

Maxillary length in euploid and aneuploid fetuses

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Received: 1 September 2016 / Accepted: 24 November 2016 / Published online: 2 December 2016
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Abstract

Purpose To examine the maxillary length of euploid and aneuploid fetuses in the second and third trimester.

Methods Retrospective study utilizing stored 2D images of second and third trimester fetal profiles obtained at the University of Tuebingen, Germany. The length of the maxilla was measured as a straight line between the anterior ventral and posterior ventral edges of the maxilla.

Results The study population consisted of 347 euploid fetuses and 122, 36, 5, 8, and 4 fetuses with trisomy 21, 18, and 13, Turner syndrome, and triploidy. In the euploid and aneuploid group, mean gestational age was 22.3 and 22.7 weeks, respectively. The maxilla length in euploid fetuses was significantly dependent on gestational age and it was significantly shorter in fetuses with trisomy 21, 18, and 13, and triploidy but not in those with Turner syndrome. In 75.4 and 14.8%, and 11 fetuses with trisomy 21, the maxilla was below the mean, the 5th and 1st centile of the euploid population.

Conclusions In fetuses with trisomy 21, 18, and 13 and triploidy, the maxilla is significantly shorter, but the difference is only settled, so that it is unlikely that the maxilla length will play a role in second and third screening for aneuploidy.

Keywords Screening · Trisomy · Maxilla · Second trimester · Profile

Introduction

Prenatal screening for aneuploidy is most effective in the first trimester. However, ultrasound examinations later in pregnancy are likely to continue to play an important role in screening and detection of fetal aneuploidy [1]. Ultrasound findings that can be used to adjust the risk of aneuploidy can be broadly divided into two categories: fetal anomalies and soft markers. In order for these to be useful in screening, their prevalence must be different in the euploid and aneuploid populations [2].

In a meta-analysis of Agathokeous et al., the authors highlighted the relevance of an intracardiac echogenic focus, ventriculomegaly, an increased nuchal fold, echogenic bowel, hydronephrosis, a short femur and humerus, an abnormal right subclavian artery, and an absent or hypoplastic nasal bone in screening for trisomy 21. The presence or absence of each of these findings is incorporated into the screening protocol by transforming it into a likelihood ratio, which is then used to adjust the *á priori* risk. These can be used either to increase or decrease the risk, and if none of the markers are present, the risk can be reduced approximately eight times [3].

Recent research has focused on the fetal profile in screening for aneuploidy. It has been shown that in addition to the absence or presence of nasal bone, several other markers, such as the nasal bone length or the prenatal thickness, are abnormal in affected fetuses [4–6]. We have recently reported on the prefrontal space ratio which combines two facial characteristics of aneuploid fetuses: the dorsal displacement of the maxilla and the thickening

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of the prenasal skin [5]. The prefrontal space ratio was abnormal in about 80% of fetuses with trisomy 21 [5–7]. Others have measured the ratio between the prenasal thickness and the nasal bone length. This combination of markers was found to be abnormal in about 85% of the cases with trisomy 21 [6, 8].

Several radiological studies reported on oligodontia in individuals with trisomy 21. It has been demonstrated that the third molar tooth is missing in about three quarters of the adults with trisomy 21 with the maxilla being more often affected than the mandible [9–11]. One speculation is that the slow rate of cell growth in individuals with trisomy 21 may be responsible for underdevelopment of the maxilla.

Cicero et al. measured the length of the maxilla between 11 and 14 weeks' gestation and evaluated its utility in the first trimester screening for aneuploidy [12]. Even though the authors did find that the maxillary measurements in fetuses with trisomy 21 were shorter than in euploid fetuses, the difference was relatively small and, therefore, difficult to employ as a screening marker.

In our study, we set out to compare the maxillary length of euploid and aneuploid fetuses in the second and third trimesters.

Methods

This was a retrospective study utilizing stored 2D images of second and third trimester fetal profiles. The prenatal ultrasound examinations used in this study were performed at the Department of Prenatal Medicine at University of Tuebingen, Germany, between 2004 and 2016.

We searched our database for pregnancies with trisomy 21, 18, and 13, triploidy, and Turner syndrome and preferentially selected images of the fetal profile that were taken between 19 and 22 weeks' gestation. In those cases where there was no image available within this time period, we used an image from the first examination that was taken after 15 weeks' gestation. We randomly selected two euploid fetuses that were matched for gestational age with the aneuploid cases and where the image of the profile met criteria. Each fetus was only included once in this study. Some cases had been used in our previous studies dealing with the fetal profile [5, 13, 14]. Care was taken to only include images with a true midsagittal profile. Fetuses with a facial cleft or cases where the maxilla was not clearly visible were excluded from the further analysis.

The length of the maxilla was measured as a straight line between the anterior ventral edge of the maxilla to the posterior ventral edge. Figures 1 and 2 demonstrate the measurement of the maxilla in a euploid fetus and in a fetus with trisomy 21.



Fig. 1 Maxilla length in a euploid fetus



Fig. 2 Maxilla length in a fetus with trisomy 21

For the assessment of the intraoperator reproducibility, one operator (DG) measured the maxillary length twice in 50 cases. The remaining ones were measured once. The investigator was blinded towards his own results and towards the karyotype.

Statistical analysis

Intraobserver repeatability was examined using 95% limits of agreement. The normal range in euploid fetuses was computed based on gestational age by applying univariate regression analysis. Maxilla length measurements were transformed into z scores on the basis of the linear relationship with GA. The distributions in fetuses with trisomy 21, 18, and 13 were compared with the distribution in euploid groups using Student's *t* test after having verified that the distributions were normal by the Kolmogorov–Smirnov test.

For the assessment of the performance in screening for trisomy 21, we used an ROC curve analysis and compared the area under the curve of each of the examined models. We examined models based on maternal age with and without the addition of the maxilla length.

Differences were considered to be significant if the p value of less than 0.05 or there was no overlap between the respective 95% confidence intervals. The analysis was performed with Microsoft Excel for Mac 2011 (Redmond/WA, USA) and IBM SPSS23 (Armonk/NY, USA).

The study was approved by the local ethical committee (No 425/2016BO2).

Results

The study population consisted of 394 euploid and 197 aneuploid fetuses. Sixty-one (10.3%) cases were excluded from the further analysis as it was not possible to visualize the whole maxilla properly and another eight cases were excluded due to a facial cleft. Thus, there were 522 fetuses in this study: 347 euploid ones and 122, 36, 5, 8, and 4 fetuses with trisomy 21, 18, and 13, Turner syndrome and triploidy, respectively.

In the euploid group, mean maternal and gestational age was 32.0 (range 17.3–47.6) years and 22.3 (range 15.0–40.3) weeks' gestation, and in the aneuploid group, it was 35.3 (range 18.2–46.5) years and 22.7 (range 15.0–40.3) weeks, respectively. In 241 (46.2%) cases, the gestational age was between 19 and 22 weeks. In 158 (30.3%) and 123 (23.6%) cases, the gestational age was 23 weeks and more or 18 weeks and less, respectively.

The difference between the first and second measurements of the maxilla length was -0.012 cm, and in 95% of the cases, the differences between both measurements were within -0.12 and 0.10 cm.

Mean maxillary length in the euploid population was 1.84 cm and ranged from 0.92 to 2.91 cm (Fig. 3). The maxillary length was significantly dependent on gestational age (Maxilla length = $0.903 + 0.042 \times$ gestational age, $p < 0.0001$, $r = 0.610$). After transformation to z values, mean maxillary length was 0.0 (SD 1.0) (Table 1).

Maxillary length measurements of the chromosomal abnormal fetuses are summarized in Table 2 and Fig. 4. The maxillary length was significantly shorter in fetuses with trisomy 21 ($p = 0.001$), trisomy 18 ($p = 0.004$), trisomy 13 ($p < 0.0001$), and triploidy ($p < 0.001$), but not in those with Turner syndrome ($p = 0.122$), respectively.

In 18 (14.8%) and 11 (9.0%) fetuses with trisomy 21, the maxilla was below the 5th and 1st centile of the euploid population. In trisomy 18, there were 2 (5.6%) fetuses with a maxilla length below the 5th and 1st centile, respectively.

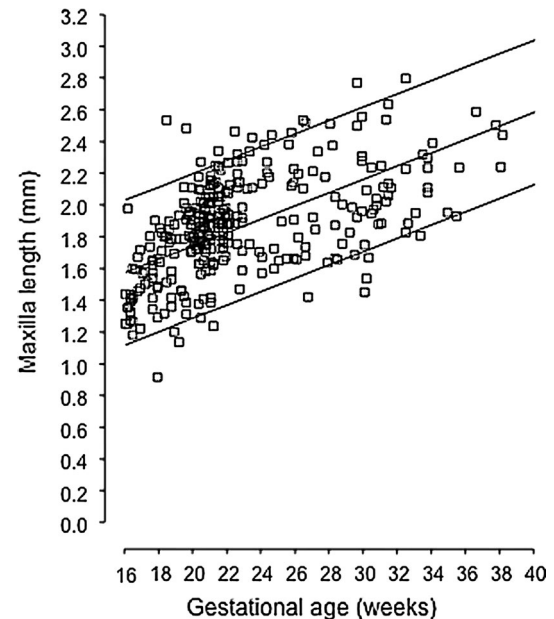


Fig. 3 Maxilla length in euploid pregnancies

Table 1 Maxillary length in euploid and aneuploid fetuses

	n	Absolute Mean (SD)	z values Mean (SD)
Normal	347	1.84 (0.35)	0.00 (1.00)
Trisomy 21	122	1.63 (0.35)	-0.71 (0.94)
Trisomy 18	36	1.79 (0.32)	-0.66 (0.96)
Trisomy 13	5	1.53 (0.47)	-1.30 (1.37)
Triploidy	4	1.17 (0.13)	-1.68 (0.47)
Turner	8	1.56 (0.38)	-0.55 (1.08)

The distribution of the other chromosomal abnormalities is summarized in Table 2 and Fig. 5.

Figure 6 shows the ROC curves in screening for trisomy 21 based on maternal age alone, and with the addition of the maxilla length. The area under the curve indicates that the addition of the maxilla length does not result in a significant improvement of the screening performance compared to maternal age alone [AUC MA 0.703 (95% CI 0.646–0.760), MA + maxilla length 0.729 (0.675–0.782)].

Discussion

This study demonstrates that fetuses with trisomy 21, 18, and 13, and triploidy have a significantly shorter maxilla in comparison to their euploid counterparts. However, the difference is relatively small, so it is unlikely that the maxillary length measurement will play a major role in second and third screening for aneuploidy.

Table 2 Maxilla length below the 1st and 5th centile of the euploid population

	<i>n</i>	Below mean <i>n</i> (%)	Below 5th centile <i>n</i> (%)	Below 1st centile <i>n</i> (%)
Normal	347	169 (48.7)	16 (4.6)	5 (1.4)
Trisomy 21	122	92 (75.4)	28 (23.0)	18 (14.8)
Trisomy 18	36	26 (72.2)	8 (22.2)	2 (5.6)
Trisomy 13	5	4 (80.0)	2 (40.0)	2 (40.0)
Triploidy	4	4 (100)	2 (50.0)	0 (0)
Turner	8	5 (62.5)	2 (25.0)	0 (0)

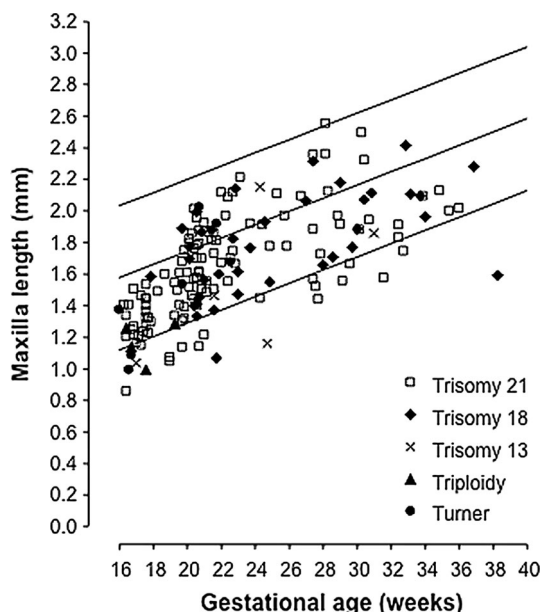


Fig. 4 Maxilla length in aneuploid pregnancies

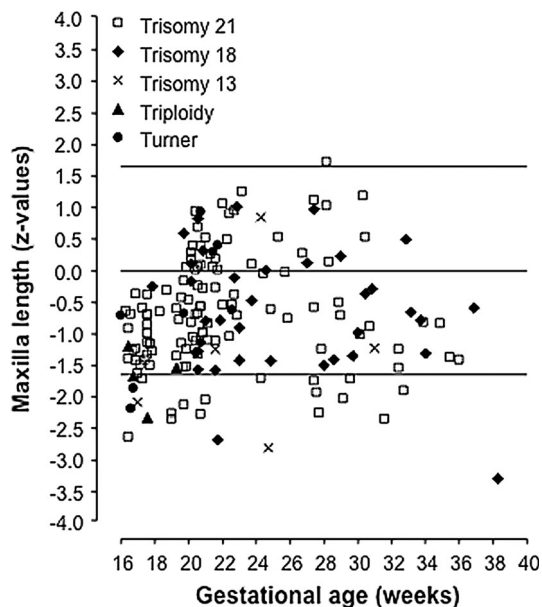


Fig. 5 Maxilla length in aneuploid pregnancies (*z* values)

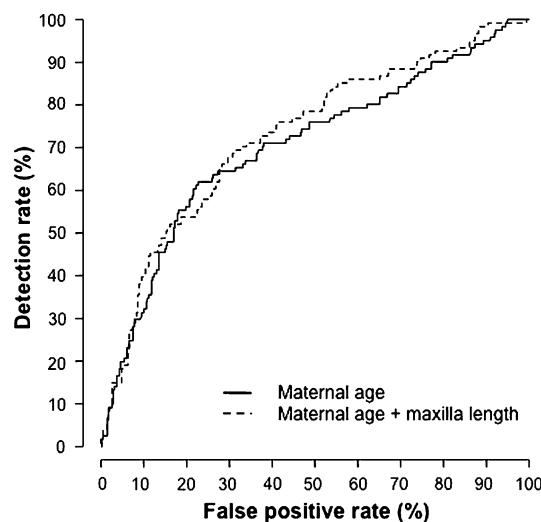


Fig. 6 ROC curves in screening for trisomy 21 based on maternal age with and without maxilla length

To the best of our knowledge, there are no previous studies focusing on the maxillary length in aneuploid pregnancies in the second and third trimesters of pregnancy. Hermann et al. used 3D ultrasound volumes to examine the length of the maxilla in euploid pregnancies between 11 and 26 weeks’ gestation [15]. In summary, they also found a linear relationship with gestational age, but their measurements were slightly larger than in our 2D study. Cicero et al. examined 839 euploid fetuses and 88 with trisomy 21 at 11–13 weeks’ gestation, and found that in 83% of the affected cases, the maxilla length was below the mean of the normal fetuses. In 24% of the cases, the measurements were below the 5th centile, respectively [12]. Daklis et al. also used 3D volumes and examined the maxillary depth (distance between the alveolus of the maxilla in the midline anteriorly and the midpoint of the line joining the rami posteriorly) at 11–13 weeks to assess the midfacial hypoplasia of trisomy 21 fetuses. The measurements were below the 5th centile in 10% of the affected cases [16]. In this respect, both studies are consistent with our results.

In a recent paper from Cossellu et al., the authors examined the spheno-frontal distance in 30 fetuses with

trisomy 21 and compared the results to 80 euploid fetuses using stored 3D volumes for both groups [17]. They found that in almost all of the affected cases, the spheno-frontal distance was below the 5th centile. One could hypothesize that both the spheno-frontal distance and the maxillary length are surrogate parameters for midfacial hypoplasia, which is a common finding in fetuses with trisomy 21. In this respect, it is surprising that our results differ substantially from the ones shown by Cosellu et al. However, in a recent paper from our group, we were not able to reproduce the good results previously shown by Cosellu et al. [14]. In our study, the spheno-frontal distance in fetuses with trisomy 21 was below the 5th centile in only about 25%. This result is in line with the results from this study dealing with maxillary length.

Numerous studies have been published that look at the effectiveness of prenatal ultrasound markers and fetal anomalies in screening for aneuploidy. In a meta-analysis of Agathokleous et al., the authors have summarized 48 of such studies and estimated the likelihood ratio for each of the commonly used markers [3]. The authors found that an echogenic focus in the left ventricle, ventriculomegaly, increased nuchal fold, echogenic bowel, mild hydronephrosis, short humerus and femur, aberrant right subclavian artery, and an abnormal nose bone was found in about 7.5–60% of the affected cases and in 0.2–6.4% of the euploid fetuses, respectively. Their meta-analysis suggested that the only markers that remain significant even as an isolated finding are ventriculomegaly, increased nuchal fold, an aberrant right subclavian artery, and an abnormal nasal bone with a combined positive likelihood ratio of 3.8–6.6.

More recent studies have focused on the fetal profile in screening for trisomy 21. Almost all research groups focused on the combination of facial markers that may reflect typical features of affected fetuses. Maymon et al. combined the prenatal thickness with the nasal bone length and detected 70% of fetuses with trisomy 21 [18]. Similarly, Vos et al. used the prenatal thickness-to-nose bone ratio and detected 86% of the affected fetuses for a false positive rate of 5% [6, 8]. Others have proposed to use the prefrontal space ratio, a marker that combines prenatal thickness and midfacial hypoplasia in fetuses with trisomy 21. The detection rates were about 80% for a false positive rate of 5% [5–7, 19]. Sonek et al. introduced the frontomaxillary angle, an angle between the top edge of the upper palate and the skin over the forehead. They reported a detection rate of almost 90% for a false positive rate of about 3% [4]. Unfortunately, other studies failed to reproduce these excellent results [20].

Compared to screening for aneuploidy with cell-free fetal DNA (cfDNA) with its detection and false positive rates of about 90–99% and 0.1%, the relevance of the

ultrasound markers could be questioned [21, 22]. However, at the present time, screening using cfDNA remains too expensive to be universally offered, so that in the foreseeable future, ultrasound markers will still play an important role in second and third trimester screening for chromosomal abnormalities.

Our study has some limitations. First, the study was performed retrospectively using stored 2D images, and second, the data were collected in a single center only. As the images were not initially taken for the purpose of the measurement of the maxilla, it was difficult to identify the posterior end of the maxilla in some cases. However, the reproducibility analysis indicates that a difference between two measurements was within an acceptable range.

In summary, the maxillary length in aneuploid fetuses is shorter than in their euploid counterparts. However, prenatal screening for trisomy 21 that combines maxillary length and maternal age is not significantly better than screening by maternal age alone. Therefore, it is unlikely that maxillary length will play an important role in screening for trisomy 21.

Compliance with ethical standards

Conflict of interest All authors declare that there is no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This is a retrospective study involving ultrasound images from patients that were seen at the University of Tuebingen, Germany. The study was approved by the local ethical committee. This is also stated in the Methods section.

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