Janhvi Manohar /J. Pharm. Sci. & Res. Vol. 8(7), 2016, 607-612

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

The Assessment of Nasal Bone during Gestation to Screen for Down Syndrome - A Review

Janhvi Manohar

Savitha Dental College and Hospitals, Chennai.

Abstract

Aim: To assess the nasal bone of the foetus during the first trimester to screen for Down Syndrome.

Objective: This review aims to evaluate fetal nasal bone in the first trimester of pregnancy and to monitor its value in the diagnosis of Down Syndrome.

Background: Fetal nasal bone assessment is a procedure that is non-evasive and provides greater assurance to patients in their first trimester about the risk of Down Syndrome in foetus. Down Syndrome also known as Trisomy 21 is a chromosomal abnormality caused by the presence of a third copy of chromosome 21 and this disorder has no cure. The presence or the absence of nasal bone in the first trimester of pregnancy states if the fetus is at risk and thus the absence of fetal nasal bone states positive for Down Syndrome.

Reason: As it is a non-evasive procedure, the fetus is safe. The financial burden of parents having children suffering from chromosomal abnormalities is high and thus early diagnosis of Down Syndrome is a huge step towards reducing the costs. This review aims to study the procedure and thus evaluate the presence or absence of Down Syndrome.

Keywords: Nasal bone, Down syndrome, First trimester, ultrasound, Trisomy 21, Non-invasive.

INTRODUCTION

Down syndrome is the most common chromosomal abnormality in neonates. [1] In 1866, Langdon Down initially described a small nasal bone as one of the many phenotypic features of Down syndrome. [2] Flattening of the facial profile and a small nose are common in neonates with Down syndrome [3] Individuals with Down syndrome have a distinct craniofacial phenotype with a prominent forehead, small overall size of the craniofacial complex and underdevelopment of the frontonasomaxillary region with missing or small nasal bones. [4] Absence or hypoplasia of the fetal nasal bone in children with Down syndrome has been detected by first and second trimester sonography. [5-7] Based on these observations, underdevelopment of the nasal bones has been proposed as an ultrasound marker for screening for Down syndrome antenatally in the second and more recently in the first trimesters of pregnancy. [8] Invasive prenatal diagnosis has been proposed for populations at risk (mainly women >35 years or who have had a previous child with Down syndrome), but this strategy only detects 20% to 25% of fetuses with Down syndrome. [9] At 11–14 weeks' gestation the nasal bone is not visible by ultrasonographic examination in about 70% of fetuses with trisomy 21 and in less than 1% of chromosomally normal fetuses. [5]

Trisomy 21, both in postnatal and in prenatal life, is associated with nasal hypoplasia. [10] First-trimester Down syndrome screening using a combination of nuchal translucency, free beta-human chorionic gonadotropin (hCG) and (pregnancy-associated plasma protein-A) PAPP-A has become common practice in many centers throughout the world. [11] Such screening can detect approximately 90% of Down syndrome cases with a false-positive rate of 5%. [12-22] The inclusion of the nasal bone in first-trimester Down syndrome screening could result in a detection efficiency as high as 98%. [23] Nasal bone screening is an invasive procedure of accurately predicting the risk of the chromosomal birth defect by making use of ultrasound images of the developing fetus during the first and second trimester. Various paradigms for first-trimester or integrated first- and second-trimester screening have resulted in the detection of 85% to 98% of fetuses with trisomy 21, with a false positive rate of 5%. [24] This review thus aims to study the procedure and thus evaluate its efficiency as one of the markers for Down Syndrome.

METHODS

The fetal facial profile was examined by ultrasonography in mothers in order to visualize the nasal bone image. Gestational age was based on the last menstrual period and confirmed by the first trimester ultrasound ranging between 11 and 13 weeks and 6 days of gestation. Pregnancies with any detected/suspicious anatomical or genetic fetal anomalies and pregnancies of artificial reproduction techniques were excluded for the data analyses. [25]

Sonek et al performed the measurement of the fetal nasal bone via a midsagittal view of the fetal head, identifying the nasal bone, lips, maxilla, and mandible with an angle between the insonation beam and nasal bone axis close to 45° or 135° (Figure 1). [26] FIGURE 1 – [27]

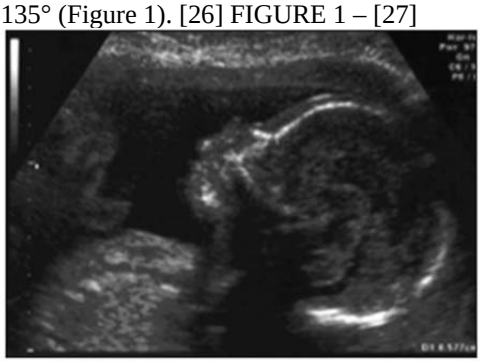

Figure 1 – Midsagittal view of a facial profile in a healthy fetus at 20 weeks' gestation. The nasal bone in this scan was measured as 5.77 mm. [26]

For examination of the nasal bone, the image was magnified so that the head and the upper thorax only were included on the screen and a mid-sagittal view of the fetal profile was obtained. [10] The NB is seen as a triangular echogenic structure in this view. [28] The ultrasound transducer was placed parallel to the direction of the nose and the probe was gently tilted from one side to the other of the fetal nose. When these criteria were satisfied, three distinct lines were seen at the level of the fetal nose. The first two, which are proximal to the forehead, are horizontal and parallel to each other, resembling an 'equals sign'. The top line represents the skin and the bottom one, which is thicker and more echogenic than the overlying skin, represents the nasal bone. A third line, almost in continuity with the skin but at a higher level, represents the tip of the nose. [10] After the NB was clearly apparent, the bony part of the nasal bridge was measured by placing the calipers in the out-to-out position. Each increment in the distance between the calipers is considered only 0.1 mm. [25]

The nasal bone is considered to be present if it is more echogenic than the overlying skin. [10] An absent fetal nasal bone in the first trimester was defined according to the protocol established by the Fetal Medicine Foundation. [29] Cases of an absent nasal bone were identified when the echogenicity of the nasal bone was not greater than that of the overlying skin. [30] The nasal bone was considered to be hypoplastic if it was absent or it appeared strikingly small, in which case it was measured and found to be always less than 2.5 mm. [31]

Other soft markers in ultrasound for detection of down syndrome:

The presence or absence of the nasal bone was found to be independent of other maternal or fetal variables and thus may be added to other sonographic markers for prenatal detection of trisomy 21. [32] It is, however, still uncertain how the NB performs as a single marker for fetal aneuploidy compared with when combined with other proven markers of aneuploidy. [28] Historically, risk assessment was based on second-trimester maternal serum screening along with genetic sonography to identify structural anomalies and "soft markers" for aneuploidy. [7], [33-34] In the last decade, risk assessment has transitioned into the first trimester, in which sonographic metrics in conjunction with serum analytes are used to confer a patient-specific risk of aneuploidy. [24], [35]

Many new tests have been reported to improve the sensitivity of screening, such as maternal serum biochemical studies and sonographic markers. [27] There are several advantages that first-trimester ultrasound offers that extend beyond simply looking for markers of aneuploidy. [36] First trimester screening, where available, is preferable because it leads to earlier diagnosis with the option of earlier termination of pregnancy or, more often, earlier reassurance for the parents. [37] Various methods are used which can also be combined to improve the sensitivity of the screening. These tests include nuchal translucency (NT), serum beta-hCG, serum pregnancy associated plasma protein A (PAPP-A) and maternal age. [37]

Nuchal Transluency:

Nuchal translucency (NT) is a measurement of the fluid in the neck region on first trimester ultrasound. [37] Nicolaides et al described it as being a sensitive marker for the chromosomal anomalies. [38] Nuchal translucency (NT) measurement is an established screening method for Down syndrome and other chromosomal abnormalities in the first trimester of pregnancy. [39 – 42] Risk calculation taking into account maternal age, fetal NT and maternal serum biochemistry at 11–14 weeks of gestation has a sensitivity of up to 85% for a false-positive rate of around 5%. [42-47] Bromley at al conducted a retrospective cohort study of all consecutive patients referred to a private ultrasound facility (Diagnostic Ultrasound Associates, PC) between January 1, 2008, and June 30, 2012, for sonographic measurement of the NT and crown-rump length (CRL) as part of a screening protocol for aneuploidy. All fetuses were initially scanned transabdominally to obtain the CRL and NT measurements as well as to evaluate the nasal bone if requested. Transvaginal scans were performed if the transabdominal imaging quality was suboptimal. In cases of a technical challenge, an NT of 3.0 mm or greater, or a suspected anomaly, the supervising sonologist scanned the patient as well. [48] Pathologic findings and pregnancy outcomes were obtained by review of the medical records for patients with an NT of 3.0 mm or greater, an absent nasal bone, a nuchal fold of 5.0 mm or greater, or a structural anomaly. [49]

Furthermore, if combined with other screening methods such as maternal serum free beta-human chorionic gonadotropin (B-hCG), maternal age, fetal nuchal translucency (NT) thickness, and pregnancy associated plasma protein (PAPP-A) at 11 – 14 weeks, it is projected to increase detection rate to 85% with a false positive rate of 5%. [5]

Short Femur Length:

A short femur length is defined as either a measurement below the 2.5th percentile for gestational age or a measurement that is less than 0.9 of that predicted by the measured biparietal diameter. [50] The femur should be measured with the bone perpendicular to the ultrasound beam and with epiphyseal cartilages visible but not included in the measurement. [51] The relation between bone length and head size may differ across racial groups. [52]

Short femur length has been found to have a sensitivity of 16% in the prediction of Down syndrome with a false positive rate of 4%. [51] A meta-analysis showed a likelihood ratio of 2.7 (95% CI 2.1–6.0). [53] If a femur appears abnormal or its length is found to be below the 2.5th percentile for gestational age, it may be indicative of fetal growth restriction or a more general skeletal malformation. In this circumstance, other long bones

should be assessed and referral with follow-up ultrasound considered. [51]

Short Humerus Length:

A short humerus length is defined as a length below the 2.5th percentile for gestational age or as a measurement less than 0.9 of that predicted by the measured biparietal diameter. [50] The humerus should be measured with the bone perpendicular to the ultrasound beam and with epiphyseal cartilages visible but not included in the measurement. Short humeral length is an ultrasound marker for fetal aneuploidy, particularly trisomy 21. Humeral length is not currently part of the screening obstetric ultrasound; however, it should be included in the panel of markers used by tertiary centres. [51] Short humeral length has been found to have a sensitivity of 9% with a false-positive rate of 3% [51] A meta-analysis showed a likelihood ratio of 7.5 (95% CI 4.5–12). [53]

RESULT & DISCUSSIONS

Second-trimester sonographic screening for Down syndrome is based on multiple morphologic and biometric parameters, such as major structural anomalies, nuchal fold thickening, a hyperechoic bowel, pyelectasis, a short humerus, and a short femur. [27] A recent study by Cicero et al. [6] found that an absent nasal bone or one shorter than expected for gestational age was observed in fetuses with Down syndrome. A study by Sonek [32] showed that assessment of the fetal nasal bone was a useful screening tool for Down syndrome in both the first and second trimesters of pregnancy. Odibo et al. [28] stated that the assessment of nasal bone has the modest efficiency as a single marker for trisomy 21. In addition, the sensitivity values of other genetic markers for predicting Down syndrome reported in this study are lower than those previously reported from most centers evaluating second-trimester genetic sonograms. [54] Absence of fetal nasal bones as assessed by ultrasound may be the consequence of delayed ossification or hypoplasia of nasal bones. [55] A valuable screening test should be both feasible and reproducible, in addition to demonstrating good sensitivity and specificity, criteria that should be evaluated before its introduction in routine settings. False positive results in screening for trisomy 21 in the general population have a major impact on the positive predictive value, as the prevalence of the disease is less than 1%. [56] The study done by Senat et al. [56] thus, concluded that assessment of fetal nasal bones by ultrasound is only fairly reproducible with good agreement in only 80.7% of the cases. Zoppi et al. [57] remarked that the ultrasound sign of an absent NB seems to be a promising marker for T21, either alone or in association with the nuchal translucency test, on condition that its reliability is proven in studies carried out on larger general series. The fetal NB first becomes histologically apparent at a crown-rump length of 42 mm, which corresponds to 11 weeks' gestation. [58] When performing fetal NB evaluation in order to determine the risk for T21, the NB absence is the most important index in the first trimester. [59]

Cicero et al. [60] found that the rate of the NB absence was 73% (43/59) for fetuses with T21. Poureisa M et al. [25] reported 3 (0.5%) cases of the NB absence among 603 fetuses with normal karyotype. The values for the absence of the NB in fetuses with DS were reported between 33% and 80% in some other studies. [61 – 64] In the study conducted by Bromley et al. [48] A total of 9331 patients were referred for the first-trimester sonographic component of aneuploidy risk assessment and had at least 1 living fetus with a CRL between 34 and 84 mm. A structural anomaly was identified in 50 of 9692 fetuses (0.5%) at the time of the first-trimester scan. The median CRL for anomalous fetuses was 55 mm (range, 36–77 mm). The most commonly identified anomalies at or before 14 weeks were abnormalities involving the fetal abdominal wall, face/profile, central nervous system. The aneuploidy status was available in 43 of 50 fetuses with an anomaly detected at or before 14 weeks in Bromley et al.'s study. [48] In a prospective study of 1148 singletons, Souka et al. [65] detected 50% of major malformations in a routinely screened population. [48] Weiner et al. [66] identified 41% of structural anomalies using an extended midsagittal view. In a randomized controlled trial of 7642 pregnancies, Chen et al. [67] detected 32.8% of anomalies during an NT scan and 47.6% with the addition of a "detailed" fetal assessment. [48] In experienced hands, the detection rate for major anomalies has been reported to be as high as 84% when using the first-trimester anomaly scan and first-trimester fetal echocardiography. [68] Becker et al. [69] identified 58.6% of major anomalies in this population. In chromosomally normal fetuses, 43% to 49% of major anomalies have been detected in the first trimester. [70-71]

It is essential to note that nasal bone length measurement is impacted by race and ethnicity. Therefore, racial adjustment is needed in the measurement of fetal nasal bone in screening for trisomy 21 during pregnancy. [72] For instance, in the Korean population, the average nasal bone length was 1.5 mm and 2.1 mm for 11 and 14 weeks' gestation. [73-74] Meanwhile, the nasal bone length in Thai fetuses was 2.1 mm (range, 1.5-2.6) at gestational age of 11, 12, and 13 weeks respectively. [75] In the study developed by Cossi et al. [76] in a Brazilian population, the nasal bone length in all cases ranged between 1.69 mm and 2.94 mm. There is ethnic variation in the incidence of an absent fetal nasal bone in the first trimester. In the first-trimester of euploid pregnancies, African American women have a higher prevalence of an absent nasal bone (5.8%) compared to white women (2.6%). In chromosomally normal cases, women of Asian background have a similar incidence of an absent fetal nasal bone as white women (2.1%). [77-78] It is essential to note therefore, based on the previous findings that race and ethnicity have an impact on fetal nasal bone length. [74] Proper training and standardization of the measurement technique with strict adherence to the criteria are of importance in avoiding false results. [25]

CONCLUSION

Non-invasive prenatal testing has been rapidly marketed for clinical use, and its application in women at high risk for aneuploidy has been supported by the American College of Obstetricians and Gynaecologists. [79-80] Given the superior performance over traditional methods of risk assessment, non-invasive prenatal testing is anticipated as a screening option for women, despite potential limitations. [79-83] The first-trimester anomaly scan does not replace the second-trimester anatomic survey, which remains the most complete fetal structural evaluation. [65] It does, however, offer the option for earlier diagnosis of major anomalies. [48] This review corroborates the findings of previous reports associating nasal bone hypoplasia and Down Syndrome thus, suggesting that such an association could be important when this finding is a single marker. Nasal hypoplasia is likely to be the single most sensitive and specific second-trimester marker of trisomy 21, indicates that examination of the nasal bone will inevitably be incorporated into a sonographic or combined screening program for trisomy 21. [6]

REFERENCES

[1] Cuckle H, Nanchahal K, Wald N. Birth prevalence of Down syndrome in England and Wales. Prenat Diagn 1991; 11:29–34.

[2] Down JL. Observations on an ethnic classification of idiots. Lond Hosp Rep1866; 3:259–262.

[3] Jones KL. Smith's Recognizable Patterns of Human Malformation. 5th ed. Philadelphia, PA: WB Saunders Co; 1997:8–14.

[4] Frostad WA, Cleall JF, Melosky LC. Craniofacial complex in the trisomy 21 syndrome (Down's syndrome). Archs Oral Biol 1971; 16: 707–722

[5] Cicero S, Curcio P, Papageorghiou A, Sonek J, Nicolaides K. Absence of nasal bone in fetuses with trisomy 21 at 11–14 weeks' gestation: an observational study. Lancet 2001; 358:1665–1667.

[6] Cicero S, Sonek JD, McKenna DS, Croom CS, Johnson L, Nicolaides KH. Nasal bone hypoplasia in trisomy 21 at 15–22 weeks' gestation. Ultrasound Obstet Gynecol 2003; 21:15–18.

[7] Bromley B, Lieberman E, Shipp TD, Benacerraf BR. Fetal nose bone length: a marker for Down syndrome in the second trimester. J Ultrasound Med 2002; 21:1387–1394

[8] C. Larose, P. Massoc, Y. Hillion, J. P. Bernard, Y. Ville. Comparison of fetal nasal bone assessment by ultrasound at 11–14 weeks and by postmortem X-ray in trisomy 21: a prospective observational study. Ultrasound Obstet Gynecol 2003; 22: 27–30

[9] Loncar J, Barnabei VM, Larsen JW Jr. Advent of maternal serum markers for Down syndrome screening. Obstet Gynecol Surv 1995; 50:316–320.

[10] K. O. Kagan, S. Cicero, I. Staboulidou, D. Wright, K. H. Nicolaides. Fetal nasal bone in screening for trisomies 21, 18 and 13 and Turner syndrome at 11–13 weeks of gestation. Ultrasound Obstet Gynecol 2009; 33: 259–264

[11] F. Orlandi, C. M. Bilardo, M. Campogrande, D. Krantz, T. Hallahan, C. Rossi, E. Viora. Measurement of nasal bone length at 11–14 weeks of pregnancy and its potential role in Down syndrome risk assessment. Ultrasound Obstet Gynecol 2003; 22: 36–39

[12] Orlandi F, Damiani G, Hallahan TW, Krantz DA, Macri JN. First-trimester screening for fetal aneuploidy: Biochemistry and nuchal translucency. Ultrasound Obstet Gynecol 1997; 10: 381–386.

[13] Biagiotti R, Brizzi L, Periti E, d'Agata A, Vanzi E, Cariati E. First trimester screening for Down's syndrome using maternal serum PAPP-A and free beta-hCG in combination with fetal nuchal translucency thickness. Br J Obstet Gynaecol 1998; 105: 917–920.

[14] Benattar C, Audibert F, Taieb J, Ville Y, Roberto A, Lindenbaum A, Frydman R. Efficiency of ultrasound and biochemical markers for Down's syndrome risk screening. A prospective study. Fetal Diagn Ther 1999; 14: 112–117.

[15] De Biasio P, Siccardi M, Volpe G, Famularo L, Santi F, Canini S. First trimester screening for Down syndrome using nuchal translucency measurement with free beta-hCG and PAPP-A between 10 and 13 weeks of pregnancy – the combined test. Prenat Diagn 1999; 19: 360 – 363.

[16] De Graaf IM, Pajkrt E, Bilardo CM, Leschot NJ, Cuckle HS, van Lith JM. Early pregnancy screening for fetal aneuploidy with serum markers and nuchal translucency. Prenat Diagn 1999; 19: 458–462.

[17] Spencer K, Souter V, Tul N, Snijders R, Nicolaides KH. A screening program for trisomy 21 at 10–14 weeks using fetal nuchal translucency, maternal serum free beta-human chorionic gonadotropin and pregnancy-associated plasma protein A. Ultrasound Obstet Gynecol 1999; 13: 231–237.

[18] Krantz DA, Hallahan TW, Orlandi F, Buchanan P, Larsen JW, Macri JN. First-trimester Down syndrome screening using dried blood biochemistry and nuchal translucency. Obstet Gynecol 2000; 96: 207–211.

[19] Spencer K, Spencer CE, Power M, Moakes A, Nicolaides KH. OSCAR – One Stop Clinic for Assessment of Risk for fetal anomalies: A report of the first year of prospective screening for chromosomal anomalies in the first trimester. Br J Obstet Gynaecol 2000; 107: 1271–1275.

[20] Wapner, R for the Bun Study Group. First trimester aneuploid screening: results of theNICHD multi-center study. AmJObstet Gynecol 2001; 185(Suppl.): S70.

[21] Schuchter K, Hafner E, Stangl G, Metzenbauer M, Hofinger D, Philipp K. The first trimester 'combined test' for the detection of Down syndrome pregnanciesin4939unselectedpregnancies. Prenat Diagn 2002; 22: 211–215.

[22] Bindra R, Heath V, Liao A, Spencer K, Nicolaides KH. One stop clinic for assessment of risk for trisomy 21 at 11–14 weeks: a prospective study of 15030 pregnancies. Ultrasound Obstet Gynecol 2002; 20: 219–225.

[23] Cuckle H. Time for total shift to first-trimester screening for Down's syndrome. Lancet 2001; 358: 1658–1659.

[24] American College of Obstetricians and Gynecologist. ACOG Practice Bulletin No. 77: screening for fetal chromosomal abnormalities. Obstet Gynecol 2007; 109:217–227.

[25] Masoud Poureisa, Mohammad Hossein Daghighi, Ramin Mazaheri Khameneh, Sanaz Salehi Majd. Fetal Nasal Bone Status in Iranian Women Undergoing First-Trimester Screening for Trisomy 21: A Review and an Observational Study. Iran J Radiol. 2015 October; 12(4): e11905.

[26] Sonek JD, McKenna D, Webb D, Croom C, Niclolaides K. Nasal bone length throughout gestation: normal ranges based on 3537 fetal ultrasound measurements. Ultrasound Obstet Gynecol 2003; 21:152–155.

[27] Suchin Sutthibenjakul, Thitima Suntharasaj, Chitkasaem Suwanrath, Ounjai Kor-anantakul, Alan Geater. A Thai Reference for Normal Fetal Nasal Bone Length at 15 to 23 Weeks' Gestation. J Ultrasound Med 2009; 28:49–53.

[28] Anthony O. Odibo, Harish M. Sehdev, Laura Sproat, Claudia Parra, Linda Odibo, Linda Dunn, George A. Macones. Evaluating the Efficiency of Using Second-Trimester Nasal Bone Hypoplasia as a Single or a Combined Marker for Fetal Aneuploidy. J Ultrasound Med 2006; 25:437–441

[29] Stephanie Dukhovny, Louise Wilkins-Haug, Thomas D. Shipp, Carol B. Benson, Anjali J. Kaimal, Rosemary Reiss. Absent Fetal Nasal Bone: What Does It Mean for the Euploid Fetus? J Ultrasound Med 2013; 32:2131–2134

[30] Fetal Medicine Foundation. Nasal bone. Fetal Medicine Foundation website; 2012. http://www.fetalmedicineusa.com/nasalbone.php.

[31] S. Cicero, J. D. Sonek, D. S. Mckenna, C. S. Croom, L. Johnson, K. H. Nicolaides. Nasal bone hypoplasia in trisomy 21 at 15–22 weeks' gestation. Ultrasound Obstet Gynecol 2003; 21: 15–18

[32] Sonek JD. Nasal bone evaluation with ultrasonography: a marker for fetal aneuploidy. Ultrasound Obstet Gynecol 2003; 22:11–15.

[33] Bromley B, Shipp TD, Lieberman E, Benacerraf BR. The genetic sonogram: A method of risk assessment for Down syndrome in the second trimester.J Ultrasound Med2002; 21:1087–1096

[34] Agathokleous M, Chaveeva P, Poon LCY, Kosinski P, Nicolaides KH. Meta-analysis of second-trimester markers for trisomy 21. Ultrasound Obstet Gynecol2013; 41:247–261.

[35] Driscoll DA, Morgan MA, Schulkin J. Screening for Down syndrome: changing practice of obstetricians. Am J Obstet Gynecol 2009; 200: 459.e1– 459.e9.

[36] J. Sonek, K. Nicolaides. Additional First-Trimester Ultrasound Markers. Clinics in Laboratory Medicine, Vol. 30, No. 3

[37] Asma Khalil, Amy Coates. Prenatal Diagnosis of Chromosomal Abnormalities. Arias' Practical Guide to High-Risk Pregnancy and Delivery: A South Asian Perspective. Fourth Edition; 1-14
[38] Nicolaides KH, Azar G, Byrne D, et al. Fetal nasal translucency: ultrasound screening for chromosomal defects in first trimester of pregnancy. BMJ. 1992;304; 867-869
[39] Snijders R, Smith E. The role of fetal nuchal translucency in prenatal screening. Curr Opin Obstet Gynecol 2002; 14: 577–585.
[40] Bindra R, Heath V, Nicolaides KH. Screening for chromosomal defects by fetal nuchal translucency at 11 to 14 weeks. Clin Obstet Gynecol 2002; 45: 661–670.
[41] Stewart TL, Malone FD. First trimester screening for aneuploidy: nuchal translucency sonography. Semin Perinatol 1999; 23: 369–381.
[42] Snijders RJ, Noble P, Sebire N, Souka A, Nicolaides KH. 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: 343–346.
[43] Wald NJ, Kennard A, Densem JW, Cuckle HS, Chard T, Butler L. Antenatal maternal serum screening for Down's syndrome: results of a demonstration project. BMJ 1992; 305: 391–394.
[44] Spencer K, Souter V, Tul N, Snijders R, Nicolaides KH. A screening program for trisomy 21 at 10–14 weeks using fetal nuchal translucency, maternal serum free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A. Ultrasound Obstet Gynecol 1999; 13: 231–237.
[45] Cuckle H. Integrating antenatal Down's syndrome screening. Curr Opin Obstet Gynecol 2001; 13: 175–181.
[46] Spencer K, Spencer CE, Power M, Dawson C, Nicolaides KH. Screening for chromosomal abnormalities in the first trimester using ultrasound and maternal serum biochemistry in a one-stop clinic: a review of three years' prospective experience. Br J Obstet Gynaecol 2003; 110: 281–286.
[47] Bindra R, Heath V, Liao A, Spencer K, Nicolaides KH. One stop clinic for assessment of risk for trisomy 21 at 11–14 weeks; a prospective study of 15030 pregnancies. Ultrasound Obstet Gynecol 2002; 20: 219–225.
[48] Bryann Bromley, Thomas D. Shipp, Jennifer Lyons, Reshama S. Navathe, Yvette Groszmann, Beryl R. Benacerraf. Detection of Fetal Structural Anomalies in a Basic First-Trimester Screening Program for Aneuploidy. J Ultrasound Med 2014; 33:1737–1745.
[49] Bryann Bromley, Thomas D. Shipp, Jennifer Lyons, Yvette Groszmann, Reshama S. Navathe, Beryl R. Benacerraf. What Is the Importance of SecondTrimester "Soft Markers" for Trisomy 21 After an 11- to 14-Week Aneuploidy Screening Scan? J Ultrasound Med 2014; 33:1747–1752.
[50] Nyberg DA, Resta RG, Luthy MA, Hickok DE, Williams MA. Humerus and femur length shortening in the detection of Down syndrome. Am J Obstet Gynecol 1993; 168:534–8.
[51] Michiel C. Van den Hof, MD, Halifax NS, R. Douglas Wilson, MD, Philadelphia PA. Fetal Soft Markers in Obstetric Ultrasound. No. 162, SOGC Clinical Practice Guidelines,2005, 592-612
[52] Shipp TD, Bromley B, Mascola M, Benacerraf B. Variation in fetal femur length with respect to maternal race. J Ultrasound Med 2001; 20:141–4.
[53] Smith-Bindman R, Hosmer W, Feldstein VA, Deeks JJ, Goldberg JD. Second-trimester ultrasound to detect fetuses with Down syndrome. JAMA 2001; 285:1044–55
[54] Bahado-Singh RO, Oz UA, Mendilcioglu I, Mahoney MJ. The mid-trimester genetic sonogram. Semin Perinatol 2005; 29:209–214
[55] Keeling JW, Fischer Hansen B, Kjaer I. Pattern of malformations in the axial section skeleton in human trisomy 21 fetuses. Am J Med Genet 1997; 68: 466–471.
[56] M. V. Senat, J. P. Bernard, M. Boulvain, Y. Ville.Intra- and interoperator variability in fetal nasal bone assessment at 11–14 weeks of gestation. Ultrasound Obstet Gynecol 2003; 22: 138–141.
[57] Orlandi F, Bilardo CM, Campogrande M, Krantz D, Hallahan T, Rossi C, et al. Measurement of nasal bone length at 11-14 weeks of pregnancy and its potential role in Down syndrome risk assessment. Ultrasound Obstet Gynecol. 2003;22(1):36–9.
[58] Bromley B, Lieberman E, Shipp TD, Benacerraf BR. Fetal nose bone length: a marker for Down syndrome in the second trimester. J Ultrasound Med. 2002;21(12):1387–94.
[59] Cusick W, Shevell T, Duchan LS, Lupinacci CA, Terranova J, Crombleholme WR. Likelihood ratios for fetal trisomy 21 based on nasal bone length in the second trimester: how best to define hypoplasia? Ultrasound Obstet Gynecol. 2007;30(3):271–4.
[60] Cicero S, Bindra R, Rembouskos G, Tripsanas C, Nicolaides KH. Fetal nasal bone length in chromosomally normal and abnormal uses at 11-14 weeks of gestation. J Matern Fetal Neonatal Med. 2002;11(6):400–2.
[61] Cicero S, Rembouskos G, Vandecruys H, Hogg M, Nicolaides KH. Likelihood ratio for trisomy 21 in fetuses with absent nasal bone at the 11-14-week scan. Ultrasound Obstet Gynecol. 2004;23(3):218–23
[62] Has R, Kalelioglu I, Yuksel A, Ibrahimoglu L, Ermis H, Yildirim A. Fetal nasal bone assessment in first trimester down syndrome screening. Fetal Diagn Ther. 2008;24(1):61–6
[63] Cicero S, Avgidou K, Rembouskos G, Kagan KO, Nicolaides KH. Nasal bone in first-trimester screening for trisomy 21. Am J Obstet Gynecol. 2006;195(1):109–14.
[64] Dhaifalah I, Mickova I, Santavy J, Vrbicka D, Zapletalova D, Curtisova V. [Efficiency of measuring nasal bone as an ultrasound marker of Down syndrome in 11th to 13th+6 week of pregnancy]. Ceska Gynekol. 2007;72(1):19–23.
[65] Souka AP, Athanasios P, Kavalakis I, et al. Screening for major structural abnormalities at the 11- to 14-week ultrasound scan. Am J Obstet Gynecol 2006; 194:393–396
[66] Weiner Z, Goldstein I, Bombard A, Applewhite L, Itzkovits-Eldor J. Screening for structural fetal anomalies during the nuchal translucency ultrasound examination. Am J Obstet Gynecol 2007; 197:181. e1–181.e5
[67] Chen M, Lee CP, Lam YH, et al. Comparison of nuchal and detailed morphology ultrasound examinations in early pregnancy for fetal structural abnormality screening: a randomized controlled trial. Ultrasound Obstet Gynecol2008; 31:136–146.
[68] Becker R, Wegner RD. Detailed screening for anomalies and cardiac defects at the 11–13-week scan. Ultrasound Obstet Gynecol 2006; 27:613– 618.
[69] Becker R, Schmitz L, Kilavus S, Stumm M, Wegner RD, Bittner U. "Normal" nuchal translucency: a justification to refrain from a detailed scan? An analysis of 6858 cases with special reference to ethical aspects. Prenat Diagn2012; 32:550–556.
[70] Syngelaki A, Chelemen T, Dagklis T, Allan L, Nicolaides KH. Challenges in the diagnosis of fetal non-chromosomal abnormalities at 11–13 weeks. Prenat Diagn2011; 31:90–102.
[71] Grande M, Arigita M, Borobio V, Jimenez JM, Fernandez S, Borrell A. First-trimester detection of structural abnormalities and the role of aneuploidy markers. Ultrasound Obstet Gynecol2012; 39:157–163.
[72] Cossi, P.S, Junior, E.A., Bussamra, L.C., Filho, H.A., Nardazzo, L.M., Moron, A.F. Measurement of fetal nasal bone length in the period between 11 and 15 gestational weeks in a Brazilian population: a preliminary study. Radiol Bras 2008; 41:3, 155-158.
[73] Moon, M. H., Cho, J. Y., Lee, Y. M., Lee, Y. H., Yang, J. H., Kim, M. Y., & Park, S. H.Nasal bone length at 11–14 weeks of pregnancy in the Korean population. Prenatal diagnosis 2006; 26:6, 524-527.
[74] Leodoro J. Labrague, Lynette C. Tan. Fetal Nasal Bone Length in the Period of 11 and 15 Weeks of Pregnancy in the Filipino Population. American Journal of Medical Sciences and Medicine, 2013, Vol. 1, No. 6, 110-113
[75] Suwanrath et al.: Reliability of fetal nasal bone length measurement at 11–14 weeks of gestation. BMC Pregnancy and Childbirth 2013 13:7.
[76] Cossi, P.S, Junior, E.A., Bussamra, L.C., Filho, H.A., Nardazzo, L.M., Moron, A.F. Measurement of fetal nasal bone length in the period between 11 and 15 gestational weeks in a Brazilian population: a preliminary study. Radiol Bras 2008; 41:3, 155-158.
[77] Prefumo F, Sairam S, Bhide A, Penna L, Hollis B, Thilaganathan B. Maternal ethnic origin and fetal nasal bones at 11–14 weeks of gestation. BJOG 2004; 111:109–112.
[78] Leung TY, Sahota D, Chan LW, Law LW, Fung TY, Lau TK. Fetal nasal bone status in Chinese women undergoing first-trimester screening for trisomy 21. Am J Obstet Gynecol 2008; 199:521. e1–521.e5.
[79] Norton ME, Rose NC, Benn P. Noninvasive prenatal testing for fetal aneuploidy: clinical assessment and a plea for restraint. Obstet Gynecol 2013; 121:847–850.

[80] American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 545: noninvasive prenatal testing for fetal aneuploidy. Obstet Gynecol2012; 120:1532–1534.
[81] Chetty S, Garabedian MJ, Norton ME. Uptake of noninvasive prenatal testing (NIPT) in women following positive aneuploidy screening. Prenat Diagn2013; 33:542–546.
[82] Nicolaides KH, Syngelaki A, Ashoor G, Birdir C, Touzet G. Noninvasive prenatal testing for fetal trisomies in a routinely screened first-trimester population. Am J Obstet Gynecol2012; 207:374. e1–374.e6.
[83] Musci TJ, Fairbrother G, Batey A, Bruusema J, Struble C, Song K. Non-invasive prenatal testing with cell-free fetal DNA: US physician attitudes toward implementation in clinical practice. Prenat Diagn2013; 33:424–428.