

Prefrontal space ratio: comparison between trisomy 21 and euploid fetuses in the second trimester

J. SONEK*†, F. MOLINA‡, A. K. HIETT*§, M. GLOVER†, D. MCKENNA*† and K. H. NICOLAIDES¶**

*Fetal Medicine Foundation USA, Dayton, OH, USA; †Division of Maternal Fetal Medicine, Wright State University, Dayton, OH, USA; ‡Maternal-Fetal Medicine Unit, Department of Obstetrics and Gynaecology, San Cecilio University Hospital and University of Granada, Granada, Spain; §Division of Maternal Fetal Medicine, St. Vincent Women's Hospital, Indianapolis, IN, USA; ¶Harris Birthright Research Center for Fetal Medicine, King's College Hospital, London, UK; **The Fetal Medicine Foundation, London, UK

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ABSTRACT

Objective To evaluate a novel ultrasound measurement, the prefrontal space ratio (PFSR), in second-trimester trisomy 21 and euploid fetuses.

Methods Stored three-dimensional volumes of fetal profiles from 26 trisomy 21 fetuses and 90 euploid fetuses at 15–25 weeks' gestation were examined. A line was drawn between the leading edge of the mandible and the maxilla (MM line) and extended in front of the forehead. The ratio of the distance between the leading edge of the skull and that of the skin (d_1) to the distance between the skin and the point where the MM line was intercepted (d_2) was calculated (d_2/d_1). The distributions of PFSR in trisomy 21 and euploid fetuses were compared, and the relationship with gestational age in each group was evaluated by Spearman's rank correlation coefficient (r_s).

Results The PFSR in trisomy 21 fetuses (mean, 0.36; range, 0–0.81) was significantly lower than in euploid fetuses (mean, 1.48; range, 0.85–2.95; $P < 0.001$ (Mann–Whitney U-test)). There was no significant association between PFSR and gestational age in either trisomy 21 ($r_s = 0.25$; 95% CI, –0.15 to 0.58) or euploid ($r_s = 0.06$; 95% CI, –0.15 to 0.27) fetuses.

Conclusion The PFSR appears to be a highly sensitive and specific marker of trisomy 21 in the second trimester of pregnancy. Copyright © 2012 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Down syndrome is associated with certain facial morphological features, including thickened skin, nasal hypoplasia and midface hypoplasia¹. Prenatal assessment

of these features has been used successfully in screening for this aneuploidy. Trisomy 21 is associated with increased nuchal translucency thickness in the first trimester^{2,3}, increased nuchal fold thickness⁴ and prenasal skin thickness^{5,6} in the second trimester, and hypoplastic nasal bone^{7–9}, hypoplastic maxilla^{10,11} and increased frontomaxillary facial angle (FMF) in both the first and second trimesters^{12–14}. The increase in FMF angle in trisomy 21 fetuses is thought to be a consequence of the smaller size and dorsal displacement of the maxilla associated with this aneuploidy. Measurement of the FMF angle, defined as the angle between a line from the prefrontal skin to the leading edge of the maxilla and another line over the hard palate, exploits both the midface hypoplasia and the thickened skin over the forehead in trisomy 21 fetuses. However, in the second trimester the upper edge of the hard palate is somewhat irregular and may be difficult to visualize clearly due to ossification of the fetal skull.

In this study, we describe a novel measurement, the prefrontal space ratio (PFSR), which also is affected by the size of the maxilla and the prefrontal skin thickness, but in contrast to the FMF angle, measurement of the PFSR avoids the need to draw a line over the hard palate and may therefore be easier to perform and more reproducible. The aims of this study were to compare PFSR values in trisomy 21 fetuses to those in euploid fetuses and to examine the repeatability of PFSR measurements in order to assess its potential value in second-trimester screening for trisomy 21.

METHODS

This was a retrospective study utilizing stored three-dimensional (3D) ultrasound volumes (RAB 4–8L probe,

Correspondence to: Dr J. Sonek, Division of Maternal Fetal Medicine, Wright State University, Dayton, OH, USA (e-mail: jdsonek@mvh.org)

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Voluson 730 Expert, GE Medical Systems, Zipf, Austria) of second-trimester fetal heads. The volumes were obtained between 2006 and 2008 at Harris Birthright Research Centre for Fetal Medicine, London, UK and at Unidad de Ecografía, Centro Gutenberg, Malaga, Spain by operators skilled in 3D ultrasound scanning. The study included 26 fetuses with trisomy 21 diagnosed by amniocentesis and 90 fetuses in low-risk pregnancies that resulted in phenotypically normal neonates. Some volumes in both populations were used previously in a study on the FMF angle¹⁴.

The following data were recorded: gestational age, fetal biometry, maternal history, karyotype, presence or absence of cardiac anomalies and markers (presence or absence of nasal bone, nasal bone hypoplasia, nuchal fold measurement > 6 mm, echogenic bowel, lateral ventricular measurement > 10 mm).

The fetal face was insonated from the front, as close to the mid-sagittal plane as possible. The face of the transducer was approximately parallel to the longitudinal axis of the nasal bone and bridge. Only those volumes where the anteriormost edge of the mandible, the maxilla, the edge of the bony forehead and the skin over the forehead could be identified confidently in the precise midline view were used in this analysis. The 3D volumes were examined offline in the multiplanar mode using 4DView (GE Medical Systems). A mid-sagittal view of the fetal profile was reconstructed using standard anatomical landmarks. The image was magnified so that the majority of the field was filled by the fetal profile. The anteriormost portions of the maxilla and the mandible were identified. The reference point was placed on the anterior edge of the mandible slightly below the tooth buds. A line was drawn between the reference point and the anterior edge of the maxilla (mandibulo-maxillary line (MML)) and this line was extended in front of the fetal forehead. A measurement (d_1) was taken between the leading edge of the bony forehead to the leading edge of the skin in a line that is roughly parallel to the inferior edge of the maxilla. The level at which this measurement was taken was located just superior to the point where the skin over the forehead turns anteriorly over the fetal nose. A second measurement (d_2) was performed at the same level as the first and along the same line. This measurement started at the leading edge of the skin at the same point as the d_1 measurement and ended at the point of intercept with the MML. The PFSR was determined by dividing d_2 by d_1 (Figure 1).

Using the stored volumes, a single operator (J.S.) who was aware of the fetal karyotype performed the initial measurements in all trisomy 21 and euploid fetuses. The same operator repeated measurements in all 26 fetuses with trisomy 21 and in 30 randomly selected euploid fetuses. A second operator (A.K.H.) who was blinded to the fetal karyotype measured the PFSR in the same 56 fetuses.

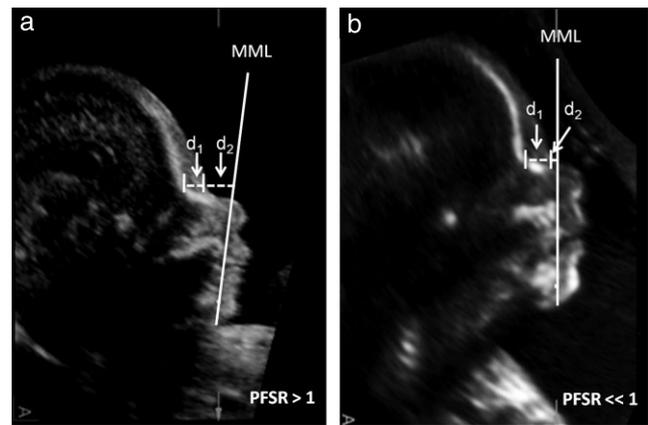


Figure 1 Measurement of prefrontal space ratio (PFSR) in: (a) a euploid fetus (PFSR > 1) and (b) a fetus with trisomy 21 (PFSR << 1). MML indicates mandibulomaxillary line, d_1 indicates distance between leading edge of frontal bone and leading edge of prefrontal skin and d_2 indicates distance between leading edge of prefrontal skin and intercept with MML (this is significantly smaller in (b) than in (a)). PFSR is calculated as d_2/d_1 .

Statistical analysis

The Kolmogorov–Smirnov test was used to check normality of the PFSR results in both trisomy 21 and euploid fetuses, and Spearman's rank regression analysis (r_s) was used to determine the association between PFSR and gestational age. The Mann–Whitney U -test was used to compare PFSR values between the two groups of fetuses and, within the trisomy 21 group, between subgroups with and without commonly recognized anomalies or markers. Bland–Altman analysis was used to analyze the measurement agreement and bias for a single examiner and between two examiners¹⁵. Data were analyzed using the statistical software GraphPad Prism for Windows (GraphPad Software, Inc., La Jolla, CA, USA). P -values of less than 0.05 were considered as statistically significant.

RESULTS

There was no significant difference in gestational age between the trisomy 21 group (mean, 20.3; range, 16.0–24.3 weeks) and the euploid group (mean, 20.4; range 15.1–25.1 weeks; $P = 0.24$). Kolmogorov–Smirnov analysis demonstrated normality of PFSR distribution in the trisomy 21 group ($P > 0.10$). However, the distribution of PFSR in the euploid group was not normal as it was skewed positively ($P = 0.002$). There was no significant association between PFSR and gestational age in either the trisomy 21 ($r_s = 0.25$; 95% CI, -0.15 to 0.58) or the euploid fetuses ($r_s = 0.06$; 95% CI, -0.15 to 0.27). The PFSR in trisomy 21 fetuses (mean, 0.36; range, 0–0.81) was significantly lower than that in euploid fetuses (mean, 1.48; range, 0.85–2.95; $P < 0.001$) (Figure 2).

There were no abnormal ultrasound findings or markers in the euploid fetuses. In the trisomy 21 group 10 (38.5%) fetuses had no anomalies or markers and one or more of the following were found in 16 (61.5%) fetuses: cardiac defects in eight (30.8%), absent or hypoplastic nasal

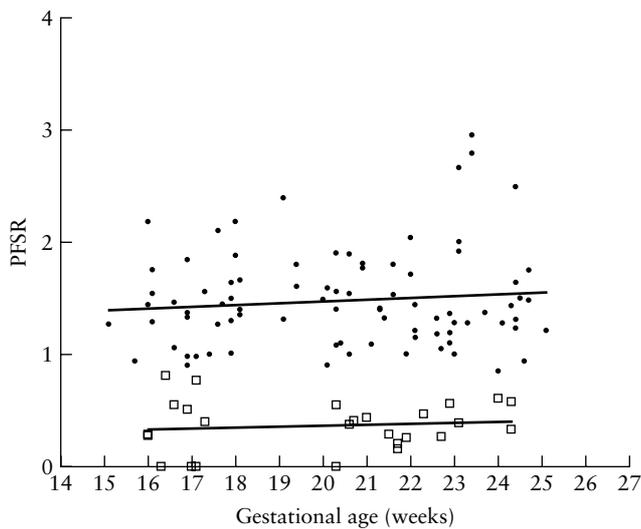


Figure 2 Prefrontal space ratio (PFSR) values for 90 euploid fetuses (●) and 26 fetuses with trisomy 21 (□) between 15.1 and 25.1 weeks' gestation. There was no statistically significant association between PFSR and gestational age for either group. Regression lines are shown.

bone in six (23.1%), nuchal fold measurement > 6 mm in five (19.2%), echogenic bowel in five (19.2%) and ventriculomegaly in five (19.2%). There was no significant difference in mean PFSR between the trisomy 21 fetuses with no markers and those with absent or hypoplastic nasal bone (0.26 vs. 0.30; $P=0.69$) nor between those with anomalies and/or markers but normal nasal bone and those with no anomalies or markers (0.45 vs. 0.26; $P=0.17$).

Bland–Altman analysis demonstrated that the intraobserver mean bias for PFSR was -0.027 (95% limits of agreement (LoA), -0.44 to 0.39) for the trisomy 21 group and -0.086 (95% LoA, -0.53 to 0.36) for the euploid group. The distribution of repeat measurements obtained by the same observer (J.S.) is shown in Figure 3a. The respective values for interobserver mean bias were 0.16 (95% LoA, -0.33 to 0.65) and -0.07 (95% LoA, -0.65 to 0.52). The distribution of measurements obtained by the second observer (A.K.H.) who was blinded to fetal karyotype is shown in Figure 3b.

DISCUSSION

The findings of this study suggest that measurement of PFSR in the second trimester of pregnancy may be effective in screening for trisomy 21. This novel measurement exploits a combination of two common differences between trisomy 21 and euploid fetuses: increased skin thickening^{1–4,11,12} and midface hypoplasia^{13,14,16–18}. It is reproducible and is independent of gestational age within the range of 15–25 weeks.

Trisomy 21 is not known to be associated with abnormalities in size of the mandible. Therefore, the anterior-most portion of the mandible is a reasonable reference point in evaluation of the fetal profile when screening for this condition. Conversely, abnormalities in size of

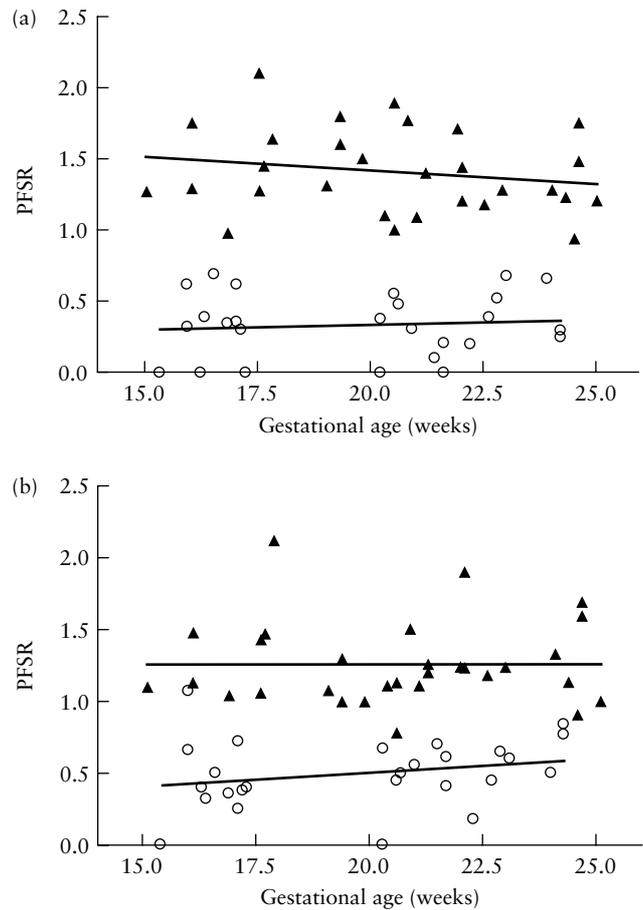


Figure 3 Prefrontal space ratio (PFSR) values for 30 randomly selected euploid fetuses (▲) and for all 26 fetuses with trisomy 21 (○) between 15.1 and 25.1 weeks' gestation, showing: (a) second set of measurements obtained by J.S. who was not blinded to the fetal karyotype; and (b) measurements by a different observer (A.K.H.), who was blinded to the fetal karyotype.

the maxilla are a well-recognized feature of trisomy 21. Three studies that addressed the question of maxillary growth in individuals with Down syndrome ranging between 6 months and 66 years of age^{16–18} all demonstrated directly or indirectly that maxillary measurements are significantly smaller than normal in individuals with Down syndrome. Allanson *et al.*¹⁸ specifically found that maxillary growth in relation to the mandible is decreased. Lauridsen *et al.*¹¹ measured the overall palatal length and the maxillary and palatine bones separately in aborted fetuses with trisomy 21 between 16 and 25 weeks' gestation. They compared these to measurements in matched euploid fetuses and found that the total palatal length was shorter in trisomy 21 fetuses, due to shortness of both maxillary and palatine components of the hard palate.

The advantage of the new approach described is that the lines and measurements used to generate the PSFR are based on topographic points on the surface of the fetal profile rather than on structures deep within the fetal face. The MM line, which delineates the anterior border of the prefrontal space, is drawn between two discreet points, the anterior edge of the maxilla and mandible, which are relatively easy to identify. In trisomy 21 fetuses

the PFSR appears to be independent of the presence of other defects, in particular, nasal hypoplasia. However, fetal conditions associated with an alteration in shape of the fetal profile, e.g. micrognathia, frontal bossing, facial clefts, and syndromes other than trisomy 21 that are associated with midface hypoplasia must be kept in mind also, as these potentially could affect the PFSR.

The main limitation of the study is its retrospective nature. The 3D volumes were originally obtained with the aim of optimizing visualization of the hard palate and forehead but not the mandible, by adjusting the face of the transducer to be roughly parallel to the skin over the nasal bridge. Despite this limitation, a major difference in PFSR was observed between the trisomy 21 and euploid groups. This difference was maintained even when measurements were repeated by either the same or a second operator. It is anticipated that when volumes are obtained expressly for the purpose of PFSR determinations the results may improve further. Measurements for PFSR in this study were made in the precise midline view of the fetal profile, which was reconstructed from a stored 3D volume. It is therefore uncertain to what extent our findings will be reproduced in prospective screening studies in which fetal profiles are obtained by two-dimensional sonography.

REFERENCES

- Down LJ. Observations on an ethnic classification of idiots. Clinical lectures and Reports. *London Hospital* 1866; 3: 259–262.
- Nicolaides KH, Azar G, Byrne D, Mansur C, Marks K. Fetal nuchal translucency: ultrasound screening for chromosomal defects in first trimester of pregnancy. *Br Med J* 1992; 304: 867–889.
- Snijders RJM, 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. *Lancet* 1998; 351: 343–346.
- Benacerraf BR, Frigoletto FD Jr. Soft tissue nuchal fold in the second-trimester fetus: standards for normal measurements compared with those in Down syndrome. *Am J Obstet Gynecol* 1987; 157: 1146–1149.
- Maymon R, Levinsohn-Tavor O, Cuckle H, Tovbin Y, Dreazen E, Wiener Y, Herman A. Second trimester ultrasound prenatal thickness combined with nasal bone length: a new method of Down syndrome screening. *Prenat Diagn* 2005; 25: 906–911.
- Persico N, Borenstein M, Molina F, Azumendi G, Nicolaides KH. Prenatal thickness in trisomy 21 fetuses at 16–24 weeks of gestation. *Ultrasound Obstet Gynecol* 2008; 32: 751–754.
- Sonek JD, Nicolaides KH. Prenatal ultrasonographic diagnosis of nasal bone abnormalities in three fetuses with Down syndrome. *Am J Obstet Gynecol* 2002; 186: 139–141.
- Cicero S, Curcio P, Papageorgiou A, Sonek J, Nicolaides KH. Absence of nasal bone in fetuses with Trisomy 21 at 11–14 weeks of gestation: an observational study. *Lancet* 2001; 358: 1665–1667.
- 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.
- Cicero S, Curcio P, Rembouskos G, Sonek J, Nicolaides KH. Maxillary length at 11–14 weeks of gestation in fetuses with Trisomy 21. *Ultrasound Obstet Gynecol* 2004; 24: 19–22.
- Lauridsen H, Hansen BF, Reintoft I, Keeling JW, Skovgaard LT, Kjaer I. Short hard palate in prenatal trisomy 21. *Orthod Craniofac Res* 2005; 8: 91–95.
- Sonek J, Borenstein M, Dagklis T, Persico N, Nicolaides KH. Frontomaxillary facial angle in fetuses with trisomy 21 at 11–13 (+6) weeks. *Am J Obstet Gynecol* 2007; 196: 271.e1–4.
- Sonek J, Borenstein M, Downing C, McKenna D, Neiger R, Croom C, Genrich T, Nicolaides KH. Frontomaxillary facial angles in screening for trisomy 21 at 14–23 weeks' gestation. *Am J Obstet Gynecol* 2007; 197: 160–161.
- Molina F, Persico N, Borenstein M, Sonek J, Nicolaides KH. Frontomaxillary facial angle in trisomy 21 fetuses at 16–24 weeks of gestation. *Ultrasound Obstet Gynecol* 2008; 31: 384–387.
- Bland JM, Altman DG. Statistical method for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 1: 307–310.
- Shapiro BL, Gorlin RJ, Redman RS, Bruhl HH. The palate and Down's syndrome. *N Engl J Med* 1967; 276: 1460–1463.
- Farkas LG, Katic MJ, Forrest CR, Litsas L. Surface anatomy of the face in Down's syndrome: linear and angular measurements in the craniofacial regions. *J Craniofac Surg* 2001; 12: 373–379.
- Allanson JE, O'Hara P, Farkas LG, Nair RC. Anthropometric craniofacial pattern profiles in Down syndrome. *Am J Med Genet* 1993; 47: 748–752.