

# МЕДИЦИНСКИ ПРЕГЛЕД MEDICAL REVIEW

vol. LIX ♦ 2023 ♦ № 1

## Редакционна колегия

Проф. д-р М. Григоров (*гл. редактор*)  
Проф. д-р М. Балева (*зам. гл. редактор*)  
Проф. д-р Е. Паскалев (*научен секретар*)

Проф. д-р Р. Аргирова  
Проф. д-р М. Боянов  
Проф. Т. Веков  
Доц. Е. Григоров  
Чл.-кор. проф. д-р А. Гудев  
Д-р Р. Икономов  
Д-р Й. П. Йорданов  
Проф. д-р А. Йотов  
Доц. д-р Р. Коларов  
Доц. М. Крупев  
Доц. д-р Л. Ламбрева  
Проф. д-р Е. Манов  
Доц. д-р Б. Маринов  
Доц. д-р М. Николова  
Проф. д-р Г. Ончев  
Доц. д-р Пл. Попиванов  
Доц. д-р Е. Стойнев  
Д-р Ж. Сурчева  
Доц. д-р А. Тончева  
Д-р С. Филчев  
Проф. д-р Св. Христова  
Доц. д-р О. Чолаков  
Доц. д-р Зл. Янкова

## Editorial Board

Prof. M. Grigorov, M.D. (*Editor-in-Chief*)  
Prof. M. Baleva, M.D. (*Deputy Editor-in-Chief*)  
Prof. E. Paskalev, M.D. (*Scientific Secretary*)  
Prof. R. Argirova, M.D.  
Prof. M. Boyanov, M.D.  
Prof. T. Vekov  
Assoc. Prof. E. Grigorov, MPharm  
Corresp. memb. Prof. A. Gudev, M.D.  
R. Ikonov, M.D.  
Y. P. Yordanov, M.D.  
Prof. A. Yotov, M.D.  
Assoc. Prof. R. Kolarov, D.D.  
Assoc. Prof. M. Krupev  
Assoc. Prof. L. Lambreva, M.D.  
Prof. E. Manov, M.D.  
Assoc. Prof. B. Marinov, M.D.  
Assoc. Prof. M. Nikolova, M.D.  
Prof. G. Onchev, M.D.  
Assoc. Prof. Pl. Popivanov, M.D.  
Assoc. Prof. E. Stoinev, M.D.  
Zh. Surcheva, D.D.  
Assoc. Prof. A. Toncheva, M.D.  
S. Filtchev, M.D.  
Prof. Sv. Hristova, D.D.  
Assoc. Prof. O. Cholakov, M.D.  
Assoc. Prof. Zl. Yankova, M.D.

M. Banach, M.D., Poland

Prof. J. Raboch, M.D., Czech Republic

Prof. J. Schoenfeld, M.D., Israel

## Редакционен съвет

Проф. д-р М. Ачкова  
Проф. д-р В. Влахов  
Акад. д-р Д. Дамянов  
Проф. д-р Т. Лисичков  
Акад. д-р Вл. Овчаров  
Чл.-кор. проф. д-р Н. Цанков  
Проф. д-р Д. Чавдаров

## Editorial Council

Prof. M. Achkova, M.D.  
Prof. V. Vlahov, M.D.  
Acad. D. Damyanov, M.D.  
Prof. T. Lisichkov, M.D.  
Acad. Vl. Ovcharov, M.D.  
Corresp. memb. Prof. N. Tsankov, M.D.  
Prof. D. Chavdarov, M.D.

Мед. преглед
Med. pregled

## СЪДЪРЖАНИЕ

### ОБЗОРИ

<i>Р. Ганчева, Ц. Петранова, И. Шейтанов, П. Янкова, Зл. Коларов, Ат. Кундурджиев.</i> Риск от карцином при пациенти със системен лупус еритематозус.....	5
<i>Н. Андонова, Г. Марков, Я. Здравков, А. Оскар.</i> Офталмия симпатика.....	11
<i>Р. Гергова, Д. Раллис, В.-М. Циту, А. Александрова.</i> Състав, развитие и значение на оралния микробиом за човешкото здраве.....	15
<i>И. Митева, В. Вълчев.</i> Допингът в спорта и разпространението му в изложени на риск групи от населението: преглед на международната литература.....	24

### ОРИГИНАЛНИ СТАТИИ

<i>Б. Илковска, Б. Котевска-Трифунова, П. Аврамовски.</i> Скрининг за Даун синдром и Едуардс синдром през първия триместър при неселектирани бременни – 6-годишен опит.....	31
<i>А. Георгиев, П. Костадинова, Р. Василева.</i> Влияние на коронавирусната инфекция върху протичане на бременността и раждането.....	35
<i>Цв. Великова, В. Велковски, А. Михова, Р. Наков, Р. Вачева-Добревска, В. Наков.</i> Приложение на <i>Lactobacillus spp.</i> и <i>Bifidobacterium spp.</i> при антибиотик-асоциирани оплаквания от страна на гастроинтестиналния тракт – предварителни данни от едноцентрово проучване.....	44

### КЛИНИЧНИ СЛУЧАИ

<i>С. Желязкова, Н. Иванова, К. Михова, Р. Кънева, Т. Чамова, С. Чернинкова, И. Търнев.</i> Атаксия при изолиран дефицит на витамин Е – клиничен случай.....	53
<i>В. Начева, Г. Ангов, П. Дачева, И. Петрова, М. Караджова, Ю. Петрова.</i> CANVAS синдром – първи генетично доказан случай в България.....	58

### ПИСМО ДО РЕДАКТОРА

<i>С. Кордева, И. Баташки, А. Баташки, Х. К. Кардозо, Г. Чернев.</i> Множествени невуси след valsartan/amlodipine: патогенетично обусловена връзка или случайност?.....	63
---	----

## МЕДИЦИНСКИ ПРЕГЛЕД 1/2023

ISSN 1312-2193

УДК 61

Организационен секретар *И. Митева*  
 Стиллова редакция и корекция *И. Митева*  
 Редакция на англ. език *В. Колев*  
 Страниране *К. Зографова*  
 Web поддръжка *М. Мухайлов*

Централна медицинска библиотека  
 1431 София, ул. "Св. Г. Софийски" № 1  
 тел. 02 952-23-93  
 e-mail: [i\\_miteva@cml.mu-sofia.bg](mailto:i_miteva@cml.mu-sofia.bg)  
<http://cml.mu-sofia.bg/>

Списанието се обработва в БД:  
**БЪЛГАРСКА МЕДИЦИНСКА ЛИТЕРАТУРА**  
**CABI: Global Health Database**  
**EBSCO**

## CONTENTS

### REVIEWS

<i>R. Gancheva, Ts. Petranova, I. Sheytanov, P. Yankova, Zl. Kolarov, A. Kundurdzhiev. Risk of cancer in patients with systemic lupus erythematosus.....</i>	5
<i>N. Andonova, G. Markov, Y. Zdravkov, A. Oscar. Sympathetic ophthalmia.....</i>	11
<i>R. Gergova, D. Rallis, V.-M. Tsitu, A. Aleksandrova. The composition, development and significance of oral microbiome for human health.....</i>	15
<i>I. Miteva, V. Valtchev. Doping in sports and its spread to at-risk populations: an international literature review.....</i>	24

### ORIGINAL ARTICLES

<i>B. Ilkovska, B. Kotevska-Trifunova, P. Avramovski. First trimester PRISCA screening for Down's syndrome and Edwards' syndrome in unselected pregnancies – report of a 6-year experience.....</i>	31
<i>A. Georgiev, P. Kostadinova, R. Vasileva. Impact of the coronavirus infection on pregnancy and birth.....</i>	35
<i>Ts. Velikova, V. Velkovski, A. Mihova, R. Nakov, R. Vatcheva-Dobrevska, V. Nakov. Role of <i>Lactobacillus spp.</i> and <i>Bifidobacterium spp.</i> in antibiotic-associated complaints from the gastrointestinal tract – preliminary data from a single-center study.....</i>	44

### CASE REPORTS

<i>S. Zhelyazkova, N. Ivanova, K. Mihova, R. Kaneva, T. Chamova, S. Cherninkova, I. Tarnev. Ataxia with isolated vitamin E deficiency: a case report.....</i>	53
<i>V. Nacheva, G. Angov, P. Dacheva, I. Petrova, M. Karadzhova, Yu. Petrova. CANVAS syndrome – the first genetically confirmed case in Bulgaria.....</i>	58

### LETTER TO THE EDITOR

<i>S. Kordeva, I. Batashki, A. Batashki, J. C. Cardoso, G. Tchernev. Multiple nevi development after valsartan/amlodipine: pathogenetic mediated relationship or pure coincidence?.....</i>	63
---	----

---

Списанието и издателят не носят отговорност за изложените в публикациите авторски мнения и становища, както и за достоверността на представените от авторите данни.

Авторите запазват всички некомерсиални права върху публикуваните си текстове.

The journal and the publisher are not legally responsible for the author opinions and statements expressed in their publications, as well as for the accuracy and sources of data, to which authors refer in their publications. Authors retain all the intellectual property rights on their own publications, except the publishing and commercial rights.

---

ОРИГИНАЛНИ СТАТИИ  
ORIGINAL ARTICLESFIRST TRIMESTER PRISCA<sup>1</sup> SCREENING FOR DOWN'S SYNDROME AND EDWARDS' SYNDROME IN UNSELECTED PREGNANCIES – REPORT OF A 6-YEAR EXPERIENCEB. Ilkowska<sup>1</sup>, B. Kotevska-Trifunova<sup>2</sup>, P. Avramovski<sup>3</sup><sup>1</sup>Department of Laboratory Medicine, PHO Clinical Hospital Dr. Trifun Panovski, Bitola, North Macedonia<sup>2</sup>Department of Dermatovenerology, Acibadem City Clinic UMHAT Tokuda, Sofia, Bulgaria<sup>3</sup>Department of Internal Medicine, PHO Clinical Hospital Dr. Trifun Panovski, Bitola, North Macedonia

## СКРИНИНГ ЗА ДАУН СИНДРОМ И ЕДУАРДС СИНДРОМ ПРЕЗ ПЪРВИЯ ТРИМЕСТЪР ПРИ НЕСЕЛЕКТИРАНИ БРЕМЕННИ – 6-ГОДИШЕН ОПИТ

Б. Илковска<sup>1</sup>, Б. Котевска-Трифунова<sup>2</sup>, П. Аврамовски<sup>3</sup><sup>1</sup>Отделение по лабораторна медицина, ОЗИ Клинична болница „Д-р Трифун Пановски“, Битоля, Северна Македония<sup>2</sup>Отделение по дерматовенерология, Аджибадем Сити Клиник, МБАЛ Токуда, София, България<sup>3</sup>Отделение по вътрешна медицина, ОЗИ Клинична болница „Д-р Трифун Пановски“, Битоля, Северна Македония**Abstract:**

*Introduction:* Screening for chromosomal abnormalities performed in the first trimester of pregnancy, including maternal age, fetal nuchal translucency thickness, and serum markers, without beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A, is an effective screening for early detection of trisomies 18 and 21. The aim of this study was to evaluate the performance of the first trimester combined test for Down's syndrome and Edwards' syndrome detection, also the aim of this study is to show the prevalence of chromosomal abnormalities in pregnant women in the first trimester of pregnancy in the second largest city with 100,000 inhabitants in North Macedonia. *Materials and methods:* This was a retrospective case-matched study involving pregnant women who were examined in the Department of Obstetrics and Gynecology at the Clinical Hospital Bitola, between January 2016 to December 2021. *Results:* The participants comprised 2975 women who participated in the screening voluntarily, mostly Caucasian (97.8%) with singleton pregnancies. Among them, there were 165 cases of trisomy 21 and 50 cases of trisomy 18. The mean gestational age, maternal age, and maternal weight were 86 days, 28 years and 67 kg, respectively. There were 257 (9%) women >35 years of age and 54 (2%) women with multiple gestations – twins. The detection rates for trisomy 21 and trisomy 18 were 8% and 1%, respectively. *Conclusion:* First trimester screening for aneuploidy is a valuable tool for the obstetrician and indications and methods of screening have evolved over the last quarter century. The main goal of screening in the first trimester is the early detection of chromosomal anomalies which gives the opportunity to remove them in a timely manner.

<sup>1</sup>PRISCA (Prenatal RISc CA) calculation software)

<b>Key words:</b>	screening, Down syndrome, Edwards' syndrome, aneuploidy, PAPP-A, free $\beta$ -hCG
<b>Address for correspondence:</b>	<i>Dr Biljana Ilkovska, MD, PhD, St. Dimce Lahcanski №29 7000 Bitola, North Macedonia Tel. +38971361262</i>
<b>Резюме:</b>	<i>Въведение:</i> Скринингът за хромозомни аномалии, който се прави през първия триместър на бременността, включва: възраст на майката, дебелина на нухалната транслюценция на плода и серумни маркери (без бета-човешки хорионгонадотропин и свързан с бременността плазмен протеин-А). Скринингът е ефективен за ранно откриване на тризомия 18 и 21. Целта на това проучване е да се оцени ефективността на комбинирания тест през първия триместър за откриване на синдром на Даун и Едуардс, както и да се определи честотата на хромозомни аномалии при бременни жени през първия триместър на бременността във втория по големина град със 100 000 жители в Северна Македония. <i>Материал и методи:</i> Това е ретроспективно проучване, включващо бременни жени, които са били прегледани в Отделението по акушерство и гинекология в Клинична болница Битоля, в периода януари 2016–декември 2021 г. <i>Резултати:</i> В проучването бяха включени 2975 жени, предимно от бялата раса (97,8%) с едноплодна бременност. При 165 от тях е открита тризомия 21 и при 50 жени тризомия 18. Средната гестационна възраст, възрастта на майката и теглото на майката бяха съответно 86 дни, 28 години и 67 kg. 257 (9%) жени са на възраст до 35 години и 54 (2%) жени са с многоплодна бременност. Степента на откриване на тризомия 21 и тризомия 18 е 8% и 1%. <i>Заключение:</i> Скринингът за анеуплоидия през първия триместър е важен диагностичен метод в гинекологията и има голямо развитие по отношение на неговото прилагане в последните години. Основната цел на скрининга през първия триместър е ранното откриване на хромозомни аномалии, което дава възможност за тяхното своевременно отстраняване.
<b>Ключови думи:</b>	скрининг, синдром на Даун, Едуардс синдром, анеуплоидия, PAPP-A, свободен $\beta$ -hCG
<b>Адрес за кореспонденция:</b>	<i>Д-р Биляна Илковска, ул. „Димче Лахчански“ №29, 7000 Битоля, Северна Македония, тел.: +38971361262, e-mail: drbiljanailkovska@yahoo.com</i>

## INTRODUCTION

Screening for chromosomal abnormalities performed in the first trimester of pregnancy, including maternal age, fetal nuchal translucency thickness, and serum markers, without beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A, is an effective screening for early detection of trisomies 18 and 21, and detection rate is about 90–95% for a false-positive rate (FPR) of 3–5% [1–3]. Macri and Spencer showed that free  $\beta$ -hCG was significantly elevated (2.20 MoM) in trisomy 21 pregnancies. They concluded that this maternal serum analyte would serve as a good marker for Down syndrome in the first trimester [4]. Maternal blood levels of PAPP-A have been found to be decreased in pregnancies with fetal aneuploidy. Wald et al. expanded on these findings, concluding that PAPP-A was a useful marker for trisomy 21 in the first trimester [5]. Muller et al. performed a study examining PAPP-A levels in blood samples collected for the detection of

toxoplasmosis in pregnant women in France and concluded that PAPP-A is a useful marker for trisomy 21 in the first trimester [6]. Increased NT thickness has been associated with Down syndrome, Turner syndrome and other chromosomal abnormalities, as well as many fetal malformations and genetic syndromes [7, 8]. The risk of Down syndrome increases with increasing NT. Therefore, in the initial studies, single millimeter cut-offs were used to conduct NT measurements [9]. The NT value was found to increase along with the crown-back length depending on the gestational age of the fetus [10]. However, it has been shown that there can be millimeter measurement and deviations in measurements, and serum markers will not increase the screening information and therefore a diagnostic procedure should be performed immediately. Since April 2015, the first trimester combined test has been offered to every pregnant woman who came to Clinical Hospital Bitola, North Macedonia, during 10–13 weeks of gestation. The aim of this study was to evaluate the performance of

the first trimester combined test for Down's syndrome and Edwards' syndrome detection; also, the aim of this study is to show the prevalence of chromosomal abnormalities in pregnant women in the first trimester of pregnancy in the second largest city with 100,000 inhabitants in North Macedonia.

## MATERIAL AND METHODS

This was a retrospective case-matched study involving pregnant women who were examined in the Department of Obstetrics and Gynecology at the Clinical Hospital Bitola, between January 2016 to December 2021. An ultrasound examination at 10–13 weeks' gestation always includes the following elements: measurement of crown–rump length (CRL) and NT and a thorough anatomical fetal assessment to look for the presence of major anatomical defects. Fetal NT measurements were made following the UK Foundation for Fetal Medicine recommendations. Gestational age was determined using fetal crown-back measurements. Maternal serum levels of free  $\beta$ -hCG and PAPP-A were determined simultaneously using a Immulite 2000 xpi analyzer. We divided NT, PAPP-A, and free  $\beta$ -hCG marker values by their day-specific mean levels to determine multiples of the mean (MoM). Down's syndrome and Edwards' syndrome risks were calculated using PRISCA Software. A positive screening result was defined as an estimated Down's syndrome and Edwards' syndrome risk  $\geq 1/270$ . All the analyses were performed using SPSS for Windows v.18 statistical software, OriginPro v. 8.

## RESULTS

The participants comprised 2975 women who participated in the screening voluntarily, mostly Caucasian (97.8%) with singleton pregnancies. On the whole the mean age of giving birth was 28.9 years and the number of women aged  $\geq 35$  years was 9%. Most cases of Down's syndrome, 85 (40%), were among those women. Mean maternal age in pregnancies involving Down's syndrome was 33.6 years.

Among the 2760 unaffected fetuses receiving the combined test during 10–13 weeks of gestation, there were 56 (2%) at 10 weeks, 605 (22%) at 11 weeks, 1365 (49%) at 12 weeks, and 733 (27%) at 13 weeks of gestation. The mean gestational age, maternal age, and maternal weight were 86 days, 28 years and 67 kg, respectively. There were 257 (9%) women  $>35$  years of age and 54 (2%) women with multiple gestations – twins. In total, 215 cases of chromosomal

abnormality were identified. Among them, there were 165 cases of trisomy 21 and 50 cases of trisomy 18. With the cut-off value of  $\geq 1/270$ , there were 216 positive-screen pregnancies which occurred in 130 (60%) of women  $<35$  years of age and 85 (40%) of women of advanced maternal age.

The detection rates for trisomy 21 and trisomy 18 were 8% and 1%, respectively. In trisomy 21, the MoM of maternal serum PAPP-A is 0.83 and free  $\beta$ -hCG is 2.43. In trisomy 18, the mean MoM of PAPP-A is 0.55 and free  $\beta$ -hCG is 1.20. Among the 215 pregnancies with chromosomal abnormality receiving the combined test during 10–13 weeks of gestation, there were 6 (3%) at 10 weeks, 34 (16%) at 11 weeks, 105 (49%) at 12 weeks, and 67 (32%) at 13 weeks of gestation.

**Table 1. Screening data of different fetal chromosome abnormalities**

Characteristics	Trisomy 18 (n = 50)	Trisomy 21 (n = 165)	Unaffected fetuses (n = 2760)
Mean NT thickness (MoM)	0.95	0.91	0.86
Mean PAPP-A (MoM)	0.55	0.83	1.12
Mean Free $\beta$ -hCG (MoM)	1.20	2.43	1.32

$\beta$ -hCG = beta human chorionic gonadotropin; NT = nuchal translucency; PAPP-A = pregnancy-associated plasma protein A

**Table 2. Maternal and pregnancy characteristics of study population of 2760 fetuses with a detailed ultrasound examination at 10 weeks to 13 weeks 6 days gestation to screen for aneuploidy**

Characteristics	Trisomy 18 (n = 50)	Trisomy 21 (n = 165)	Unaffected fetuses (n = 2760)
Maternal age (years)	32.44	33.63	28
Gestational age (weeks)	12.12	12.12	12
Crown–rump length (mm)	62.45	62.56	61.91
Fetal NT (mm)	1.50	1.45	1.36

NT, nuchal translucency thickness

## DISCUSSION

The first trimester screen has been available in North Macedonia for several years, but only recently have been determined effective means of early chromosomal abnormality screening. This screening is the most accurate, non-invasive screening method available. In this prospective study of first-trimester screening for chromosomal abnormalities by a combination of maternal serum biochemical markers and ultrasound markers in among the 2975 pregnant women overall, 9% of fetuses had an estimated risk for trisomy 21 and trisomy 18. Out of the 2975 women, 2760 (91%) were



cases where chromosomal abnormality was not found. The first trimester biochemical markers in this study showed that the mean values of free  $\beta$ -hCG MoM and PAPP-A MoM of 1.32 vs 1.12 (both in unaffected pregnancies) were similar with Poon et al. study [11]. In trisomy 21 pregnancies, the mean MoM value decreased to 0.83 for PAPP-A, and increased to 2.43 for free  $\beta$ -hCG in our study population, which is consistent with what had been found in the Caucasian population (0.5 MoM for PAPP-A and 2.0 MoM for free  $\beta$ -hCG) [12]. Detection rates of first trimester abnormalities screening at 10, 11, 12, and 13 weeks were 6 (3%), 34 (16%), 105 (49%) and 67 (32%), respectively. Fetal NT measurement is an effective ultrasound marker for Down's syndrome risk assessment, but the effectiveness of the combined test of hormone measurement and NT measurement largely depends on the accuracy and quality of NT measurement. Previous publications indicated that NT thickness increases between 10 and 14 weeks of gestation due to physiological change. Pajkr et al. (1998) did a study in which they found that NT thickness increased from 0.7 mm at 10 weeks of gestation to 1.7 mm at 13 weeks of gestation, after which NT decreased to 1.0 mm in the 14th week [13]. The median MoM of NT in unaffected fetuses was 0.86 and 0.91 in pregnancies with Down syndrome. Maymon et al. found higher values for median MoM of NT in pregnancies with Down syndrome 1.844 and similar values for median MoM of NT in unaffected fetuses 1.003 [14]. In this study, we have outlined our 6-year experience in screening pregnancies. Our study is quite small compared to larger studies and that is one of its weaknesses, also this study was conducted only in one city in the country and the result cannot fully represent the performance of screening in the Macedonian population, but this is a good base for further research. In summary, the purpose of this study was to provide information on screening performance of the first trimester combined test, in a medical center of Bitola. To our knowledge, this study is the second population study analyzing the result of the first trimester combined test performed in North Macedonia.

### CONCLUSION

The screening of chromosomal abnormalities in pregnancy and the assessing risk of Down's syndrome and Edwards' syndrome are of utmost importance for all pregnant women and the society as well. Screening allows us to timely detect chromosomal anomalies and will reduce the psychological and physical suffering of parents and society. The clear advantages of a screening test in the first trimester included earlier

reassurance to low risk patients, more time to consider options for diagnosis, and the possibility of earlier, safer termination in affected pregnancies. First trimester screening for aneuploidy is a valuable tool for the obstetrician, and indications and methods of screening have evolved over the last quarter century. The main goal of screening in the first trimester is the early detection of chromosomal anomalies which gives the opportunity to remove them in a timely manner. The first trimester combined test is an effective screening tool for Down's syndrome detection, with an acceptable low false positive rate. The best timing of screening will be between 11 and 12 weeks' gestation.

### References

1. Kagan KO, Etchegaray A, Zhou Y et al. Prospective validation of first-trimester combined screening for trisomy 21. *Ultrasound Obstet Gynecol*, 2009, 34: 14-18.
2. Kagan KO, Wright D, Baker A et al. Screening for trisomy 21 by maternal age, fetal nuchal translucency thickness, free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A. *Ultrasound Obstet Gynecol*, 2008, 31: 618-624.
3. Wright D, Syngelaki A, Bradbury I et al. First-trimester screening for trisomies 21, 18 and 13 by ultrasound and biochemical testing. *Fetal Diagn Ther*, 2014, 35: 118-126.
4. Macri JN, Spencer K, Aitken D et al. First-trimester free beta (hCG) screening for Down syndrome. *Prenat Diagn*, 1993, 13:557-62.
5. Wald N, Stone R, Cuckle HS et al. First trimester concentrations of pregnancy associated plasma protein A and placental protein 14 in Down's syndrome. *BMJ*, 1992, 305:28.
6. Muller F, Cuckle H, Teisner B et al. Serum PAPP-A levels are depressed in women with fetal Down syndrome in early pregnancy. *Prenat Diagn*, 1993, 13:633-6.
7. Souka AP, Snijders RJ, Novakov A et al. Defects and syndromes in chromosomally normal fetuses with increased nuchal translucency thickness at 10-14 weeks of gestation. *Ultrasound Obstet Gynecol*, 1998, 11: 391-400.
8. Souka AP, Von Kaisenberg CS, Hyett JA et al. Increased nuchal translucency with normal karyotype. *Am J Obstet Gynecol*, 2005, 192: 1005-21.
9. Snijders RJ, Noble P, Sebire N et al. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10-14 weeks of gestation. Fetal medicine foundation first trimester screening group. *Lancet*, 1998, 352: 343-6.
10. Braithwaite JM, Morris RW, Economides DL. Nuchal translucency measurements: frequency distribution and changes with gestation in a general population. *Br J Obstet Gynaecol*, 1996, 103:1201-4.
11. Poon LC, Maiz N, Valencia C et al. First-trimester maternal serum pregnancy-associated plasma protein-A and pre-eclampsia. *Ultrasound Obstet Gynecol*, 2009, 33(1):23-33.
12. Nicolaidis KH. Screening for fetal aneuploidies at 11 to 13 weeks. *Prenat Diagn*, 2011,31(1):7-15.
13. Pajkr E, de Graaf IM, Mol BW et al. Weekly nuchal translucency measurements in normal fetuses. *Obstet Gynecol*, 1998, 91(2):208-11.
14. Maymon R, Zimerman AL, Weinraub Z et al. Correlation between nuchal translucency and nuchal skin-fold measurements in Down syndrome and unaffected fetuses. *Ultrasound Obstet Gynecol*, 2008, 32(4):501-5.