RESEARCH

OUTCOME OF ISOLATED ABSENT FETAL NASAL BONE AND ITS ASSOCIATION WITH ANEUPLOIDY

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Abstract

Background: The study's objective was to assess absent foetal nasal bone (AFNB) in order to follow its outcomes and relevance in identifying chromosomal abnormalities. The lack of the nasal bone is another indicator of prenatal aneuploidy in foetal sonography. **Materials and Methods:** Between 2017 and 2022, we found 79 cases of AFNB in foetuses with gestational ages ranging from 11 to 40 weeks. A detailed structural examination was performed in cases where nasal bone was missing, taking into consideration soft indications, maternal age, and maternal blood serum factors. Finally, the risk of trisomy was calculated. **Result:** This study was based on 79 foetuses having an AFNB. Six of them were executed since they were born with various congenital abnormalities. Aneuploidy was diagnosed in 7 of 9 persons with high-risk biochemical indications, or 24 of 73 patients (comparison group: 32%). The remaining 15/24 (62%) biochemical markers suggested low risk and advised amniocentesis; four of them were found to have Down syndrome. The remaining 49 cases (67%) in the research group had isolated AFNB, whereas 44 (89%) were at low risk for aneuploidy and rejected an amniocentesis. Only two of the 44 patients (42 of whom were normal after delivery) had an abnormal karyotype. The other 5 cases (10%) were at high risk for aneuploidy, and amniocentesis was recommended since trisomy 21 was discovered in three of them. The frequency of missing foetal nasal bone in our study was 0.15% (73/50600). **Conclusion:** Biochemical screening and amniocentesis are advised in addition to isolated AFNB to determine extra risk since they may be more effective in diagnosing Down syndrome. To search for structural defects or other soft signs, a skilled ultrasonologist should extensively examine foetuses.

INTRODUCTION

Down's syndrome (DS), one of the most common clinical illnesses, affects one in every 800-1000 live newborns. This is one of the uncommon illnesses in which the foetus survives after birth, but there are enormous social and financial costs. Langdon Down discovered a small nasal bone as one of the several phenotypic markers of Down syndrome in 1866.[1] The absence of the foetal nasal bone on sonography has been studied as a marker of Down syndrome in both the first and second trimesters, according to this description. Other chromosomal abnormalities, such as trisomy 13 and 18, are also connected to an embryonic nasal bone that is absent.[2,3,4] The loss of the embryonic nasal bone has been associated to cases of B-cell immunodeficiency, cri du chat (5p-) syndrome, and partial trisomy 20q.[5,6,7,8] Despite the fact that both 5p- and 20q- are apparent on an ordinary karyotype, testing for these later anomalies is not routine when a missing foetal nasal bone is discovered owing to their rarity. The embryonic nasal bone first appears histologically when the crown-rump length is 42 mm, or 11 weeks gestation.[9] In the first trimester, the absence of the foetal nasal bone resulted in a likelihood ratio for Down syndrome of 27.8 and 83 in the second trimester.[10,11,12] It has been projected that 0.5% to 2.8% of euploid foetuses will display images consistent with delayed ossification of the nasal bone on first- or second-trimester sonography.[1] Because there aren't many systematic studies that look at how these patients turn out, the relevance of AFNB after aneuploidy isn't well recognised. In this case, a therapeutic quandary develops. The goal of this study was to examine the outcomes of foetuses with a missing nasal bone in the

prenatal period after analysing the risk of aneuploidy using sonographic data and blood biochemical markers. Pregnancy screening treatments include measuring nuchal translucency (NT) between 11 and 14 weeks and looking for chromosomal abnormalities using soft markers in the second trimester. Other blood markers used to diagnose chromosomal abnormalities in the second trimester include free HCG, PAPP-A as a double marker done before 13 weeks and 6 days, HCG, AFP, Estriol, and Inhibin A. (quadruple marker). A genetic ultrasonography is a thorough evaluation of ultrasound abnormalities that are known to be associated with foetal aneuploidy at the appropriate gestational age. Maternal biochemical screening may improve sensitivity and reduce false positives for trisomy 21, allowing for the avoidance of unnecessary invasive diagnostic procedures. The relationship between a missing nasal bone and other sonographic indicators, after controlling for maternal and gestational age risks. Along with missing nasal bone, additional soft indications connected to aneuploidy that might increase the detection probability in NT scans include increased nuchal translucency (NT), absence, or reversal. Waves in the Ductus Venosus and tricuspid valve regurgitation, as well as in second trimester scans, include a single umbilical artery, soft markers such as mild ventriculomegaly, increased nuchal fold, choroid plexus cyst, small echogenic intra cardiac focus, echogenic bowel loops, pyelectasis, and short femur.

MATERIALS AND METHODS

All regular and referral sonographic exams conducted at the Government Maternity Hospital in Warangal and the Vinoothna Scan Center in Warangal between January 2017 and August 2022 were included in this hospital-based retrospective cohort analysis. The permission of the ethics committee was necessary to conduct the study. Participants in this study gave written informed consent. The Esoate My Lab 40 and Voluson E8 (GE Healthcare) transabdominally conducted the ultrasonography in each instance. In AFNB aneuploidy was excluded by correlating with other maternal biochemical markers and if necessary, with amniocentesis, and in isolated AFNB cases newborn examinations were available for review. We followed the approach for sonographically evaluating the nasal bone based on Cicero et al study's.[13] 1. Enlarge the picture such that each calliper distance increment is just 0.1 mm. (2). A mid-sagittal view of the foetal profile should be obtained in the supine position. (3). The transducer's face should be positioned such that it closely parallels the skin along the nasal bridge. There should be a 45-degree angle between the ultrasound transducer and a hypothetical line running across the foetal profile in this position. When all of these parameters were met, the probe was adjusted from side to side to ensure that the nasal bone and skin could be identified. Three critical indicators for imaging the foetal nose are the nasal bone, skin that mimics an equal sign, and the cartilaginous tip of the nose (Fig 2a&2b). Nasal bone was considered deficient if it was not visible or was thin and less echogenic than the skin above it (Fig. 2c & 2d). In all patients, we employed two phased screening techniques: first, we examined an AFNB before analysing the nasal bone. Second, we have counted the number of maternal years, NT, soft aneuploidy markers, and triple/quadruple biochemical markers. There was genetic counselling available to patients. All patients were advised to have the necessary invasive tests, such as chorionic villus collection or amniocentesis, if they had an isolated AFNB, other ultrasonography findings, or elevated biochemical markers for trisomy. The chromosomal numbers 13, 18, 21, and sex chromosomes were examined using FISH tests on chorionic villi or amniotic fluid cells, and the whole karyotype was also cultured. For those who continued the pregnancy, second-trimester sonographic exams, comprising a complete structural assessment and biometric measures, were done and compared with biochemical data. Newborn assessments were completed, and follow-up sonograms were acquired for examination.

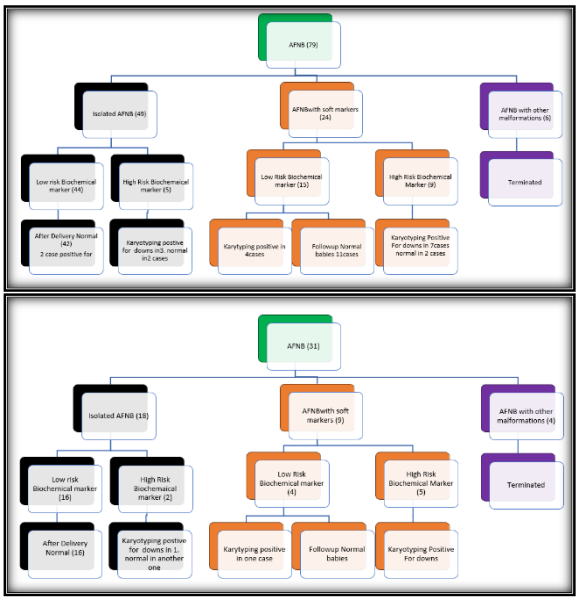

Figure 1: flow chart showing absent nasal bone

RESULTS

This study included 50,814 pregnant South Indian women between the ages of 18 and 35 who were referred for regular prenatal tests between 2017 and 2022. We were unable to examine the nasal bone in 214 cases due to maternal obesity and the placement of the foetus. In the remaining cases (50600), the foetal nasal bone was evaluated and classified as present or absent. We were able to identify 79 foetuses who lacked a nasal bone using sonography. All ultrasound findings, including structural abnormalities and soft indicators for Down

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syndrome, were examined in instances with an AFNB. Six of them were put to death since they were linked to other congenital defects. The remaining 73 individuals were split into two groups: those who had a single absent or hypoplastic nasal bone and those who had another ultrasonography result. Based on biochemical markers, the predicted frequencies of Down syndrome in the two groups were compared.

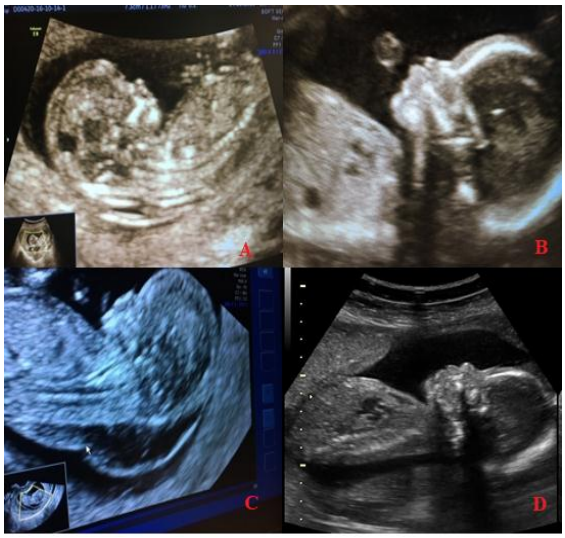

Figure 2: Appearances of Normal Nasal Bone and Absent Nasal Bone. a: Positive equal sign. Normal nasal bone. NT – Normal, b: Normal nasal bone with positive equal sign at genetic sonogram. Arrow 1 indicates skin layer. Arrow 2 indicates nasal bone. Arrow 3 indicates tip of the nose, c: Absent nasal bone. Increased NT, d: Absent nasal bone at genetic sonogram.

Other soft indicators and ultrasound abnormalities are connected with those 24 individuals (comparison group (32%), who came for NT (5) and genetic scans (19). Nine (37%) of the 24 showed an elevated risk for aneuploidy in biochemical screening and were recommended karyotype out of 9 seven showed aneuploidy and two were normal. The remaining 15 (62%) individuals with a low risk of aneuploidy in biochemical screening were recommended to undergo amniocentesis. Six individuals received amniocentesis, four of whom had Down syndrome; the other nine were not eligible for invasive testing. The records and follow-up scans of a baby indicated no aneuploidy. In biochemical screening, 44 (89%) of the remaining 49 individuals (study group 67%) exhibited minimal risk. The average maternal age was 23.5 years. The mean gestational age at diagnosis in the genetic sonogram was 20 weeks, with a range of 17 to 24 weeks, while the mean gestational age at diagnosis in the NT scan was 12.5 weeks, with a range of 11 to 14 weeks [Table 1]. Six cases revealed AFNB via NT scans (as first-trimester screening was not yet a standard practise in our region previously), 72 cases were diagnosed with AFNB via genetic sonography, and one case was discovered at 36 weeks; the patient underwent the first growth scan our centre had ever done at this gestational age. The average birth weight was 2650 g, with a gestational age of 36 weeks and 2 days. 44 low risk people were denied invasive karyotype testing during pregnancy, and when newborn checks were conducted after birth and there was no indication of any trisomy, they were believed to be euploid. With isolated AFNB biochemical markers, the remaining 5/49 cases (10%) were determined to be at high risk for aneuploidy and were referred for amniocentesis, with three of them being found to be aneuploid. Minor abnormalities or soft signs associated with AFNB included an echogenic intracardiac focus (n = 11), ventriculomegaly (n = 4), pyelectasis (n = 7), first-trimester increased nuchal translucency (n = 5), and choroid plexus cysts (n = 1). [Figure 2,3].

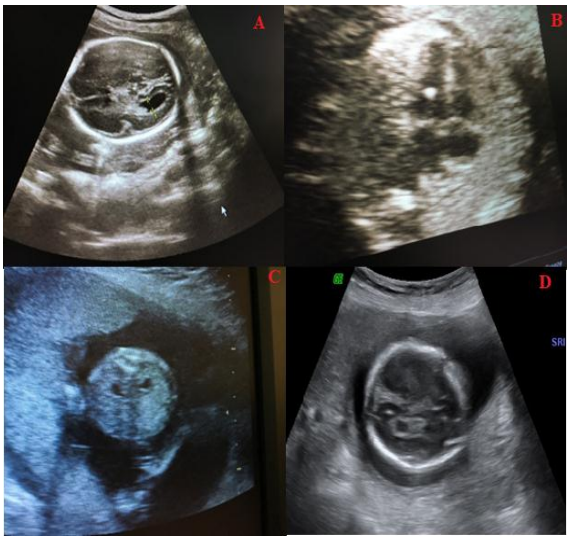

Figure 3: Other Soft Markers for Aneuploidy In Fetuses With Absent Nasal Bone, a- Ventriculomegaly, b- Echogenic intracardiac focus, c- Bilateral pyelectasis, d- Choroid plexus cyst.

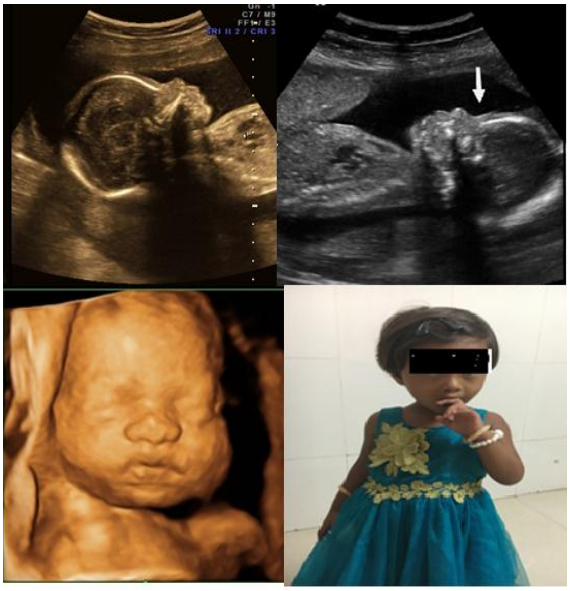

Figure 4: Absent Nasal Bone with Different Gestational Age Groups, 3D reconstruction, 2 years old child of AFNB.

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Table 1: showing absent nasal bone

Group	Nasal bone absent	Additional ultrasound findings	Biochemical screening	no of cases (Total 31)	No of abnormal cases	Abnormal karyotype	Post-delivery follow up
1	Isolated absent nasal bone	nil	Low risk High risk	16 2	Nill 1	Karyotype not done Karyotype positive in one case.	16new borns are normal.
2	Absent nasal bone	Soft markers present	Low risk	4	1	Karyotype positive in one case and not done in rest of the 3cases	3 new born recdords were normal.
3	Absent nasal bone	Soft markers present	High risk	5 cases	All 5 cases are abnormal	Aneuploidy present	Terminated pregnancy
4	Absent nasal bone	Other congenital abnormalities	Not done	4 cases	All are abnormal	Not done	Terminated pregnancy.

DISCUSSION

AFNB may be one of the most prominent indications of foetal Down syndrome during NT scans and genetic sonograms. Down syndrome (DS) is the most common chromosomal aneuploidy that results in a live birth. Using a number of sonographic markers, prenatal sonography has proved useful in identifying afflicted foetuses. The characteristic for identifying foetuses with DS has been strong nuchal translucency during the 11- to 14-week gestational age window.[13,14] The nasal bone was shown to be absent in 73% of foetuses with DS in the first trimester, together with increased nuchal translucency, suggesting that this might be a sonographic sign.[10] As a DS marker in the second trimester, the nasal bone has received relatively little systematic investigation.[12] With false-positive rates of 5% to 15%, sonographic identification of related soft markers has made it possible to identify 60% to 80% of foetuses with Down syndrome.[15,16] A pathologic study revealed that ossification of the nasal bones was absent in one-fourth of trisomyfetuses,[17] regardless of gestational age. According to studies, the Indian population has a shorter foetal nasal bone length than other races.[18]

At the moment, the most accurate approach for screening for anuploidy is a combination of maternal age, foetal NT, maternal serum free beta-HCG, and pregnancy-associated plasma protein-A at 11-14 weeks, with a detection rate of 90% and a false-positive rate of 5%.[19,20,21] Furthermore, it has been projected that examining the foetal profile for the presence or absence of the nasal bone as part of the combined first-trimester trisomy 21 screening would increase the sensitivity to 97% with a false positive rate of 5%.[22] Pinette et al,[23] observed that the inclusion of sonographic markers may greatly reduce the false positive rate of second trimester biochemical screening without affecting the detection rate. The screening sensitivity increases when combined with nuchal translucency (NT) assessment and maternal age, boosting detection rates by lowering false-positive rates. The likelihood ratio for trisomy 21 was 50.5 (95% CI 27.1-92.7) for the hypoplastic nasal bone, while it was 0.38 (95% CI 0.24-0.56) for the current nasal bone.[24] AFNB in the first trimester may achieve a DS detection rate of 97.5% with a false-positive rate of 5% by combining blood biochemical indicators with sonographic examination of nuchal translucency and the presence/absence of the NB.[25] The receiver operating characteristic curve of the biparietal diameter-nasal bone length ratio found that a value of 9 or above identified 100% of Down syndrome pregnancies and 22% of euploid foetuses. If the ratio was 10 or higher, 81% of Down syndrome-positive pregnancies and 11% of euploid foetuses would have been found. In comparison to 5% of euploid pregnancies, 69% of Down syndrome foetuses would be recognised if the ratio was 11 or higher.[26]

In our study abnormal karyotype in AFNB associated with other soft markers [45% (11/24) vs. isolated AFNB10% (5/49), Fisher's exact test $\chi 2 = 0.0017$, $p < 0.5$] was observed.

In our study AFNB on ultrasound in diagnosing downs has sensitivity of 66.67% & specificity of 94.44 with likelihood ratio 12 (95%CI 1.69-85.19). Biochemical marker alone in diagnosising downs has sensitivity of 60% & specificity of 94.12% with likelihood ratio 10.20 (95%CI 1.43-72.97). The use of ultrasonography and biochemical markers to diagnose downs has a sensitivity of 75% and a specificity of 89%, with a likelihood ratio of 6.94 (95% CI 2.64-18.26).

When performed at our centre, NT scans at 11-13 weeks and 6 days, as well as second trimester genetic sonography, have a high detection rate for trisomy 21, ranging from 60-90%, and the combination of ultrasound and biochemical screen increases the detection rate to more than 90%. The chromosomes of 83–93% of foetuses with isolated AFNB are found to be normal.

As shown in our research, 85–90% of isolated AFNB instances were seen with a normal end [Figure 4], which gives the pair a great degree of comfort.[18]

CONCLUSION

The study's findings that about 85–90% of isolated AFNB instances with low-risk biochemical indicators are seen with normal chromosomes give

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the pair a great lot of comfort. By combining missing nasal bone with other sonographic indications and accounting for the background risk for maternal and gestational age, maternal biochemical screening may boost sensitivity and minimise false positives of trisomy 21. Isolated AFNB on ultrasound screening with a minimal risk of anueploidy on biochemical markers may avoid invasive diagnostic procedures and allow the pregnancy to continue.

In the current investigation, aberrant chromosomes were found in a considerably higher proportion of patients when AFNB was linked to additional abnormalities or high risk biochemical testing. Therefore, it is advised that this population be routinely examined for chromosomal abnormalities. When a foetus nasal bone is lacking after the first or second trimester, a detailed study of foetal anatomy is necessary. It is important to reassure pregnant moms that if no additional problems are discovered and biochemical indicators show little danger, there is a good likelihood of a happy neonatal outcome.

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REFERENCES

1. Dukhovny S, Wilkins-Haug L, Shipp TD, Benson CB, Kaimal AJ, Reiss R. Absent fetal nasal bone: what does it mean for the euploid fetus? J Ultrasound Med. 2013;32(12):2131-4. doi: 10.7863/ultra.32.12.2131.
2. Kagan KO, Cicero S, Staboulidou I, Wright D, Nicolaides KH. 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(3):259-64. doi: 10.1002/uog.6318.
3. Kjaer I, Keeling JW, Hansen BF. Pattern of malformations in the axial skeleton in human trisomy 18 fetuses. Am J Med Genet. 1996;65(4):332-6. doi: 10.1002/(SICI)1096-8628(19961111)65:4<332::AID-AJMG16>3.0.CO;2-V.
4. Sepulveda W, Wong AE, Dezerega V. First-trimester sonographic findings in trisomy 18: a review of 53 cases. Prenat Diagn. 2010;30(3):256-9. doi: 10.1002/pd.2462.
5. Soto E, Richani K, Gonçalves LF, Devers P, Espinoza J, Lee W, et al. Three-dimensional ultrasound in the prenatal diagnosis of cleidocranial dysplasia associated with B-cell immunodeficiency. Ultrasound Obstet Gynecol. 2006;27(5):574-9. doi: 10.1002/uog.2770.
6. Traisrisilp K, Yanase Y, Ake-Sittipaisarn S, Tongsong T. Prenatal Sonographic Features of Cri-du-Chat Syndrome: A Case Report and Analytical Literature Review. Diagnostics (Basel). 2022;12(2):421. doi: 10.3390/diagnostics12020421.
7. Teoh XH, Tan TY, Chow KK, Lee IW. Prenatal diagnosis of cri-du-chat syndrome: importance of ultrasonographical markers. Singapore Med J. 2009;50(5):e181-4.
8. Sepulveda W, Be C. Partial trisomy 20q in a fetus with hypoplastic nasal bone, mild ventriculomegaly, and short femur. Prenat Diagn. 2008;28(9):868-70. doi: 10.1002/pd.2062.
9. Poureisa M, Daghighi MH, Mazaheri Khameneh R, Salehi Majd S. Fetal Nasal Bone Status In Iranian Women Undergoing First-Trimester Screening For Trisomy 21: A Review and an Observational Study. Iran J Radiol. 2015;12(4):e11905. doi: 10.5812/iranjradiol.11905.
10. Cicero S, Curcio P, Papageorghiou A, Sonek J, Nicolaides K. Absence of nasal bone in fetuses with trisomy 21 at 11-14 weeks of gestation: an observational study. Lancet. 2001;358(9294):1665-7. doi: 10.1016/S0140-6736(01)06709-5.
11. 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. doi: 10.7863/jum.2002.21.12.1387.
12. Sonek JD, Cicero S, Neiger R, Nicolaides KH. Nasal bone assessment in prenatal screening for trisomy 21. Am J Obstet Gynecol. 2006;195(5):1219-30. doi: 10.1016/j.ajog.2005.11.042.
13. Cicero S, Dezerega V, Andrade E, Scheier M, Nicolaides KH. Learning curve for sonographic examination of the fetal nasal bone at 11-14 weeks. Ultrasound Obstet Gynecol. 2003;22(2):135-7. doi: 10.1002/uog.176.
14. 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(9125):343-6. doi: 10.1016/s0140-6736(97)11280-6.
15. Nyberg DA, Souter VL, El-Bastawissi A, Young S, Luthhardt F, Luthy DA. Isolated sonographic markers for detection of fetal Down syndrome in the second trimester of pregnancy. J Ultrasound Med. 2001;20(10):1053-63. doi: 10.7863/jum.2001.20.10.1053.
16. Bromley B, Lieberman E, Benacerraf BR. The incorporation of maternal age into the sonographic scoring index for the detection at 14-20 weeks of fetuses with Down's syndrome. Ultrasound Obstet Gynecol. 1997;10(5):321-4. doi: 10.1046/j.1469-0705.1997.10050321.x.
17. Stempfle N, Huten Y, Fredouille C, Brisse H, Nessmann C. Skeletal abnormalities in fetuses with Down's syndrome: a radiographic post-mortem study. Pediatr Radiol. 1999;29(9):682-8. doi: 10.1007/s002470050675.
18. Odibo AO, Sehdev HM, Dunn L, McDonald R, Macones GA. The association between fetal nasal bone hypoplasia and aneuploidy. Obstet Gynecol. 2004;104(6):1229-33. doi: 10.1097/01.AOG.0000148848.49752.37.
19. 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. BJOG. 2003;110(3):281-6.
20. Krantz DA, Hallahan TW, Orlandi F, Buchanan P, Larsen JW Jr, Macri JN. First-trimester Down syndrome screening using dried blood biochemistry and nuchal translucency. Obstet Gynecol. 2000;96(2):207-13. doi: 10.1016/s0029-7844(00)00881-4.
21. O'Leary P, Breheny N, Dickinson JE, Bower C, Goldblatt J, Hewitt B, et al. First-trimester combined screening for Down syndrome and other fetal anomalies. Obstet Gynecol. 2006;107(4):869-76. doi: 10.1097/01.AOG.0000207562.09858.16.
22. Cicero S, Bindra R, Rembouskos G, Spencer K, Nicolaides KH. Integrated ultrasound and biochemical screening for trisomy 21 using fetal nuchal translucency, absent fetal nasal bone, free beta-hCG and PAPP-A at 11 to 14 weeks. Prenat Diagn. 2003;23(4):306-10. doi: 10.1002/pd.588.
23. Pinette MG, Egan JF, Wax JR, Blackstone J, Cartin A, Benn PA. Combined sonographic and biochemical markers for Down syndrome screening. J Ultrasound Med. 2003;22(11):1185-90. doi: 10.7863/jum.2003.22.11.1185.
24. Minderer S, Gloning KP, Henrich W, Stöger H. The nasal bone in fetuses with trisomy 21: sonographic versus pathomorphological findings. Ultrasound Obstet Gynecol. 2003;22(1):16-21. doi: 10.1002/uog.160.
25. Cicero S, Longo D, Rembouskos G, Sacchini C, Nicolaides KH. Absent nasal bone at 11-14 weeks of gestation and chromosomal defects. Ultrasound Obstet Gynecol. 2003;22(1):31-5. doi: 10.1002/uog.170.
26. 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(1):15-8. doi: 10.1002/uog.19.

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