Ultrasonography of the fetal nose, maxilla, mandible and forehead as markers for aneuploidy

Vos, Fedia

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CHAPTER 8

Fetal facial profile markers in second and third trimester fetuses with Edwards syndrome

Vos FI, de Jong-Pleij EA, Bakker M, Tromp E, Manten GT, Bilardo CM

ABSTRACT

Objectives
To evaluate the nasal bone length (NBL), the maxilla-nasion-mandible (MNM) angle, the fetal profile (FP) line, the prenasal thickness (PT), the prenasal thickness to nasal bone length (PT-NBL) ratio and the prefrontal space ratio (PFSR) as second and third trimester markers for Edwards syndrome (also known as trisomy 18).

Methods
The NBL, MNM angle, FP line, PT, PT-NBL ratio and PFSR were measured retrospectively in stored 2D pictures or 3D volumes corrected to the midsagittal plane of fetuses with Edwards syndrome (ES). Data were collected from March 2007 to January 2014. Measurements were performed by 2 examiners and compared to previously reported normal ranges. Additional ultrasound findings (markers, structural anomalies, IUGR) were noted, specifying whether they were detected at the initial routine second trimester scan or at the subsequent advanced ultrasound examination after referral for karyotyping.

Results
43 ES fetuses were included. Median maternal age was 37 years and median gestational age 21+2 weeks. NBL and PT were correlated to gestational age (p < 0.001), the other markers were not. The mean NBL, MNM angle, PT, PT-NBL ratio and PFSR were 3.76, 16.67, 4.25, 1.39 and 0.87, respectively. The FP line was zero (normal) in 53.7% of cases and negative (abnormal) in 46.3%. All markers were significantly correlated to ES. In the detection rate for ES, the PT-NBL ratio yielded the highest detection rate (88.4%), followed by the NBL (83.7%), MNM angle (56.4%), FP line (46.3%), PT (27.9%) and the PFSR (20.5%). The false positive rate was 5%, except for the FP line, where it was 0%. Various combinations of the 4 best markers (NBL, FP line, MNM angle and PT-NBL ratio) yielded detection rates ranging between 90% and 95%. No structural anomalies were detected in 22% of fetuses at the initial scan and in 2% at the advanced scan.

Conclusions
The PT-NBL ratio and NBL are strong second and third trimester markers for ES. A negative FP line has a 0% false positive rate and the potential to differentiate between ES and Down syndrome, as in the latter the FP line is often positive. No major anomaly was observed at the initial scan in about 1/4 fetuses, underlining the role of second trimester facial marker evaluation.
INTRODUCTION

After trisomy 21, commonly known as Down syndrome (DS), Edwards syndrome (ES; also known as trisomy 18) is the second most common autosomal trisomic disorder in live born babies. The prevalence of live born ES babies varies between countries from 1.0 per 10,000 registered births in 2003 – 2007 in the UK, to 2.66 between 2004 – 2006 in the USA. As the risk of fetal loss is high (72% at 12 weeks gestation and 65% at 18 weeks) and termination of pregnancy is carried out in a large percentage of affected pregnancies (83% – 86%), the number of affected pregnancies is much higher (an estimated 6.5 in 10,000 registries) than recorded live births.

In the late first trimester, the combined test is used, next to DS screening, as screening for ES, providing individual risk calculations in pregnancy. Not all women undergo this early form of aneuploidy screening, with wide differences in uptake reported across Europe, varying from 90% in Denmark and France to 20% and 32% in parts of England and The Netherlands, respectively. This means that a substantial group of ES fetuses remains undetected until the routine 20-weeks scan. In the Netherlands, more than 90% of the pregnant population undergoes this routine anomaly scan. Some of the major and minor structural anomalies associated with ES can already be observed in the first trimester. However, the sensitivity of ultrasound examination is higher at the time of the 20-weeks scan. Among other anomalies, typical subtle ultrasound features, located in the head and neck region are reported in ES fetuses. These are: absent/hypoplastic nasal bone, thickened nuchal fold, abnormal facial features (micrognathia, flat profile, sloping forehead), abnormal shape of the skull, and micrognathia. We have previously investigated the performance of the profile markers nasal bone length (NBL), maxilla-nasion-mandible (MNM) angle, fetal profile (FP) line, prenasal thickness (PT), prenasal thickness to nasal bone length (PT-NBL) ratio and prefrontal space ratio (PFSR) in euploid and DS fetuses.

Aim of this retrospective study is to investigate the performance of the same markers in ES fetuses.

METHODS

All cases where ES was suspected and later diagnosed at the mid trimester scan or at later scans, were selected from the databases of the University Medical Centre Groningen, of the University Medical Centre Utrecht and of the Saint Antonius Hospital in Nieuwegein, which act as referral centers. Databases of the participating centers were searched for good quality 3D volumes and 2D images of ES cases from Caucasian parents (as our population was mainly Caucasian). Images were acquired in the second and third trimester, between March 2007 and January 2014. All diagnoses were confirmed by karyotyping (pre- or postnatally).

Only true midsagittal pictures of the fetal profile were selected and considered for further analysis; we considered as such profile pictures showing the forehead, nose, lips and chin, the maxilla as a single horizontal line without zygomatic bone. Pictures with a visible zygomatic bone or ramus of the mandibula were excluded. Volumes were acquired during periods of quiescence from
fetuses facing the transducer, starting from as close as possible to the exact mid-sagittal profile view and with an insonation angle of less than 45° with respect to the nasal bone.

The NBL, PT, PT-NBL ratio, MNM angle, FP line and PFSR were measured as described in our previous studies\textsuperscript{23-27} (Figure 1).

Figure 1 | Ultrasound images of the markers in T18 fetuses, except for the fetus in image c, which is euploid. (a) FP line position ‘zero; (b) FP line position ‘negative; (c) FP line position ‘positive; (d) MNM angle; (e) NBL (A), PT (B), PT-NBL ratio (B/A), PFSR (C/B); (f) 3D reconstruction of T18 fetus. FP, fetal profile; MNM, maxilla-nasion-mandible; NBL, nasal bone length; PT, prenasal thickness; PFSR, prefrontal space ratio.
The FP line was defined as the line that passes through the middle point of the anterior border of the mandible and the nasion. The nasion was defined as the most anterior point in the junction between the frontal and nasal bones. When the FP line passed lengthwise through the frontal bone, this was called ‘zero’ (Figure 1,a). When the FP line passed the frontal bone anteriorly its position was called ‘negative’ (Figure 1, b). When the FP line passed the frontal bone posteriorly, its position was called ‘positive’ (Figure 1, c). The MNM angle was defined as the angle in the median plane between the lines maxilla-nasion and mandible-nasion (Figure 1, d). NBL was measured from the nasion to the end of the white distal ossification line (Figure 1, e A). In cases in which there was a gap between the nasal and the frontal bones (disjunction), the NBL was measured from the distal to the proximal end of the ossification line. To measure the PFSR, first the maxilla-mandible line was drawn between the midpoint of the anterior edge of the mandible and the anterior edge of the maxilla. The line was then extended cranially towards the forehead. Subsequently, the skin covering the forehead was measured between the anterior edge of the bony forehead and the anterior edge of the skin in a line that is parallel to the maxilla and that is traced from the nasion. This measurement is called the prenasal thickness (PT, Figure 1, e B). A second measurement d (Figure 1, e C), was taken starting from the anterior edge of the skin (where PT ended), to the point of interception with the MM line. The PFSR was determined by dividing d by PT. The PT-NBL ratio was constructed by dividing PT by NBL. All markers were measured in the same plane.

All ultrasound examinations were performed by experienced sonographers and images were obtained by a General Electric Voluson 730 Expert ultrasound or E8 system equipped with a RAB4-8L probe (GE Medical Systems, Kretz Ultrasound, Zipf, Austria).

For assessing reproducibility, all markers were measured by two examiners in all cases (F.I.V. and E.J.P.), who were blinded to gestational age and to previous measurements, but not to karyotype. Data were compared to the reference values derived from previous reports on euploid fetuses\(^23-25,27\): the NBL and PT increased with gestation from 3.3 mm at 15 weeks’ gestation to 9.6 mm at 33 weeks (NBL = -6.927 + (0.83*GA)-(0.01*GA\(^2\))) and from 2.3 mm at 15 weeks to 6.1 mm at 33 weeks (PT = 0.212 × GA – 0.873), respectively. The MNM angle, PT-NBL ratio and PFSR were stable throughout gestation, with a mean of 13.5 degrees (95\(^{th}\) percentile = 16.9), 0.61 (95\(^{th}\) percentile = 0.80) and 0.97 (5\(^{th}\) percentile = 0.55), respectively. Measurements below the 5\(^{th}\) percentile (for NBL and PFSR) or above the 95\(^{th}\) percentile (for MNM angle, PT, and PT-NBL ratio) of the reference ranges, were considered abnormal. An FP line that was not ‘zero’, was considered abnormal\(^26,28\). Multiple of the Median (MoM) values were created for the PT and NBL, in order to correct for gestational age.

In all cases, intraclass correlation coefficients (ICC’s) were calculated to analyze intra- and interobserver variability. The students t-test was used to analyze differences between measurements. A p-value of less than 0.05 was considered statistically significant. MoM values were calculated for gestation dependent markers. Data were analyzed using the statistical software SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA) and Excel for windows 2000.

Additional ultrasound findings such as markers\(^29\) and/or structural anomalies were documented, specifying whether they were described at the initial routine 20-weeks scan or during subsequent advanced morphological ultrasound examination after referral for karyotyping.
RESULTS

A total of 45 ES cases were available for analysis (6 on stored 3D volumes, 39 on stored 2D images). Median maternal age was 37 (range 26 – 46) years, and median gestational age 21\(^{+}2\) (range 14\(^{+}5\) – 31\(^{+}5\)) weeks. Two cases were excluded because the profile view was not midsagittal. In 2 cases, the fetal mandible was not optimally visualized, and consequently the FP line, MNM angle and PFSR could not be analyzed. In another case, the maxilla was not optimally visualized and in another case the fetus had an oro-facial cleft, therefore the MNM angle and PFSR could not be measured. All markers could be successfully measured in the same fetus in 39 cases.

The intra- and inter-observer variability of the measurements is presented in table 1.

Table 1 | Intra- and interobserver variability in ES fetuses.

<table>
<thead>
<tr>
<th>Intraobserver variability</th>
<th>Interobserver variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean difference (SD, 95% CI)</td>
<td>Mean difference (SD, 95% CI)</td>
</tr>
<tr>
<td>NBL</td>
<td>-0.17 (0.59, -0.4 – 0.1)</td>
</tr>
<tr>
<td>MNM angle</td>
<td>-0.54 (0.24, -1.9 – 0.8)</td>
</tr>
<tr>
<td>FP line</td>
<td>*</td>
</tr>
<tr>
<td>PT</td>
<td>-0.09 (0.40, -0.2 – 0.1)</td>
</tr>
<tr>
<td>PT-NBL ratio</td>
<td>-0.05 (0.28, -0.1 – 0.2)</td>
</tr>
<tr>
<td>PFSR</td>
<td>-0.01 (0.24, -0.1 – 0.1)</td>
</tr>
</tbody>
</table>

CI, confidence interval; ICC, intraclass correlation coefficient; NBL, nasal bone length; MNM, maxilla-nasion-mandible; FP, fetal profile; PT, prenasal thickness; PFSR, prefrontal space ratio. * As the outcome of the FP line was not continues (negative, zero or positive), it was not possible to calculate mean differences.

The mean (+- SD) NBL, MNM angle, PT, PT-NBL ratio and PFSR were 3.76 (1.62), 16.67 (3.61), 4.25 (1.33), 1.39 (1.00) and 0.87 (0.40), respectively. The nasal bone was absent in 3 (7.0%) cases. The FP line was negative in 46.3% of cases, zero in 53.7%, and in no case positive. The MNM angle, FP line, PT-NBL ratio and PFSR did not change significantly with gestational age, whereas NBL and PT were significantly correlated with gestational age (p < 0.001). All markers were correlated with ES. All showed a p-value below 0.001, except for the PSFR (p = 0.044).

The detection rate (DR), false-positive rate (FPR), positive likelihood ratio and negative likelihood ratio of all markers are shown in table 2.
Table 2 | The performance of the NBL, MNM angle, FP line, PT, PT-NBL ratio and PFSR.

<table>
<thead>
<tr>
<th>Marker</th>
<th>DR (95% CI)</th>
<th>FPR (95% CI)</th>
<th>PLR (95% CI)</th>
<th>NLR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NBL (mm)</td>
<td>83.7% (68.6% – 93.0%)</td>
<td>5.0% (1.7% – 11.3%)</td>
<td>16.7 (7.0 – 39.6)</td>
<td>0.17 (0.09 – 0.35)</td>
</tr>
<tr>
<td>MNM angle (degrees)</td>
<td>56.4% (38.3% – 71.4%)</td>
<td>5.0% (1.7% – 11.3%)</td>
<td>11.3 (4.3 – 27.2)</td>
<td>0.46 (0.33 – 0.67)</td>
</tr>
<tr>
<td>FP line</td>
<td>46.3% (29.3% – 61.5%)</td>
<td>0% (0% – 3.7%)</td>
<td>∞ (0.42 – 0.73)</td>
<td>0.54 (0.42 – 0.73)</td>
</tr>
<tr>
<td>PT (mm)</td>
<td>27.9% (13.9% – 42.0%)</td>
<td>5.0% (1.7% – 11.3%)</td>
<td>5.6 (1.9 – 14.2)</td>
<td>0.76 (0.65 – 0.94)</td>
</tr>
<tr>
<td>PT-NBL ratio</td>
<td>88.4% (74.4% – 96.0%)</td>
<td>5.0% (1.7% – 11.3%)</td>
<td>17.7 (7.4 – 41.7)</td>
<td>0.12 (0.05 – 0.29)</td>
</tr>
<tr>
<td>PFSR</td>
<td>20.5% (9.6% – 37.3%)</td>
<td>5.0% (1.7% – 11.3%)</td>
<td>4.1 (1.5 – 12.1)</td>
<td>0.84 (0.70 – 0.99)</td>
</tr>
</tbody>
</table>

NBL: nasal bone length, MNM angle, maxilla-nasion-mandible angle; FP line, fetal profile line; PT; prenatal thickness; PT-NBL ratio; prenatal thickness to nasal bone length ratio; PFSR; prefrontal space ratio; DR; detection rate; FPR; false positive rate; PLR; positive likelihood ratio, NLR; negative likelihood ratio, ∞; infinity.

Of the six markers, the PT-NBL ratio had the best screening performance with a DR of 88%, followed by the NBL with a DR of 84%.

There was no case in which the 6 markers were all normal or all abnormal. In all cases at least 1 of the six markers was abnormal. Various combinations of the 4 strongest markers (NBL, FP line, MNM angle and PT-NBL ratio) yielded similar DR’s ranging between 90% and 95% (Table 3).

Table 3 | Detection rates of various combinations of ES markers.

<table>
<thead>
<tr>
<th>NBL and other markers</th>
<th>NBL</th>
<th>FP line</th>
<th>MNM angle</th>
<th>PT-NBL ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>NBL</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FP line</td>
<td>90%</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MNM angle</td>
<td>95%</td>
<td>72%</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>PT-NBL ratio</td>
<td>93%</td>
<td>93%</td>
<td>93%</td>
<td>X</td>
</tr>
</tbody>
</table>

NBL: nasal bone length, MNM angle, maxilla-nasion-mandible angle; FP line, fetal profile line; PT-NBL ratio; prenatal thickness to nasal bone length ratio

When MoM NBL, MNM angle, FP line, MoM PT, PT-NBL ratio and PFSR were compared, the PT-NBL ratio was significantly correlated to MoM NBL and MoM PT (p < 0.01). The MNM angle was correlated to the FP line and PFSR (p = 0.015 and p < 0.01, respectively). Gestational age at the time of detection did not influence DR in any of the markers, with the exception of PT, where DR was significantly higher with advancing gestation (p < 0.01). Figures 2-7 show the six individual markers plotted against their normal ranges throughout gestation23-27.
Figure 2-7 | NBL (n = 43), FP line (n = 41), MNM angle (n = 39), PT (n = 43), PT-NBL ratio (n = 43) and PFSR (n = 39) in ES fetuses, plotted on normal ranges²⁴,²⁶,²⁷ (mean, 5th centile and 95th centile).

NBL: nasal bone length, MNM angle, maxilla-nasion-mandible angle; FP line, fetal profile line; PT; prenasal thickness, PT-NBL ratio; prenasal thickness to nasal bone length ratio, PFSR; prefrontal space ratio,
Table 4 | Abnormal ultrasound findings in T18 fetuses at initial and advanced second trimester ultrasound scan. Nuchal fold: > 5 mm before 20 weeks GA and > 6 mm over 20 weeks GA. Renal pyelectasis: 5 – 10 mm in the second trimester and 10 – 15 mm in the third trimester. Short humerus: below the 5th percentile, growth restriction: below the 5th percentile.

<table>
<thead>
<tr>
<th>Soft markers(^a) and abnormal findings (besides profile markers)</th>
<th>Initial 20-weeks scan ((n = 27))</th>
<th>Advanced scan ((n = 43))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Choroid plexus cyst</td>
<td>44%</td>
<td>70%</td>
</tr>
<tr>
<td>2. Single umbilical artery</td>
<td>26%</td>
<td>33%</td>
</tr>
<tr>
<td>3. Short femur</td>
<td>11%</td>
<td>12%</td>
</tr>
<tr>
<td>4. NF</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>5. Overlapping fingers</td>
<td>7%</td>
<td>60%</td>
</tr>
<tr>
<td>6. Renal pyelectasis</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>7. Echogenic bowel</td>
<td>-</td>
<td>7%</td>
</tr>
<tr>
<td>8. Clinodactyly</td>
<td>-</td>
<td>5%</td>
</tr>
<tr>
<td>9. Echogenic intracardiac focus</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10. Short humerus</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11. Other</td>
<td>4%</td>
<td>26%</td>
</tr>
</tbody>
</table>

Structural anomalies

<table>
<thead>
<tr>
<th>Structural anomalies</th>
<th>Initial 20-weeks scan ((n = 27))</th>
<th>Advanced scan ((n = 43))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Heart</td>
<td>52%</td>
<td>77%</td>
</tr>
<tr>
<td>2. Growth restriction</td>
<td>11%</td>
<td>37%</td>
</tr>
<tr>
<td>3. Skeletal (including facial cleft and anomalies of the feet)</td>
<td>7%</td>
<td>67%</td>
</tr>
<tr>
<td>4. Central Nervous system</td>
<td>7%</td>
<td>35%</td>
</tr>
<tr>
<td>5. Chest</td>
<td>7%</td>
<td>16%</td>
</tr>
<tr>
<td>6. Abdomen</td>
<td>7%</td>
<td>16%</td>
</tr>
<tr>
<td>7. Genitourinary</td>
<td>-</td>
<td>9%</td>
</tr>
<tr>
<td>8. Cystic hygroma</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Average number of soft markers observed: 1.4  
Average number of structural anomalies observed: 0.9  
≥ 1 soft marker: 100%  
No structural anomaly observed: 22%  

Table 4 shows the percentage of ES fetuses showing abnormal features (markers other than profile markers, pathological conditions or structural anomalies) at the initial ultrasound scan and at the advanced ultrasound examination at the referral center. It was not possible to retrieve data of the initial scan in all fetuses. In this cohort a mean of 1.4 ‘soft’ ultrasound markers or other abnormal
findings (such as choroid plexus cyst or polyhydramnios) and 0.9 structural anomalies were observed at the 20-weeks scan and 2.6 soft markers and structural anomalies at the advanced referral scan (Table 4). All fetuses had at least one soft marker at both the initial 20-weeks scan and advanced scan. In 22% of fetuses no structural anomalies were observed at the initial 20-weeks scan compared to 2% at the advanced scan.

**DISCUSSION**

In this study we report for the first time of the use of profile markers already extensively investigated in DS, in another trisomy, namely ES. We show that the highest detection rate is obtained when the PT-NBL ratio (88%) is used, closely followed by the NBL (84%).

One of the main findings of this study is that in second trimester ES fetuses, the NBL is exceptionally small, even smaller than in DS. Nasal hypoplasia has been reported in several chromosomal disorders including DS, ES, T13 and Turner syndrome, of which DS is the most extensively investigated. A short nasal bone has been reported in about 53% of first trimester ES fetuses and in 67% of second trimester ES fetuses when combined with an enlarged nuchal fold. It is not surprising that markers taking into account micrognathia, such as the MNM angle and the FP line, have a better performance in ES than in DS.

This study indicates that nasal bone hypoplasia in ES seems to become more pronounced with advancing gestation. Growth restriction, a very common feature in ES, may be an explanation for this finding. Another common feature in ES is microgynathia. Microgynathia is also a common finding in triploidy and Turner’s syndrome and it is suggested to be associated with an abnormal karyotype in 66% of the cases when observed prenatally. It is not surprising that markers taking into account micrognathia, such as the MNM angle and the FP line, have a better performance in ES than in DS.

This is the first study investigating the MNM angle and the FP line in ES. Two other facial angles, the fronto-maxillary-facial (FMF) angle and the mandibulo-maxillary-facial (MMF) angle, are described by Borenstein in first trimester ES fetuses. The FMF angle reflects mid-facial hypoplasia and the MMF the relationship between mandible and maxilla. The DR of the MMF angle in ES (33%) is lower than the DR of 56% of the MNM angle, reported in this study (at 5% FPR). However, The MNM angle has a wide standard deviation and a high inter- and intraobserver-variability. A negative FP line is caused by microgynathia and/or a sloping forehead, both common in ES. In this cohort we found a negative FP line in 46% of cases. This is a modest DR compared to NBL and PT-NBL ratio. The additional value of this marker in ES is the fact that the FP line is never negative in euploid fetuses, implying a 0% FPR. Moreover, DS fetuses show more frequently a positive FP line. Hence, in the presence of nasal hypoplasia, a negative FP line of is suggestive of ES and a positive FP line of DS. Prenasal edema, a common feature in DS, is far less common in ES, as reflected by the poor performance of PT and PSFR. However PT did slightly improve the DR of NBL when combined in a ratio.

The PFSR is a marker taking into account the position of the mandible and prenasal thickening. Microgynathia increases the PFSR value, however prenasal thickening reduces it (as it is the case in DS). The DR of the PFSR in ES was 21% (PFSR value below the 5th percentile). We therefore
hypothesize that in ES fetuses, the effect of micrognathia on the PFSR may be counterbalanced by
the presence of prenasal thickening.

In reporting additional ultrasound findings in this cohort we make a distinction between
findings observed at the initial (usually routine) second trimester ultrasound examination, and
findings at the advanced ultrasound examination carried out by Fetal Medicine experts after referral.
In women who did not undergo first trimester screening, a systematic evaluation of facial markers
at the 20-weeks scan may alert the ultrasonographer about a possible aneuploidy, especially when
obvious structural anomalies are not observed. This is substantially different than when (subtle)
anomalies are observed when there is already a suspicion of aneuploidy that has warranted referral
to a Fetal Medicine Unit.

At the routine 20-weeks scan, an average of 1.4 soft markers and abnormal findings—mostly
choroid plexus cysts (CPC) and single umbilical artery—and 1 structural anomaly were seen.
Interestingly, next to congenital heart disease and major skeletal defects, CPC and overlapping
fingers were the most frequently observed minor anomalies at the advanced ultrasound examination
(70% and 60%, respectively). Overlapping fingers are highly associated with ES, in contrast to CPC
(as an isolated finding). In almost 1/4 ES fetuses, no major anomaly was observed at the initial
scan. This strengthens our belief that there may be a role for the systematic and routine evaluation
of facial markers at the 20-weeks scan. In fact, in our experience, even women who have declined DS
screening value to be informed about the chance of their fetus to be affected by a lethal condition,
such as ES.

A limitation of this study is its retrospective nature and the fact that examiners were not blinded
to the karyotype. Ideally, a repeatability and reproducibility study should be performed not only by
re-measuring ultrasound markers on stored pictures, but also by re-acquiring the desired image.
Due to the retrospective nature of this study the latter was not possible, and the reproducibility
figures therefore relate exclusively to the reproducibility of the measurement. Furthermore, it was
not possible to retrieve data on additional ultrasound findings at the initial scan in all fetuses.

In conclusion, this study shows that when at second trimester ultrasound gross anomalies are
not observed, ES can be can effectively detected by the combination of markers for micrognathia
(MNM angle and FP line) and by a small nasal bone (NBL and PT-NBL ratio). We prefer a combination
of PT-NBL ratio and FP line; the PT-NBL ratio is in fact the strongest marker for ES (and DS), while
the FP line can differentiate between ES and DS. Furthermore, both markers are independent of
gestation and therefore a fixed cut-off can be used.
REFERENCES


