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Prenatal intrauterine maxillary development — An evaluation with three-dimensional ultrasound

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ABSTRACT

Objectives: The aim of this prospective study was to investigate normal fetal maxillary development with volume ultrasound during the prenatal phase, for a better estimation of maxillary growth processes.
Methods: Some 210 3D volumes were obtained in two measurement series from 38 healthy women (gestational age: 19^{+2} to 31^{+4} weeks) using a GE Voluson™ E10 ultrasound system. Maxillary length and width were determined in the axial and sagittal planes. Clearly defined, reproducible landmarks were used for measurements. The results were correlated with gestational age and compared with previously reported studies.
Results: Total maxillary length ranged from 10.30 to 24.75 mm, total maxillary width from 13.65 to 37.30 mm in an observation period during the second trimester, with high reproducibility for all landmarks. All evaluation results showed steep growth with exponential character. Length growth was determined to be more dominant than width growth. Intra-rater correlation was evaluated to be almost perfect (ICC (3) > 0.8).
Conclusion: This study presents measurements of physiological fetal maxillary development. The defined landmarks proved to be representative for further investigations. This study serves as a baseline for a better understanding of fetal maxillary growth processes, and may be useful for standardising detection of malformations or intrauterine growth restrictions.

1. Introduction

Ongoing developments in sonographic equipment are steadily optimizing the prenatal assessment of anatomical facial structures and the detection of congenital malformations in the cephalic region. The use of 3D ultrasound offers additional diagnostic benefits compared with conventional 2D ultrasound. These include the simultaneous visualization of images in multiplanar mode, the capacity to evaluate stored volume in off-line mode, the use of render mode to visualize different components of the same structure, improvements in volume measurements, and the implementation of standardized examinations (Araujo Junior et al., 2015; Conner et al., 2014).

Routine prenatal sonographic examinations include the evaluation of facial structures, with a focus on the fetal profile, eyes, and upper lip. An index for prenatal recognition of retrognathia/micrognathia has been recently reported, highlighting the possibility to analyze facial bones more effectively than before (Neuschulz et al., 2015; Wilhelm and Braumann, 2012). However, the facial bones are much more difficult to visualize than soft tissue due to phase cancellations. By acquiring a 3D volume and using the multiplanar mode, standardized displaying of the osseous

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structures is possible, and can be simplified (Rubin et al., 1991; Vos et al., 2012). This technical process may also allow prenatal growth processes to be retraced and the development of facial bones to be evaluated.

Several studies have previously aimed to gain reference values or to investigate technical applications for evaluating facial structures (Koo et al., 2014; Neuschulz et al., 2015). Also, the appearance of normal and abnormal fetal maxillary bone anatomy has been examined, using a skeletal rendering mode and comparing the success rates of acquiring volumes in different gestational age groups (12th–40th weeks) (Zheng et al., 2015). Measurements of fetal maxillary length (11th–26th week) have been taken from stored volumes and compared with values for mandibular and biparietal diameter growth rates from earlier investigations (Hermann et al., 2015). Shyu et al. established a normal range of maxillary and mandibular length (weeks 11–13^{+6}) (Shyu et al., 2014), and Goldstein et al. defined a nomogram for maxillary bone length using 2D ultrasound (13th–40th week) (Goldstein et al., 2005). At present, standardized osseous maxillary landmarks, with appropriate growth curves, have not yet been established, although they would be highly relevant for retracing prenatal jaw growth processes.

The aim of our study was to obtain data for the growing maxilla, using volume ultrasound, and to create a representative growth curve for the fetal upper jaw in the second and third trimester, to serve as a potential base and reference for a better understanding of maxillary growth processes.

2. Material and methods

In this prospective study, only fetuses without malformations were included. Volumes were stored during routine second and third trimester examinations, up to the 32nd week of pregnancy, starting at week 19. All recordings and measurements were carried out by one highly experienced investigator (TE). Overall, two measurement series were obtained. The first one was taken after obtaining the volumes, while the second was performed as a remeasurement of the stored volumes.

To display 3D data volume, 'cross-sectional' mode was used to allow different cross–sectional planes (axial, sagittal, and coronal views) to be displayed. This so-called multiplanar imaging formed the basis for all scans in our study. The axial plane (*x*-plane) represented the original plane, while the sagittal (*z*) and coronal (*y*) planes were reconstructed from data for the axial plane. In the axial plane, the reference point (RP) used as a landmark for our measurements was situated halfway on the connecting line between the two tuber maxillae (Fig. 1). Data collection was performed using the *x*-plane and *z*-plane, but excluding the *y*-plane (Figs. 1 and 2). Measurements were performed without using volume contrast imaging (VCI) mode, to keep all images at the original picture quality. Therefore, a possible lower contrast resolution was acceptable.

Sonographic examinations were performed in all patients, using a GE Voluson™ E10 ultrasound system and a convex RM6C probe. An opening angle of 40–45° was used for volume acquisition in all examinations.

Measurements were categorized into 'successful' and 'erroneous'. Erroneous values were furthermore subcategorized into 'inaccurate' and 'nonviable' values. The term 'nonviable' defined measurements that would not be reproducible because of an absence of clearly defined anatomical facial structures. Successful and inaccurate results were all included; all nonviable results were excluded.

The following landmarks were defined on the axial scan (Fig. 1): papilla incisive (PI), dorsal edge tuber maxillae (DETM), reference point (RP; defined as halfway along the connecting line of the DETM),

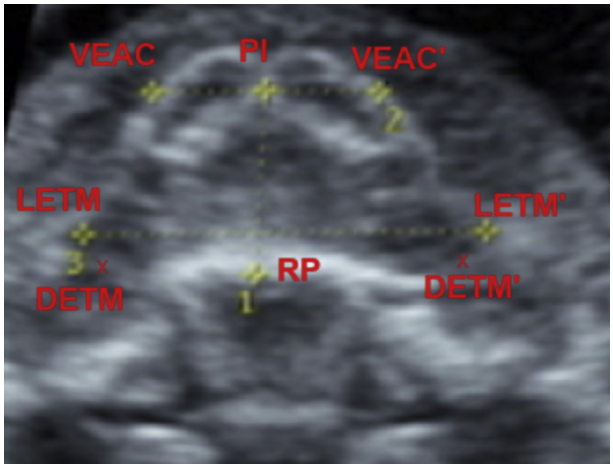

Fig. 1. Selected sonographic plane and landmarks on the alveolar ridge and hard palate. Axial scan (*x*-plane) of the fetal face, with defined landmarks, showing the maxillary bone at the level of the whole hard palate. Abbreviations: PI — papilla incisiva; VEAC — right vestibular edge on alveolar crest; VEAC' — left vestibular edge on alveolar crest; LETM — right lateral edge of tuber maxillae; LETM' — left lateral edge of tuber maxillae; RP — reference point; DETM — right dorsal edge of tuber maxillae; DETM' — left dorsal edge of tuber maxillae.

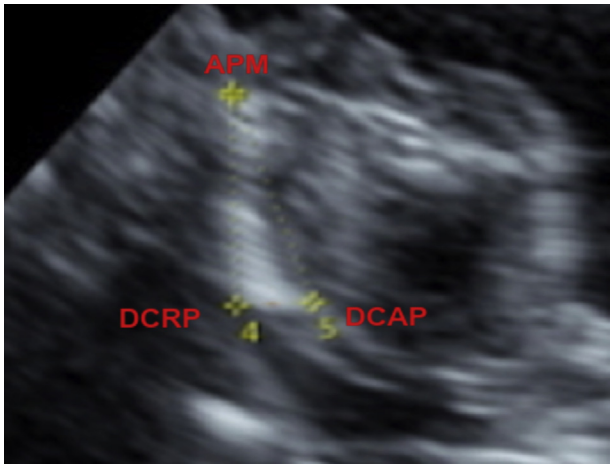

Fig. 2. Selected sonographic plane and landmarks on the maxilla in the sagittal plane. Sagittal scan (*z*-plane) of the fetal face, with defined landmarks, showing the maxillary bone at the level of the upper lip. Abbreviations: APM — most anterior point of the maxilla; DCRP — dorso-cranial edge of the hard palate; DCAP — dorso-caudal edge of the hard palate.

vestibular edge on alveolar crest (VEAC; at papilla incisiva level), and lateral edges of the tuber maxillae (LETM). The maxillary length was obtained by connecting the PI and the RP. The maxillary width was obtained by connecting VEAC and VEAC', and LETM and LETM'.

Three measurement distances were defined by the landmarks in the axial scan (Fig. 1):

- Distance 1: connection between the RP and the PI (MD_1)
- Distance 2: connection between the VEAC halfway point and the PI (MD_2)
- Distance 3: connection between the LETM halfway points and the RP (MD_3)

The following landmarks were defined in the sagittal scan (Fig. 2): most anterior point of the maxilla (APM), dorso-cranial edge of the hard palate (DCRP), and dorso-caudal edge of the hard palate (DCAP).

Table 1
Intrarater agreement analyses for each landmark by calculating an intrarater correlation coefficient, ICC (3, 1) and the 95% confidence interval. $n = 203$.

Variable	MD_1	MD_2	MD_3	MD_4	MD_5
ICC (%)	0.982	0.982	0.993	0.986	0.990
95% CI	0.967–0.991	0.967–0.991	0.986–0.996	0.975–0.993	0.981–0.995

Abbreviations: MD_1 — connection between the reference point and the papilla incisiva; MD_2 — connection between the vestibular edge on the alveolar crest halfway point and the papilla incisiva; MD_3 — connection between the lateral edges of the tuber maxillae; MD_4 — connection between the most anterior point of the maxilla and the dorso-cranial edge of the hard palate; MD_5 — Connection between the most anterior point of the maxilla and the dorso-caudal edge of the hard palate; ICC — intrarater correlation coefficient; 95% CI — 95% confidence interval.

Two measurement distances were defined by the landmarks in the sagittal scan (Fig. 2):

- Distance 4: connection between the APM and the DCRP (MD_4)
- Distance 5: connection between the APM and the DCAP (MD_5)

Prognostic relationships between gestational age and the measurements were evaluated by correlation. Pearson's correlation coefficients were determined to assess the strength of the relationships. A p-value <0.05 was considered to be statistically significant. Intrarater reliability was determined using intraclass correlation coefficients (ICCs). Two-way mixed single measures ICCs were performed according to the guidelines proposed by Shrout and Fleiss (Shrout and Fleiss, 1979). Collected data were analyzed using IBM SPSS 21.0 (released 2012; IBM Corp., Armonk, NY).

3. Results

In total, 210 valid measurement values were obtained over two measurement series from 42 fetuses (five measurements per fetus) in 38 healthy women, with four participants having a twin pregnancy. Evaluated intrarater correlation coefficients indicated excellent agreements between the two series of measurements by the investigator (Table 1).

The first series involved 185 successfully performed measurements, 18 inaccurate ones (including one pair of twins), and seven that were nonviable (MP_1–MP_5 in one embryo of a pair of twins, MD_3 in an axial scan, and MD_5 in a sagittal scan). The second series achieved 202 successful measurements, one inaccurate (not matching any of the 18 inaccurate measurements in the first measuring cycle), and five nonviable (MD_1–MD_5 in one embryo of a pair of twins, and MD_3 in an axial scan, all matching those found in the first series). MD_1 and MD_2 were carried out in all 38 patients, producing the lowest number of erroneous results (three erroneous values in each case in the first series, one erroneous result in the second). Descriptive statistics are shown in Table 2.

Inaccurate measurements occurred when distinction of the structures was unclear, whereas nonviable measurements were found especially in early or advanced pregnancy. All detected landmarks were intended to be reproducible in the registration process in every section plane, to guarantee that all measurements were as accurate as possible. There were limitations in this study due to technical and anatomical preconditions. Measurements were limited to up to week 31^{+4} of pregnancy due to a noticeable increase in shadowing, which was most evident with distance MD_3 and its SD. Similar difficulties occurred in identifying the landmarks LETM, APM, DCRP, and DCAP. The collection of data on the y-plane was deemed unsuitable due to a lack of reproducibility of the landmark position.

Longitudinal growth achieved the highest correlation results, which were also supported by a large effect size according to Cohen's d (MD_5, 0.90; MD_4, 0.85; MD_1, 0.80). Longitudinal and transverse correlations were highly statistically significant ($p < 0.001$) (Table 3) — a correlation over 0.7 was considered to be high (Mukaka, 2012).

A low number of outliners was noted for all reference distances. Most measurements were carried out between the 20th and the 22nd weeks of pregnancy. Residuals were normally distributed.

Longitudinal measurements showed the highest growth rates, but the measured increase in weekly maxillary growth was not statistically significant. However, from the beginning of the observation period to the end, calculated differences were statistically significant (Table 4).

During the observation period, total growth in length reached a maximum of 9.00 mm (MD_1), 10.15 (MD_4), and 10.15 mm (MD_5), with increases of 187% (MD_1), 175% (MD_4), and 169% (MD_5). Total width increased from 13.65 mm to 24.65 mm (MD_2) and from 19.30 mm to 34.30 mm (MD_3). Therefore, MD_1 (longitudinal growth) had increased the most among the analyzed distances. Fig. 3A–E represent growth curves for all parameters.

4. Discussion

To our knowledge, this is one of very few studies to have evaluated prenatal maxillary growth processes three-dimensionally, in

Table 2
Descriptive statistics for each variable — medium, standard deviation (SD), minimum, and maximum. $n = 205$.

Variable	MD_1	MD_2	MD_3	MD_4	MD_5	WOP
Median	12.62	16.57	24.12	16.95	17.57	21.35
SD	2.31	2.80	4.95	2.68	2.90	3.77
Minimum	10.30	13.65	19.30	13.50	14.60	19.2
Maximum	19.30	24.65	37.30	23.65	24.75	31.4

Abbreviations: WOP — week of pregnancy; SD — standard deviation.

Table 3
Pearson's correlation for all variables against gestational age.

Variable	MD_1	MD_2	MD_3	MD_4	MD_5	WOP
MD_1 PC	1	0.589*	0.445*	0.921*	0.921*	0.807*
		<0.000	<0.002	<0.001	<0.000	<0.000
MD_2 PC	0.589*	1	0.635*	0.673*	0.566*	0.756*
	<0.000		<0.000	<0.000	<0.000	<0.000
MD_3 PC	0.445*	0.635*	1	0.527*	0.456*	0.540*
	<0.002	<0.000		<0.000	<0.001	<0.000

*Correlation is considered to be statistically significant at $p < 0.01$.
Abbreviations: WOP — week of pregnancy; PC — Pearson correlation.

Table 4
Average growth rates and growth differences during the investigation period.

Variable	*MD_1*	*MD_2*	*MD_3*	*MD_4*	*MD_5*
Median (%)[a]	3.34	1.25	0.18	1.94	2.76
Difference (mm)	9.00	4.55	15.00	10.15	10.15
Sig.[b]	0.002	0.002	0.002	0.002	0.002

[a] Growth rate.
[b] Significance of calculated differences.

order to create a prenatal growth curve. Original-quality images were used without auxiliary modes for improving picture quality. However, the original data were automatically altered.

Abnormal development of the maxilla can be found among a wide range of genetic diseases and facial malformations, for example in maxillonasal dysplasia (Drozdowski et al., 2017), and cleft lip and palate (CLP) (Gopinath et al., 2017). New ultrasound techniques have the potential to improve prenatal detection of facial dysmorphism with a high sensitivity (Dall'Asta et al., 2017). Due to different published assessment techniques, it is difficult to

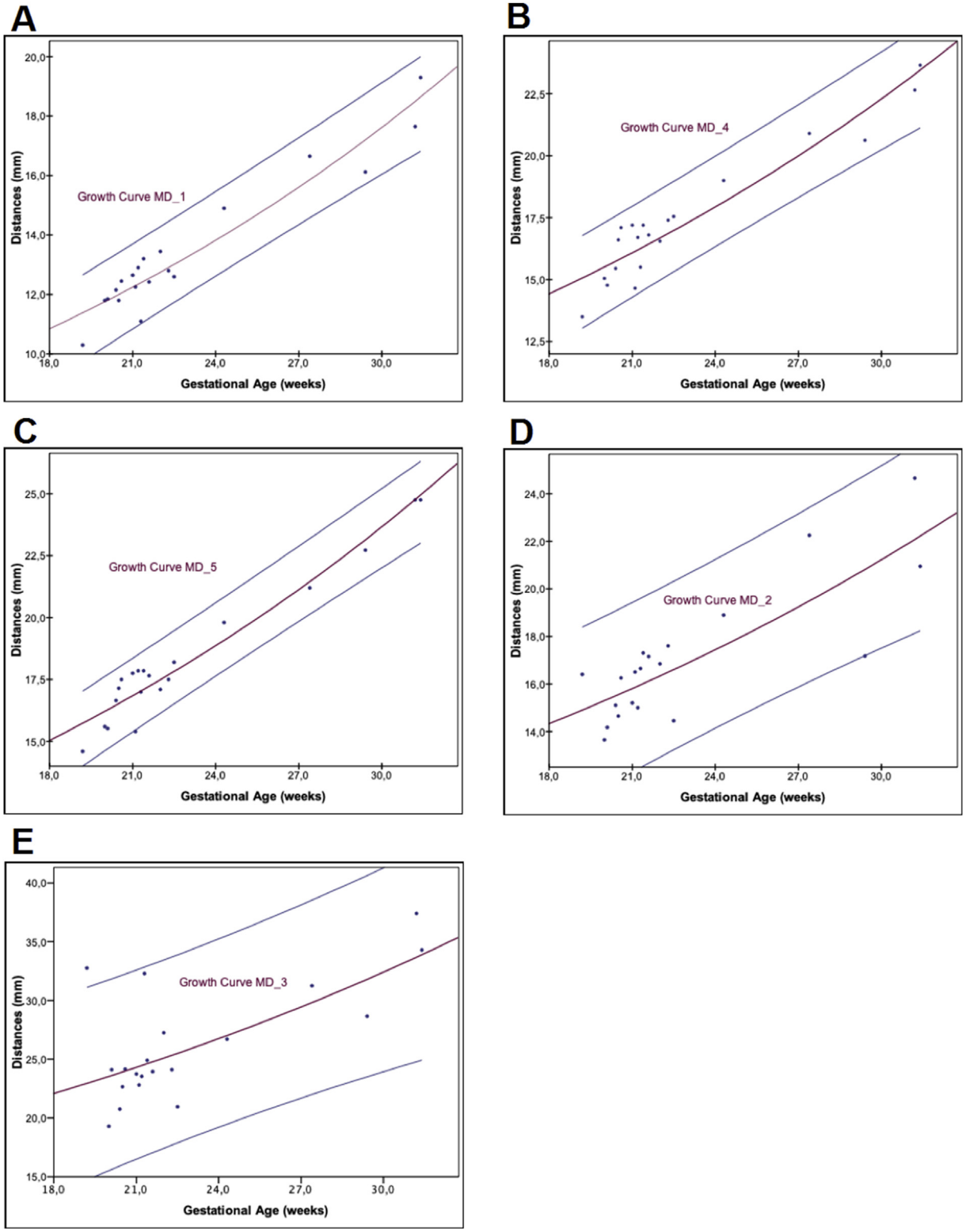

Fig. 3. Longitudinal (A–C) and transversal (D, E) growth curves. Relationship between longitudinal and transversal growth distances in mm and gestational age in weeks. Key: blue dots = values observed; purple lines = 95% confidence interval; red line = growth curves for longitudinal (A–C) and transversal (D, E) development.

make comparisons between the various findings. In order to supplement previously reported prenatal facial structures, our study focused on prenatal maxillary growth with special regard to establishing newly defined landmarks that were both useful and reproducible (Gopinath et al., 2017; Koo et al., 2014).

To increase the reproducibility, the defined insonation angle was set up as 40–45°, without using volume rendering mode for collection of data. To supplement preexisting data collected for the mid–sagittal plane, we additionally analyzed the axial plane using our landmarks (Chaoui et al., 2015; Hermann et al., 2015; Panigassi et al., 2013; Shyu et al., 2014).

Although MR imaging has also proved to be a valuable tool for assessing fetal structures in prenatal diagnosis, ultrasound offers advantages such as cost-effectiveness, 3D reconstructions, and wider availability. Furthermore, ultrasound diagnostics require less examination time and do not pose any risks to the unborn child's health (Abramowicz et al., 2012; Pugash et al., 2008).

Overall, maxillary growth showed an steep growth pattern in all measured dimensions, with a statistically significant, positive, linear growth correlation of the maxilla with gestational age for all defined landmarks ($p < 0.001$). These results confirm previous reports on fetal jaw length evaluations (Shyu et al., 2014).

Roelfsema et al., in another three-dimensional study, also noticed a significant gestational age-related increase in different craniofacial parameters, in particular maxillary and mandibular corpus length (Roelfsema et al., 2006). However, the maxillary width (MD_3) showed a lower correlation than the maxillary length (correlation for MD_1, $R^2 = 65.1\%$; correlation for MD_4, $R^2 = 73.4\%$; correlation for MD_5, $R^2 = 59.9\%$). There are four possible explanations for these values. The most likely could be artefacts affecting the measurements or leading to measurement inaccuracies, which can occur even within the insonation angle, due to the small size of the fetal maxilla. Another reason could be the reduced data associated with increased gestational age, as a result of difficulties such as shadowing accumulating with ongoing pregnancy, adding to the complexity of obtaining data. Thirdly, our investigator's experience shows that the currently available software seems to have shortcomings in the detection of curved forms, as present in the maxilla. This will hopefully be improved in future systems. The final explanation for a possible relative deficit in (transversal) maxillary growth is the presence of internal and external factors that might affect pregnancy and maxillary development. However, Turnout et al. found greater increases in growth rates for facial length than for facial width (Trenouth, 1991), supporting our findings.

In general, longitudinal growth has been found to be sensitive to chemicals, smoking, alcohol, and metabolic disorders (Feldkamp et al., 2017). Altogether, length growth assessment seems to be more reliable than transverse measurements, which is supported in our study by the statistical analysis of the linear models, as well as by the calculation of Cohen's d.

Siebert et al. described a prenatal developmental hierarchy in the face region, and independent growth processes for each facial region being under the control of different developmental factors (Siebert, 1986). Our study found a dynamic change in all landmarks, with an almost exponential character, intermittent plateaus, and decreasing parts. Berraquero et al. found that prenatal growth can be oscillating. They provided data on the growth of condylar structures that are subject to increasing and decreasing growth developments due to local factors (Berraquero et al., 1995). This could, in addition to artefacts, explain the oscillating aspects found in our growth curves. In accordance with Siebert et al. and Trenouth et al., when comparing our landmarks MD_4 and MD_5 (for the maxillary corpus length), we can assume a similar dominant length growth process. Outliers can be explained by measurement inaccuracies caused by curved structures, some above-average jaw sizes, or gender differences.

Although the average growth rates between all landmarks were not significantly different, the total growth rates from the beginning of the period to the end showed statistical differences. This could imply consistent growth in all directions and indicates a regular growth process. Overall, our evaluation showed a steep growth with exponential character.

This study provides detailed data about fetal maxillary growth. Knowledge of this topic could be relevant for the early and safe recognition of deficiencies in maxillary growth. It also presents a reference growth curve, which could help to determine the optimal point of time for the beginning of presurgical cleft treatment in premature babies. Our data supplement perinatal growth investigations that show an steep increase in prenatal growth and postnatal dentoalveolar growth deceleration (Bauer et al., 2017).

The collection of data focused on the period between week 19^{+2} and week 31^{+4} of pregnancy because of technical limitations such as acoustic shadowing, artefacts, and unpredictable fetal movements, which would have negatively affected the measurements (Duckelmann and Kalache , 2010). Furthermore, it was not always possible to scan the maxilla due to an inconvenient intrauterine fetal position.

Bones covered by thick, soft tissue layers are prone to shadowing and require an optimum insonation angle and good technique (Wilhelm and Braumann, 2012). From our experience, a dorsoposterior position of the fetus is the best for sonographic assessment, while results are also dependent on the operator's expertise (Goncalves, 2016).

Besides generating further valuable insights into the sonographic assessment of growth, future studies with larger study cohorts should confirm these findings and underline the importance of having sufficient knowledge on fetal growth processes to create a reliable basis for prenatal imaging and clinical research.

5. Conclusion

This study demonstrates regular prenatal maxillary growth processes and serves as a reference database. It fills the gap in the existing literature on postnatal maxillary growth. The described method is standardized and reproducible, and seems useful in the detection of anomalies of the maxilla or even the median face. The study supplements previous investigations on fetal maxillary growth with newly defined and useful landmarks.

The presented results are valuable for all postnatal clinical applications concerning or affecting maxillary or intraoral development.

Ethical statement and patient recruitment

All clinical investigations and procedures were conducted according to the principles expressed in the Declaration of Helsinki. Ethical approval for the prospective study was granted by the ethical committee of the Technische Universität München (approval No. 474/15s). All interactions with each patient were performed with written consent.

Thirty-eight healthy, pregnant women with normal prenatal check-ups were enrolled in this prospective study.

Conflicts of interest

All authors declare that they have no conflict of interest.

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