Chapter 2

Increased Fetal Nuchal Translucency Thickness and Normal Karyotype: Prenatal and Postnatal Outcome

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1. Introduction

Nuchal translucency (NT) is the assessment of the amount of fluid behind the neck of the fetus, also known as the nuchal fold. An anechoic space is visible and measurable sonographically in all fetuses between the 11th and the 14th week of the pregnancy (Figure 1). Underlying pathophysiological mechanisms for nuchal fluid collection under the skin include cardiac dysfunction, venous congestion in the head and neck, altered composition of the extracellular matrix, failure of lymphatic drainage, fetal anemia or hypoproteinemia and congenital infection [1]. The abnormal accumulation of nuchal fluid decreases after the 14th week.

Figure 1. Normal nuchal translucency thickness (NT)

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1.1. Increased NT in chromosomally abnormal fetuses

The association between the increased NT and the chromosomal abnormalities has been well documented (Figure 2). It helps us identify the high-risk fetuses for trisomy 21 and other chromosomal abnormalities [2,3].

Figure 2. Increased nuchal translucency thickness (NT)

The findings of numerous studies suggest that an effective first trimester screening for trisomy 21 can be obtained by the combination of maternal age and measurement of fetal NT [4-11]. At a risk cut-off of 1 in100, the detection rate of trisomy 21 is about 75%, at a false positive rate of about 2%. The detection rate can be improved to 85% by the additional assessment of the fetal nasal bone and even more by the Doppler assessment of blood flow across the tricuspid valve or blood flow in the ductus venosus, which has increased the detection rate to about 95% at a false positive rate of 2.5% [11].

Our retrospective study of the first trimester screening for trisomy 21 in 5-year period from 2005 to 2010 by employing the combination of maternal age, sonographic measurement of the fetal NT thickness and assessment of the fetal nasal bone, included 13,049 pregnant women [12]. The sample represented an unselected population of women with singleton pregnancies. The cut-off risk for trisomy 21 was set at 1 in 300. The distribution of maternal age of the examined women was compared to the age distribution in the pregnant population in Slovenia for the same time interval (2005-2010). The balance between the false positive rate and the detection rate was studied and the trends were inspected graphically. The cut-off risk that would yield 5% false positives was calculated for trisomy 21. The average gestation was 12 4/7 weeks (range from 11 1/7 weeks to 14 0/7 weeks). The average fetal CRL was 63.2 mm (from 45 mm to 83 mm). The average NT thickness was 1.7 mm (range from 0.9 mm to 13.4 mm). The NT was above the 95th centile of the normal range for the CRL in 75% (15 out of 20) of trisomy 21 pregnancies and in 64% (16 out of 25) pregnancies with other chromosomal abnormalities. At the time of the testing the estimated risk for trisomy 21 was 1 in 300 or higher in 3% of all the pregnancies (394 out of 13,049), considering the calculation based on FMF program. Three hundred and sixty cases (2.8%) turned out to be false

positive. At the invasive testing, chromosomal abnormalities were identified in 8.6% of high risk cases (34 out of 394), which represented one case of fetal chromosomal abnormality, detected per 12 invasive diagnostic procedures. Consequently we believe that the effective screening for trisomy 21 can be achieved in the first trimester of pregnancy by the combination of maternal age, sonographic measurement of the fetal NT thickness and assessment of the fetal nasal bone, with detection rate of 85% at a false positive rate of less than 3%.

Karyotype	n
Trisomy 21	20
Trisomy 18	10
Trisomy 13	2
45,X (Turner syndrom)	3
47,XXY	2
Mosaic structure	3
Unbalanced structural rearrangements	5
Total	45

Table 1. Chromosomal abnormalities in fetuses and newborns in our sample of 13,049 women with singleton pregnancies [12].

1.2. Increased NT in chromosomally normal fetuses

The NT can be increased also in chromosomally normal fetuses. When the karyotype is normal, the fetus is still at a significant risk of adverse pregnancy outcome e.g. fetal loss, structural abnormalities, particularly cardiac defects, various genetic syndromes and delayed neurodevelopment [9,13]. The prevalence of fetal abnormalities and adverse pregnancy outcomes increases with the thickness of NT.

The impact of the increased nuchal fluid collection, seen during the ultrasound examination, raises the parents' great anxiety about future fetal development [13]. The risks of adverse pregnancy outcomes have to be discussed with the parents and an objective counseling has to be offered to them together with detailed ultrasound examinations later in the pregnancy. But even in the absence of clear fetal abnormalities, some couples request pregnancy termination in such circumstances [14].

Therefore, the aim of this study was to evaluate the pregnancy outcomes of fetuses with increased NT thickness and normal karyotype in an unselected pregnant population.

2. Subjects and methods

2.1. Study design

The retrospective study included unselected population of pregnant women of Caucasian ethnic origin appointed for the first trimester ultrasound screening examination at a single

outpatient clinic between January 4, 2005 and April 30, 2010. Included in the study population were only singleton pregnancies with live fetus from the 11th to the 14th week of gestation with the CRL of 45-83 mm.

Before the screening they had all received counseling by their level one gynecologists and an information leaflet about the ultrasound examination and the aim of the screening. In the majority of cases the examination of early fetal morphology and other measurements was performed transabdominally within 20 minutes. In less than 1% of the cases a transvaginal ultrasound examination had to be carried out.

For the examinations we used 2-5 MHz and 3.7-9.3 MHz transducers GE Healthcare Voluson 730 Pro, Milwaukee, USA, 4–6 MHz, 4–7 MHz, 5–9 MHz and 7–9 MHz transducers Acuson S2000, Siemens Medical Solution, Mountain View CA, USA.

The measurement of fetal NT followed the criteria recommended by the Fetal Medicine Foundation (FMF). The increased NT thickness was defined as a measurement above the 95th percentile for the normal range. Risks were calculated according to the FMF program, following its guidelines [15,16].

The women with an increased risk for chromosomal anomalies (≥ 1:300) calculated on the basis of maternal age, NT and fetal crown-rump length (CRL) were offered invasive testing for fetal karyotyping. The karyotyping was performed by using chorionic villus sampling or amniocentesis in three cytogenetic laboratories.

The fetuses with increased fetal NT and normal karyotype were followed by detailed structural ultrasound evaluation between the 20th and the 24th week of gestation. Fetal echocardiography was performed in cases in which NT exceeded 3.5 mm.

After an informed consent had been signed, pregnancy outcomes were obtained from the participating women by written questionnaires. In cases of non-responders or uncertainty, telephone contact with the parents was established. The length of follow-up ranged from 18 months to 5 years.

2.2. Exclusion criteria

The exclusion criteria were the loss to follow-up, the chromosomal abnormalities or no information on karyotype in a fetal loss.

2.3. Classification of adverse outcome

Adverse pregnancy outcome was defined as fetal loss (miscarriage, intrauterine death, termination of pregnancy), and as liveborn infant with structural abnormality, genetic disorders and/or neurodevelopmental delay diagnosed before or after delivery. Stillbirth <22 weeks of pregnancy was defined as miscarriage, and stillbirth ≥22 weeks of pregnancy or birth of a child of at least 500 g weight without vital signs as intrauterine fetal death.

2.4. Statistical analysis

Descriptive statistics were used to describe our sample. Means, standard deviations and ranges are reported for continuous variables, numbers and proportions are reported for categorical variables. Statistical analysis was performed using R statistical package, version 2.14.

3. Results

3.1. Study population

The sample represented 11,980 unselected pregnant women appointed for the first trimester ultrasound screening examination at a single outpatient clinic between January 4, 2005 and April 30, 2010.

Five hundred and fifty-eight fetuses had an increased fetal NT and normal karyotype (558/11,980; 4.7%). In 46 cases (46/558; 8.2%) the outcome of the pregnancy was unknown; therefore 512 singleton pregnancies were included in the further analysis.

The mean maternal age was 30.2 years (range from 17 to 46 years, SD=4.8). There were 421 out of 512 pregnancies (82.2%) conceived naturally and 91 (17.8%; 91/512) after in vitro fertilization. The mean NT ≥95th percentile was of 2.5 mm (range from 1.3 to 13.4 mm).

3.2. Fetal loss

The fetal loss was registered in 36 pregnancies (36/512; 7%). Twelve women (2.3%; 12/512) had miscarriage, 19 pregnancies (3.7%; 19/512) were terminated at parental request or due to the finding of structural abnormalities, and 1% of pregnancies (5/512) ended with intrauterine death. The outcomes with respect to the NT thickness are presented in Table 2. Table 3 provides details on all the types of fetal loss. The most common causes of termination were hydrops fetalis, increased NT or cystic hygroma (Figure 3).

NT (mm)	≤ 3.4	3.5-4.4	4.5-5.4	5.5-6.4	≥ 6.5	Total
Outcome						
Delivery	436	34	5	1	0	476 (93%)
Miscarriage	11	0	1	0	0	12 (2.3%)
Intrauterine death	1	3	0	0	1	5 (1%)
Termination	8	2	3	2	4	19 (3.7%)
Total	456	39	9	3	5	512

Table 2. Outcome of pregnancies with respect to the NT thickness.

Fetal loss	n	NT (mm)
Miscarriage (unspecified)	10	2.1/2.2/2.3/2.5/2.6/ 2.9/2.9/3.0/3.0/4.6
Spontaneous abortion after amniocentesis	2	2.5/3.0
Intrauterine death (unspecified)	4	3.0/3.5/3.7/4.2
Intrauterine death/tetralogy of Fallot	1	7.8
Termination:	19	
Hydrops fetalis	5	2.7/3.7/6.4/7.4/12.0
Increased NT	4	2.9/3.0/5.0/5.2
Cystic hygroma	3	12.2/13.4
Hydrocephalus	2	2.5/4.9
VSD/valve anomaly	1	3.7
Dandy-Walker malformation	1	5.6
Diaphragmatic hernia	1	3.2
Renal dysplasia	1	2.2
Neurofibromatosis type I (inherit)	1	2.1

Table 3. Fetal loss with respect to the NT thickness.

3.3. Liveborn infants with abnormalities

Four hundred and seventy-six pregnancies ended with delivery of a viable infant (93%). Among them we found 48 newborns (9.5%; 48/476) with either single or multiple abnormalities. The clinical findings in 476 liveborn infants with respect to the NT thickness are presented in Table 4. There were 8 cases (1.7%, 8/476) born with heart defects, other structural abnormalities were found in 30 newborns (6.3%; 30/476). During the first year of life some genetic syndromes or neurodevelopmental delay were recorded in 10 cases (2.1%; 10/476). All abnormalities were found in the group of newborns with mildly enlarged NT, between 95th percentiles to 4.4 mm. Among healthy babies, there was no NT thicker than 6.4 mm. Table 5 describes the disorders of 48 babies in more detail.

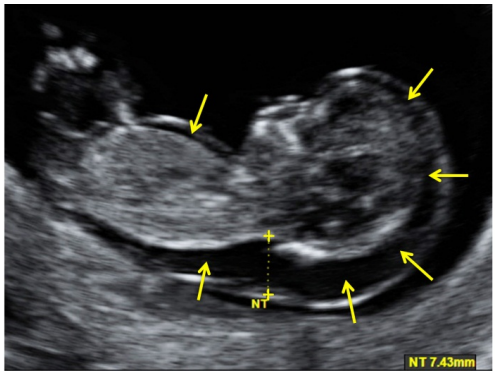

Figure 3. Hydrops fetalis

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	NT (mm)≤ 3.4	3.5-4.4	4.5-5.4	5.5-6.4	≥ 6.5	Total
Clinical findings						
Healthy	393	29	5	1	0	431
Heart defect	6	2	0	0	0	8
Structural abnormalities	29	1	0	0	0	30
Genetic syndromes	5	0	0	0	0	5
Neurodevelopmental delay	4	1	0	0	0	5
Total	**437**	**33**	**5**	**1**	**0**	**476**

Table 4. Clinical findings in liveborn infants with respect to the NT thickness.

Disorder	n	NT (mm)
Heart defects:	8	
VSD	3	2.6/3.0/3.2
VSD, ASD and aortic coarctation	1	3.9
VSD, ASD and tricuspid valve anomaly	1	4.0
Hypoplastic left ventricle	1	3.4
Isolated valve anomaly	2	3.4/2.6
Other abnormalities:	30	
Hydronephrosis (isolated)	4	1.8/2.5/2.8/3.1
Hydronephrosis and ureteral stenosis	2	2.8/3.1
Vesicouretheral reflux	2	2.6/2.8
Cleft lip and/or cleft palate	4	1.5/2.1/3.1/3.1
Craniosynostosis	1	2.3
Hypoplasia of the corpus callosum	1	2.5
Hydrocephalus	1	3.2
Micrognathia	1	2.6
Hemangioma	2	1.8/1.9
Cystic adenomatoid malformation	1	2.4
Diaphragmatic hernia	1	3.2
Atresia of the duodenum	1	3.0
Unilateral renal agenesis	1	2.7

Disorder	n	NT (mm)
Cryptorchidism	2	3.2/4.4
Hypospadias	1	3.2
Polydactyly	1	2.3
Hip dysplasia	3	1.8/1.8/2.2
Talipes	1	2.9
Genetic syndromes and neurodevelopmental delay:	10	
Adrenogenital syndrome	1	3.0
Lipid metabolism disorder	1	1.9
Coeliac disease	1	1.6
Polycystic kidney disease	2	2.4/2.4
Unspecific genetic syndrome and neurodevelopmental delay	2	2.6/3.0
Neurodevelopmental delay	3	2.5/2.9/3.5

Table 5. Disorders described in forty-eight euploid infants.

3.4. Gender and preterm labor

The overall male: female ratio was 1.37:1. In the group of fetuses with NT thickness between 95th percentile to ≤ 3.4 mm the ratio was 1.27:1 and in the group with NT ≥ 3.5 mm 2.64:1.

The gender distribution of liveborn infants with respect to the abnormalities is presented in Table 6. Male gender was predominant among healthy infants and in the group with genetic syndromes neurodevelopmental delay.

Preterm delivery was registered in 41 cases (41/476; 8.6%). Thirty-one healthy babies (31/431; 9.5%) and 10 infants with abnormalities (10/48; 20.8%) were born preterm.

Infants	Males	Females
Healthy	253	175
Heart defect	1	7
Structural abnormalities	15	15
Genetic syndromes/ neurodevelopmental delay	8	2
Total	276	198

Table 6. Gender distribution of liveborn infants with respect to the abnormalities.

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4. Discussion

We evaluated the pregnancy outcome of a subgroup of 512 fetuses with increased NT thickness and normal karyotype referring to 11,980 unselected pregnancies. According to the data of fetal loss, structural abnormalities, genetic disorders and neurodevelopmental delay, one out of 6 fetuses had an increased risk ≥1:300 of trisomy 21 calculated on the basis of maternal age, NT and fetal crown-rump length. The study confirms that 16.4% fetuses (84/512) were at increased risk of adverse pregnancy outcome.

The number of studies, which examined unselected pregnancy population with clear description of all adverse pregnancy outcomes, is limited [9]. Bilardo CM et al [14] noted that one out of five fetuses with increased NT had an adverse pregnancy outcome. Their study provides an overview of the selected pregnancy of 675 fetuses referred from other centers because of an increased NT measurement.

4.1. Fetal loss

In some studies it is not clear whether the fetuses with an unknown karyotype were included [17,18]. This is particularly important in the cases of fetal loss. We included only fetuses with known normal karyotypes. Karyotyping was provided in all cases of miscarriages, intrauterine deaths and terminations of pregnancies using amniocentesis or tissue samples obtained during surgical evacuation of the products of conception.

The increased NT thickness augments the risk of fetal loss. The allover fetal loss in our subgroup of fetuses was 7% (Table 2). We share the opinion that fetal loss in studies without a control group is very difficult to interpret [9,17-20]. The reported rates of spontaneous loss are 0.5-3.8% and the reported rates of termination of pregnancy are 2.3-16.9%.

Fifteen women terminated their pregnancies because of the fetal abnormalities (Table 3). But in 4 cases the pregnancy was terminated at the request of the parents because of an increased risk of trisomy 21, despite of the fact that no fetal malformation had been detected at the ultrasound examination. Westin M et al [9] describe similar experiences.

Our study shows similar weakness compared to the related studies, namely not all fetuses lost having undergone autopsy for ascertainment of fetal abnormalities, especially in the group of miscarriages [9,17-20].

4.2. Liveborn infants with abnormalities

The prevalence of structural abnormalities in our subgroup of newborns with increased NT was 8%. The percentage is higher than expected in general population (2-3%). A similar finding can be encountered in the studies without a control group (9.5-30.3%) [9].

Heart defects were confirmed in 8 out of 38 infants with structural abnormalities. The median NT thickness was significantly higher in fetuses with major heart defects compared to those with normal hearts [21-24]. In 8 infants with heart defects we found NT measurement between 3.4 and 4.4 mm. Although the measurement of NT thickness alone appears to be a

moderately effective screening pool for the detection of heart abnormalities, its role in detection of specific congenital heart defects seems more promising [24]. When an increased NT is found, the fetus has to be screened for additional sonographic markers such as tricuspid regurgitation and abnormal ductus venosus Doppler flow profile. We share the opinion that in fetuses with an NT measurement ≥99th percentile, and/or in which tricuspid regurgitation and/or abnormal ductus venosus Doppler flow pattern is found, an earlier fetal echocardiograpy is indicated [23,24].

The second most common isolated structural abnormality was hydronephrosis followed by cleft lip and/or cleft palate (Table 5).

In 5 cases genetic syndromes were found. There were two cases of inherited polycystic kidney disease, and three "de novo" genetic syndromes. In comparison with other studies we detected no infants with neuromuscular disorders [13,14].

As Bilardo CM et al [14] pointed out, the most unpredictable aspect of increased NT is neurodevelopmental delay, which could be manifested unexpectedly, in the postnatal period. The reported incidence of neurodevelopmental delay in fetuses with or without recognizable genetic syndrome varies from 0 to 13% [14,25,26]. In our study 10.4% of newborns (5 out of 48) were diagnosed during the follow-up period of at least 18-months.

4.3. Gender and preterm labor

In our population of fetuses with increased NT thickness, male gender was predominant, especially in the group with NT ≥ 3.5 mm. The impact of male: female ratio on the degree of nuchal fluid accumulation has been reported with controversial results. Yaron et al [27] and Prefumo et al [28] did not find NT to be significantly related to gender, but Lam et al [29] and Timmerman et al [30] reported significantly larger NT in male fetuses. Also Spencer et al [31] found NT to be 3-4% smaller in both chromosomally normal and Down syndrome female fetuses.

5. Conclusion

Many couples enter any of the screening programs without an intricate understanding of the potential fetal and newborn complications. While it is reasonable for the future parents to consider normal karyotype as a "good" result, the healthcare professionals should counsel them that enlarged NT thickness is a strong marker for adverse pregnancy outcome, associated with miscarriage, intrauterine death, heart defects, numerous other structural abnormalities and genetic syndromes. Although the measurement of the nuchal translucency thickness was introduced over 15 years ago, we share the opinion that a general consensus on how to counsel parents of an euploid fetus with enlarged NT has not yet been achieved [13]. The larger studies with uniform protocols and long-term follow-up are needed to recommend the guidelines for objective parental counseling.

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References

[1] Nicolaides KH. The 11-13+6 weeks scan. London: Fetal Medicine Foundation; 2004.

[2] Nicolaides KH, Azar G, Byrne D, et al. Fetal nuchal translucency: ultrasound screening for chromosomal defects in the first trimester of pregnancy. BMJ 1992;304(6831): 867-9.

[3] Nicolaides KH, Brizot ML, Snijders RJM. Fetal nuchal translucency: ultrasound screening for fetal trisomy in the first trimester of pregnancy. BJOG 1994;101:782-6.

[4] Pajkrt E, van Lith JMM, Mol BWJ, et al. Screening for Down's syndrome by fetal nuchal translucency measurement in a general obstetric population. Ultrasound Obstet Gynecol 1998;12:163–9.

[5] Economides DL, Whitlow BJ, Kadir R, et al. First trimester sonografic detection of chromosomal abnormalities in an unselected population. Br J Obstet Gynaecol 1998;105:58–62.

[6] Bindra R, Heath V, Liao A, et al. One stop assessment of risk for trisomy 21 at 11–14 weeks a prospective study of 15030 pregnancies. Ultrasound Obstet Gynecol 2002;20:219–25.

[7] Liu SS, Lee FK, Lee JL, et al. Pregnancy outcomes in unselected singleton pregnant women with an increased risk of first-trimester Down's syndrome. Acta Obstet Gynecol Scand 2004;83:1130–4.

[8] Rozenberg P, Bussières L, Chevret S, et al. Screening for Down syndrome using first-trimester combined screening followed by second-trimester ultrasound examination in an unselected population. Am J Obstet Gynecol 2006;195:1379–87.

[9] Westin M, Saltvedt S, Bergman G, et al. Is measurement of nuchal translucency thickness a useful screening tool for heart defects? A study of 16,383 fetuses. Ultrasound Obstet Gynecol 2006;27:632–9.

[10] Czuba B, Borowski D, Cnota W, et al. Ultrasonographic assessment of fetal nuchal translucency (NT) at 11th and 14th week of gestation-Polish multicentre study. Neuro Endocrinol Lett 2007;28:175–81.

[11] Kagan KO, Staboulidou I, Cruz J, et al. Two-stage first-trimester screening for trisomy 21 by ultrasound assessment and biochemical testing. Ultrasound Obstet Gynecol 2010;36:542–7.

[12] Gersak K, Pohar-Perme M, Strah DM. First trimester screening for trisomy 21 by maternal age, nuchal translucency and fetal nasal bone in unselected pregnancies. In: Day S, ed. Genetics and etiology of Down syndrome. Rijeka: Intech; 2011:301-312.

[13] Bilardo CM, Timmerman E, Pajkrt E, et al. Increased nuchal translucency in euploid fetuses-what should we be telling the parents? Prenat Diagn 2010;30:93-102.

[14] Bilardo CM, Müller MA, Pajkrt, E, et al. Increased nuchal translucency thickness and normal karyotype: time for parental reassurance. Ultrasound Obstet Gynecol 2007;30:11-8.

[15] Snijders RJM, Noble P, Sebire N, et al. UK multicentre project on assessment of risk for trisomy 21 by maternal age and fetal nuchal translucency thickness at 10 – 14 weeks of gestation. Lancet 1999;18:519–21.

[16] The Fetal Medicine Centre. Ultrasound scan procedures. http://www.fetalmedicine.com(accessed 1 July 2012).

[17] Maymon R, Jauniaux E, Cohen O, et al. Pregnancy outcome and infant follow-up of fetuses with abnormally increased first trimester nuchal translucency. Hum Reprod 2000;15:2023-7.

[18] Cheng CC, Bahado-Singh RO, Chen SC, et al. Pregnancy outcomes with increased nuchal translucency after routine Down syndrome screening. Int J Gynaecol Obstet 2004;84:5-9.

[19] Souka AP, Krampl E, Bakalis S, et al. Outcome of pregnancy in chromosomally normal fetuses with increased nuchal translucency in the first trimester. Ultrasound Obstet Gynecol 2001;18:9-17.

[20] Senat MV, De Keersmaecker B, Audibert F, et al. Pregnancy outcome in fetuses with increased nuchal translucency and normal karyotype. Prenat Diagn 2002;22:345-9.

[21] Ghi T, Huggon IC, Zosmer N, et al. Incidence of major structural cardiac defects associated with increased nuchal translucency but normal karyotype. Ultrasound Obstet Gynecol 2001;18:610-4.

[22] Müller MA, Bleker P, Bonsel GJ, et al. Nuchal translucency screening and anxiety levels in pregnancy and puerperium. Ultrasound Obstet Gynecol 2007;27:357-61.

[23] Vogel M, Sharland GK, McElhinney DB, et al. Prevalence of increased nuchal translucency in fetuses with congenital cardiac disease and a normal karyotype. Cardiol Young 2009;19:441-5.

[24] Clur SA, Ottenkamp J, Bilardo CM. The nuchal translucency and the fetal heart: a literature review. Prenat Diagn 2009;29:739-48.

[25] Maymon R, Herman A. The clinical evaluation and pregnancy outcome of euploid fetuses with increased nuchal translucency. Clin Genet 2004;66:426-36.

[26] Souka AP, Von Kaisenberg CS, Hyett JA, et al. Increased nuchal translucency with normal karyotype. Am J Obstet Gynecol 2005;192:1005-21.

[27] Yaron Y, Wolman I, Kupferminc MJ, et al. Effect of fetal gender on first trimester markers and on Down syndrome screening. Prenat Diagn 2001;21:1027-30.

[28] Prefumo F, Venturini PL, De Biasio P. Effect of fetal gender on first-trimester ductus-venosus blood flow. Ultrasound Obstet Gynecol 2003;22:268-70.

[29] Lam YH, Tang MH, Lee CP, et al. The effect of fetal gender on nuchal translucency at 10-14 weeks of gestation. Prenat Diagn 2001;21:627-9.

[30] Timmerman E, Pajkrt E, Bilardo CM. Male gender as a favorable prognostic factor in pregnancies with enlarged nuchal translucency. Ultrasound Obstet Gynecol 2009;34:373-8.

[31] Spencer K, Ong CY, Liao AW, et al. The influence of fetal sex in screening for trisomy 21 by fetal nuchal translucency, maternal serum free beta-hCG and PAPP-A at 10-14 weeks of gestation. Prenat Diagn 2000;20:673-5.