Assessment of Midfacial Hypoplasia in Down Syndrome Fetuses – Validity of a Two-Line Approach and Introduction of a Novel Angle (Maxilla-Mandible-Nasion Angle)

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Abstract

Purpose: To scrutinize the validity of a novel angle (maxilla-mandible-nasion angle, MMN) as objective proof of midfacial hypoplasia in trisomy 21 fetuses.

Materials and Methods: Volume data sets of 2nd trimester fetuses were reviewed in this retrospective study. After achievement of the correct midsagittal position, the fetal profile line (FP line) and the mandibulo-maxillary line (MML) were applied and the resulting angle was calculated. Additionally, the prefrontal space ratio (PFSR) was assessed. Both measurements were obtained from 401 euploid fetuses and 42 fetuses with trisomy 21. Values for MMN and PFSR < 5th percentile were considered abnormal.

Results: The study included 443 fetuses with a mean gestational age of 21.3 weeks (range: 14.0–26.3). The MMN angle sufficiently identified hypoplasia of the midface in trisomy 21 fetuses (mean: 14.6°; range: 10.1°–22.0°) compared to controls (mean: 20.5°; range: 17.3°–23.7°; p < 0.0001). Concomitantly, the PFSR of Down syndrome fetuses was significantly lower (mean: 0.53; range: 0.21–1.22) than in euploid individuals (1.38; range: 0.54–2.23; p < 0.0001).

Conclusion: Calculation of the novel MMN angle in 2nd trimester fetuses reliably allows rapid assessment of craniofacial anatomy in order to rule out the midfacial hypoplasia frequently found in trisomy 21.

Introduction

Over 40 years ago, Westerman analyzed palatal casts of individuals with Down syndrome (DS) and described the palatal dimensions as markedly narrower in width, shorter in depth and lower in height than in normal controls [1]. The mean maxillary depth as a measure of midfacial hypoplasia was significantly smaller in 3D volume data sets of first-trimester fetuses with trisomy 21 compared to normal [2]. Accordingly, Alió et al. also reported maxillary hypoplasia of about 10 mm in children with Down syndrome compared to controls [3]. Beside a shortened maxilla, an absent vomer has recently been described in first- and second-trimester fetuses, thus emphasizing midfacial hypoplasia as a consistent finding in trisomy 21 [4]. Hypo- or oligodontia found in up to 60% of patients with DS [5] constitutes another frequent abnormality, which is in line with the finding of an underdevelopment of the upper jaw compared to the mandibular growth [6]. Farkas et al. provided further evidence for an abnormal craniofacial surface anatomy in trisomy 21 patients assessed by linear and angular measurements [7].

In the recent past a growing number of different angles have been introduced, all developed for an exact and reproducible assessment of craniofacial integrity. With regard to prenatal identification of trisomy 21 fetuses, application of the frontomaxillary angle [8, 9] and the recently introduced calculation of the prefrontal space ratio (PFSR) are of diagnostic value [10]. De Jong-Pleij et al. established the fetal profile line (FPL) drawn from the nasion to the mandible in order to get information about forehead anomalies and/or anomalies of the maxilla-mandible complex [11].

In this study we examined the applicability and clinical value of a novel angle combining 2 lines: the fetal profile line and the maxilla-mandibular line (essential for assessment of the PFSR) in order to obtain information about craniofacial architecture and abnormalities and the use of angle calculation for aiding the diagnosis of aneuploidy in 2nd trimester pregnancies.
Methods

The protocol for this retrospective study (11/2009-2-2/2014) was approved by the local ethics committee and all patients enrolled in this analysis gave informed consent. Stored three-dimensional (3D) volume data sets were reviewed, all being obtained transabdominally in second-trimester fetuses referred for targeted ultrasound examination with Voluson E8 expert and 730 expert systems (GE Healthcare, Zipf, Austria) equipped with a RM6C matrix and RAB4.8L convex probe, respectively. All sonographic examinations were performed by a single experienced operator. The volumes were acquired with the fetus facing the transducer. The 3D sweep acquisition angle ranged from 45–55° to ensure depiction of the entire face. After volume adjustment for an exact midsagittal section approved in corresponding transverse and coronal sections (multiplanar mode) and subsequent magnification, all included profiles were assessed with the fetal head in a vertical position (no flexion or extension and the mouth closed in order to prevent displacement of the mandible) as displayed in Fig. 1. The anatomical landmarks essential for angle calculation were the nasion (defined as the intersection of the frontal and nasal bones) and the anteriormost points of both the mandible and the maxilla. Calipers were placed and 2 lines were drawn connecting the ventral edge of the mandible with the nasion (fetal profile line; FPL) and a second one from the mandible to the anterior edge of the maxilla as recently described (mandibulo-maxillary line; MML). The resulting angle was introduced as the maxilla-mandible-nasion angle (MMN, Fig. 1,2). Additionally, we calculated the prefrontal space ratio (PFSR) by measuring the distance between the fetal profile line traversing the nasion (at the level of the nasion) and the leading edge of the frontal skin and a second one between the skin and the interception with the MML as introduced by Sonek et al. [10]. The PFSR was subsequently estimated by division of the latter by the distance between the FPL and skin. All MMN values assessed in trisomy 21 fetuses were compared to those derived from normal controls (healthy fetuses with known perinatal outcome).

Statistical analysis

Mann-Whitney U-test for independent samples was used for comparison of the mean MMN and PFSR values measured in normal controls and trisomy 21 fetuses. Correlation was assessed using Pearson’s correlation test. The data were analyzed using the statistical software SPSS 21.0 (Chicago, IL) and Microsoft Excel 2010 (Microsoft Corp, Redmond, WA). P-values of less than 0.05 were considered statistically significant.

Results

A total of 471 volume data sets were reviewed. The mean gestational age was 21.3 weeks (ranging from 14.0 to 26.3 gestational weeks) with no significant difference between the control and the trisomy 21 group. The mean maternal age was slightly higher in the trisomy 21 group (35.9 years; ranging from 21 to 48 years) than in the control group (32.4 years; ranging from 16 to 50 years). All women enrolled in this study were of Caucasian

![Fig. 1](image1.png) Fetal profiles obtained from facial volumes of a trisomy 21 fetus (a) and an euploid fetus (b) at 22 weeks of gestation. Left panel corresponds to the coronal view with the reference dot placed between the nostrils. Sagittal plane showing 2 lines tracing the mandible, the nasion and the anteriormost border of the maxilla, respectively. The resulting novel MMN angle is significantly more acute in a Down syndrome fetus. In addition, the PFSR is markedly decreased (panel a) in this fetus compared to controls (panel b).

![Fig. 2](image2.png) Midsagittal view of a Down syndrome fetus at 21 gestational weeks demonstrating an acute MMN < 5th percentile (panel a). Macroscopic specimen of the same fetus after TOP clearly depicting anatomical landmarks for assessing midfacial hypoplasia (panel b). FPL: fetal profile line; N: nasion; Mb: mandible; MML: mandibulo-maxillary line; Mx: maxilla.
ethnicity. 28 cases were excluded because of other structural or genetic anomalies or had an initial acquisition plane too far from the true midsagittal plane, leaving 443 eligible cases for final analyses. Of those, 42 fetuses had trisomy 21 confirmed by antenatal karyotyping. The remaining 401 patients had a normal appearance during targeted ultrasound, with 19 cases (4.7%) being found to have a positive fetal profile line (FPL passing the frontal bone posteriorly). In contrast, none of the Down syndrome fetuses presented with forehead anomalies. Neither in euploid controls nor in trisomy 21 fetuses could a negative FPL (position anterior to the frontal bone) be demonstrated. Correct identification of anatomical landmarks enabled sufficient angle calculation in all study cases enrolled in the final assessment. The MMN angle in normal controls was 20.5° (range from 17.3° to 23.7°), whereas this measurement was significantly more acute (mean: 14.6°; range: 10.1° to 22.0°) in cases with trisomy 21 as shown in (Fig. 3) (p < 0.0001). The 5th and 95th percentiles were 18.4° and 22.7°, respectively. The prefrontal space ratio could readily be calculated in both groups, showing that the PFSR in trisomy 21 cases was significantly smaller (mean: 0.53; range: 0.21–1.22) compared to euploid fetuses who had a mean PFSR of 1.38, ranging from 0.54 to 2.23 (p < 0.0001). The 5th and 95th percentiles for PFSR in our cohort were 1.02 and 1.89, respectively. In 2 fetuses with trisomy 21 a normal nasal bone length (>5th percentile) could be noticed, and both had a normal PFSR (>5th percentile). In 18/401 normal fetuses (4.5%), the PFSR was <1, and in another 11/401 cases (2.7%) the MMN was below the 5th percentile.

Receiver operating characteristic curves (ROC) were used to emphasize the predictive accuracy of angle assessment and calculation of the PFSR for the detection of trisomy 21. The AUC for both variables were 0.976 (MMN) and 0.987 (PFSR), respectively (Fig. 5).

In euploid fetuses we found no correlation between gestational age and the MMN angle (Pearson r = 0.06, P = 0.12) and PFSR (r = 0.45, P = 0.20). A slight increase in MMN values with advancing GA in Down syndrome fetuses was observed (Pearson r = 0.27, P = 0.04) exclusively when assessed in early second trimester. Again, no correlation between PFSR and GA in trisomy 21 cases could be demonstrated (r = −0.02, P = 0.46).
Discussion

In our study on 3D volume data sets of mid-trimester fetuses, we were able to demonstrate significant differences in craniofacial anatomy in euploid and trisomy 21 fetuses. These changes in craniofacial architecture of individuals with Down syndrome are confined to midfacial hypoplasia. However, there are other changes that often are not postnatally as well, such as narrow nasal airways, macroglossia, glossoptosis, tonsil and adenoid hypertrophy, and increased collapsibility of the upper airway [12, 13]. In fact, hypoplasia of the midface in addition to other well-described structural markers has been confirmed to be a common prenatal feature of trisomy 21 fetuses. The main morphological determinant is a hypoplastic and dorsally retracted maxilla present as early as the first trimester [2, 14, 15]. Based on both the dorsal displacement of the maxilla and the observation that prenasal thickness is above the 95th percentile in > 70% of mid-trimester Down syndrome fetuses [16], the prefrontal space ratio (PFSR) has been introduced as a highly effective tool incorporating both variables [10]. In this regard the predictive value of another marker for trisomy 21, namely the prenasal thickness-to-nasal bone length ratio (PT-NBL), has recently been confirmed in high-risk [17, 18] and low-risk prenatal populations [19].

The novel maxilla-mandible-nasion angle (MMN) proved to be a valid and useful tool in the rapid assessment of craniofacial integrity as this measure yields valuable information taken from 2 independent reference lines (FPL and MML).

As our data suggest, an acute MMN (mean: 14.6 °, SD: 2.30) appears to be predictive of midfacial hypoplasia found in 41/42 trisomy 21 fetuses compared to normal fetuses having a mean MMN value of 20.5 (SD: 1.33). The significantly lower PFSR in Down syndrome fetuses (mean: 0.53; SD: 0.21) compared to euploid controls (mean: 1.38; SD: 0.29) in our study is consistent with the observations made in previous studies using either 3D volumes [10] or 2D images [20]. According to recent data, we were able to reproduce the robustness of the PFSR in Down syndrome risk assessment irrespective of gestational age [21]. Despite a slight increase of MMN in trisomic fetuses during the early second trimester, this measurement remained stable below the 5th percentile in all affected fetuses.

As previously published, the FPL is reported to be always zero in euploid fetuses (FPL traverses the frontal bone lengthwise) until 27 gestational weeks. It was therefore reasonable to implement this line in PFSR calculation as described. Recent data provided by Vos et al. suggest that in second and particularly in third trimester Down syndrome fetuses a positive FPL could be noticed [22]. However, in our study none of the trisomy 21 fetuses had forehead anomalies corresponding to a positive FPL. Yazdi et al. found that the MML course behind the prenasal skin in a considerable number of Down syndrome cases which is potentially predictive of fetal aneuploidy in the second and third trimester [20]. Recently, the same group reported significant differences between euploid and aneuploid fetuses (including trisomy 21, 18 and 13) regarding the frontal space assessed at 11–13 gestational weeks and the impact on first-trimester combined aneuploidy screening [23]. In contrast to the described MMN angle having its vertex on the anterior edge of the mandible, the previously described MMN (between 2 lines originating from the nasion and tracing the anterior borders of the mandible and the maxilla, respectively) [24] is found to be a weak DS marker as less than 25% of trisomy 21 fetuses had abnormal values [22].

There have been a number of publications dealing with the potential superiority of 3D vs. 2D-based studies on facial integrity in normal and aneuploid fetuses [25–28]. It has been shown that the facial maxillary angle is significantly larger when assessed via a three-dimensional approach. Similarly, nasal bone length measured in an exact midsagittal plane is proven to be significantly smaller [28]. Recently, a study on 105 fetuses demonstrated that the maxilla-nasion-mandible angle (MMN) calculated on 2D images was significantly larger than on 3D images [29]. In terms of the ability to sufficiently discriminate between euploid and Down syndrome fetuses, neither assessment of the MMN angle nor all other markers analyzed in this study revealed statistically significant differences when measured on two- or three-dimensionally acquired images (data not shown). However, three-dimensional multiplanar confirmation of a true midsagittal section was thought to be mandatory in our study in order to provide precise and reliable values of MMN and to preclude parasagittal shifting.

The study has several limitations including the retrospective design and the fact that the measurements were made by a single operator not blinded to the fetal karyotype.

In conclusion, the present study demonstrates that combining the advantages of both the FPL and the mandibulo-maxillary line using identical midsagittal sonographic planes of the fetal profile offers the opportunity to rapidly detect 2nd trimester fetuses (from 14 completed weeks onwards) at risk for trisomy 21 (assessed by the novel MMN angle). Regardless of the recent advances in noninvasive prenatal testing utilizing cell-free fetal DNA, this is still an important issue during targeted ultrasound and subsequent prenatal counseling [30].

The reliability of MMN angle assessment to identify other fetal conditions influencing craniofacial integrity (e.g., micrognathia, facial clefting) has to be established in future studies.

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