) (411/16144)	3.7 (16/427)	5.5 (3.1–9.1)	0.86 (0.80–0.94)	<0.001
NT≥3.0mm	11.2 (5.4–17.0) (13/116)	0.7 (0.6–0.9) (120/16144)	9.8 (13/133)	15.0 (7.0–28.6)	0.89 (0.81–0.95)	<0.001
NT≥3.5mm	8.6 (3.4–13.8) (10/116)	0.2 (0.2–0.3) (36/16144)	21.7 (10/46)	43.0 (14.3–93.4)	0.92 (0.84–0.96)	<0.001
NT≥4.5mm	6.0 (2.5–12.0) (7/116)	0.1 (0.0–0.1) (12/16144)	36.8 (7/19)	81.2 (19.1–323.7)	0.94 (0.87–0.98)	<0.001
Malformation of at least intermediate severity *(n=333)*						
NT≥95th percentile	7.8 (4.9–10.7) (26/333)	2.5 (2.3 –2.8) (401/15927)	6.1 (26/427)	3.1 (2.0–4.8)	0.95 (0.91–0.97)	<0.001
NT≥3.0mm	5.7 (3.2–8.2) (19/333)	0.7 (0.6 – 0.8) (114/15927)	14.3 (19/133)	8.1 (4.3–14.0)	0.95 (0.92–0.97)	<0.001
NT≥3.5mm	3.6 (1.6–5.6) (12/333)	0.2 (0.1–0.3) (34/15927)	26.1 (12/46)	18.0 (6.9–39.6)	0.97 (0.94–0.98)	<0.001
NT≥4.5mm	2.7 (1.2–5.1) (9/333)	0.1 (0.0–0.1) (10/15927)	47.4 (9/19)	43.0 (11.8–174.5)	0.97 (0.95–0.99)	<0.001
Malformation of intermediate severity *(n = 217)* **vs. no or minor malformation** *(n = 15 927)*						
NT≥95th percentile	4.6 (1.8–7.4) (10/217)	2.5 (2.2–2.7) (401/15927)	2.4 (10/411)	1.8 (0.9–33.6)	0.98 (0.94–1.0)	0.08
NT≥3.0mm	2.8 (0.6–5.0) (6/217)	0.7 (0.6–0.9 (114/15927)	5.0 (6/120)	3.9 (1.2–10.1)	0.98 (0.94–1.0)	0.006
NT≥3.5mm	0.9 (0.3–22.0) (2/217)	0.2 (0.1–0.3) (34/15927)	5.5 (2/36)	4.3 (0.1–25.2)	0.99 (0.96–1.0)	0.08
NT≥4.5mm	0.9 (0.3–22.0) (2/217)	0.06 (0.02–0.1) (10/15927)	16.6 (2/12)	14.7 (0.6–147.7)	0.99 (0.96–1.0)	0.01

CI, confidence interval; PPV, positive predictive value; +LR, positive likelihood ratio; -LR, negative likelihood ratio.
*Statistical significance of the difference between sensitivity and false positive rate determined by Fisher´s exact test or the Chi square test

Table 4. Adverse outcome in fetuses with increased nuchal translucency and normal karyotype – summary of studies with a control group

	Pajkrt *et al.* 1999[16]	Bilardo *et al.* 1998[8]	Westin et al. current study	Michailides *et al.* 2001[5]	Westin *et al*. current study
Study population	High risk	High risk	Unselected	Unselected	Unselected
Definition of increased NT	≥ 3.0mm	≥ 3.0mm	≥ 3.0mm	≥ 99th percentile	≥ 3.5mm
Number of fetuses with increased NT	64	49	133	73	46
Number of fetuses with normal NT	1977	1543	16127	6533	16214
Method of establishing karyotype	AC/CVS (all)	Not stated, probably AC/CVS in most cases	AC/CVS/newborn with no stigmata/ karyotyping of losses	AC/CVS/newborn with no stigmata	AC/CVS/newborn with no stigmata/ karyotyping of losses
Included fetuses with unknown karyotype?	No	Probably a few miscarriages	No	Probably a few miscarriages	No
Definition of malformation	Not defined	Not defined	Defined	Not defined	Defined
Definition of miscarriage	Spontaneous loss < 17 gestational weeks	Not defined	Stillbirth < 28 completed gestational weeks	Not defined	Stillbirth < 28 completed gestational weeks
Definition of perinatal death	Intrauterine death > 17 gestational weeks; neonatal death (not defined)	Intrauterine death (not defined); neonatal death (not defined)	Intrauterine death ≥28 gestational weeks or death ≤ 7 days after birth	Intrauterine death (not defined)	Intrauterine death ≥28 gestational weeks or death ≤ 7 days after birth
Malformations					
Prevalence, %	-	2.8	2.0	1.7	2.0
Sensitivity, % (95% CI)	-	24.4[1](11.4 – 37.5)	5.7 (3.2 – 8.2)	5.3 (1.1 – 9.4)	3.6 (1.6 – 5.6)
False positive rate, % (95% CI)	-	2.5 (1.7 – 3.2)	0.7 (0.6 – 0.8)	1.0 (0.8 – 1.3)	0.2 (0.1 – 0.3)
+LR, (95% CI)	-	9.8 (4.1 – 22.0)	8.1 (4.3 – 14.0)	5.3 (1.4 – 13.9)	18.0 (6.9 – 39.6)
-LR, (95% CI)	-	0.78 (0.6 – 0.89)	0.95 (0.92 – 0.97)	0.96 (0.89 – 0.99)	0.97 (0.94 – 0.98
P-value[2]	-	<0.001	<0.001	0.002	<0.001
Miscarriage					
Prevalence, %	2.3	2.2	0.1	0.9	0.1
Sensitivity, % (95% CI)	12.8 (2.9 – 22.7)	14.3 (2.1 – 26.5)	4.3 (0.1 – 22.0)	12.1 (3.4 – 20.7)	4.3 (0.1 – 22.0)
False positive rate, %, (95% CI)	2.9 (2.2 – 3.6)	2.8 (2.0 – 3.7)	0.8 (0.76 – 1.0)	1.0 (0.8 – 1.2)	0.3 (0.2 – 0.4)
+LR, (95% CI)	4.4 (1.1 – 11.6)	5.1 (1.1 – 15.2)	5.4 (0.2 – 36.9)	12.1 (3.7 – 29.6)	14.3 (0.5 – 137.2)
-LR, (95% CI)	0.90 (0.74 – 0.98)	0.88 (0.69 – 0.98)	0.96 (0.73 – 1.0)	0.89 (0.76 – 0.96)	0.96 (0.72 –1.0)
P-value[2]	0.003	0.004	0.172	<0.001	0.063

Table 5.
continued

	Pajkrt et al 1999[16]	Bilardo et al 1998[8]	Westin et al current study	Michailides et al 2001[5]	Westin et al current study
Perinatal death					
Prevalence,%	1.7	1.9	0.6	0.5	0.6
Sensitivity, %, (95% CI)	2.9 (0.1 – 14.9)	3.3 (0.1 – 17.2)	0 (0 – 3.9)	6.1 (0.7 – 20.2)	0 (0 – 3.9)
False positive rate, % (95% CI)	3.1 (2.4 – 3.9)	3.1 (2.4 – 3.9)	0.8 (0.7 – 1.0)	1.1 (0.1 – 1.3)	0.3 (0.2 – 0.4)
+LR (95% CI)	0.9 (0.03 –7.48)	1.1 (0.03 – 9.5)	0 (0 – 6.5)	5.5 (0.4 – 27.6)	0 (0 – 23.9)
-LR (95% CI)	1.00 (0.88 –1.05)	1.00 (0.81 –1.04)	1.00 (0.97 –1.0)	0.95 (0.77 –1.00)	1.00 (0.96 –1.00)
P-value[2]	1.00	0.612	1.00	0.051	1.00
TOP					
Prevalence,%	-	-	0.1	0.3	0.1
Sensitivity, % (95% CI)	-	-	33.3 (13.0–53.7)	23.5 (10.5–46.0)	33.3 (13.0–53.7)
False positive rate, % (95% CI)	-	-	0.8 (0.6 – 0.9)	1.0 (0.8 –1.3)	0.2 (0.2 – 0.3)
+LR, (95% CI)	-	-	41.6 (17.1 – 86.6)	23.5 (4.3 – 64.6)	166.5 (49.2 – 336.5)
-LR, (95% CI)	-	-	0.67 (0.41 – 0.85)	0.77 (0.44 – 0.94)	0.67 (0.41– 0.85)
P-value[2]	-	-	<0.001	<0.001	<0.001

AC, amniocentesis; CVS, chorion villus sampling; CI, confidence interval; NT, nuchal translucency; +LR, positive likelihood ratio; -LR, negative likelihood ratio; TOP, termination of pregnancy

[1] In the study by Bilardo et al malformations include single gene disorders.

[2] The p-value signifies the statistical significance of the difference in rate of fetuses with increased NT between fetuses with and without the respective outcome; this p-value has been calculated by us on the basis of the raw data presented in the articles cited using Fisher's exact test or the Chi-2 test

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