Ultrasonography of the fetal face in the second and third trimester of pregnancy

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Ultrasonography of the fetal face in the second and third trimester of pregnancy

(Echografie van het foetale gezicht in het tweede en derde trimester van de zwangerschap)

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To my parents

&

To Cees, Julia and Jelle

Colofon

de Jong-Pleij, E.A.P.

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CHAPTER 1

General introduction

1.1 INTRODUCTION

The face, the most visible part of the human body, is a special and very personal part of a human being. All major senses are located in the face. They determine to a large extend our ability to communicate and to function in all kinds of situations. The face also facilitates two major body-functions of vital interest: breathing and swallowing. The facial movements can be subtle and the face can speak a universally understood emotional language. The face 'the mirror of the soul' has a tremendous influence on the social and emotional well-being of a person and should be treated with respect and dignity, regardless of its appearance.

The face is anatomically and functionally a complex structure which poses several challenges for prenatal imaging. The complexity is caused by its particular varied three-dimensional morphology and curved nature. Almost no anatomical line is linear, nor are two lines perpendicular. The development involves the differentiation of many tissues with different growth in all directions[1-4]. The face develops between 5 and 9 weeks' gestation (postmenstrual age), although the palate only closes at 12 weeks' gestation. Hereafter the face continues to grow and proportional changes occur until long after birth[3-7].
Improvements in ultrasound techniques, especially the development of three-dimensional (3D) ultrasound, facilitate better prenatal recognition of facial anomalies[8-17]. The visualisation of a facial anomaly gives parents the opportunity to prepare for the birth of a child with an anomaly. Mourning for the loss of the expected normal-looking child which is necessary for the acceptance can start before the child is actually born[18-20].
The recognition and diagnosis of conditions that have a profound impact on the well-being of the unborn child, gives parents the opportunity to make decisions related to their unborn child, themselves and other (future) offspring.
Facial anomalies can be clinically relevant themselves but also will alert the physician to the possible presence of a genetic syndrome or a chromosomal anomaly[21-29]. This may profoundly change the medical management of the pregnancy and neonatal care, which aims to improve the initial condition and early development of the child. This will have an impact on the entire life of the child and its family.

1.2 EMBRYOLOGY OF THE FACE

In a developing fetus the face undergoes dramatic changes from a hardly human mask-like, presence in the first months of pregnancy to a clearly human attractive appearance in the last months of pregnancy. Complex events, occurring within the first months of intrauterine life, dictate future developments.

Face[1, 30, 31]
The formation of the fetal face starts between the fifth and sixth week of gestation when the cranial neuropore is closed and the primitive shallow stomodeal depression appears. The ultimately deep oral cavity is formed by forward growth of surrounding processes rather than deepening of the stomodeum. Five mesenchymal processes are visible at six weeks gestation situated around the stomodeum. One process, the frontal prominence, develops in the midline, cranial to the stomodeum. Two processes, the paired maxillary and mandibular processes,

developing on each side of the stomodeum, arise from the first pharyngeal arch. In the seventh week of gestation two widely separated nasal placodes arise on the frontal prominence. In the middle of these 'horseshoe-shaped' nasal placodes the nasal pits sink into the mesenchyme to form the future nostrils. These nasal placodes dominate the superficial appearance of the face (figure 1).

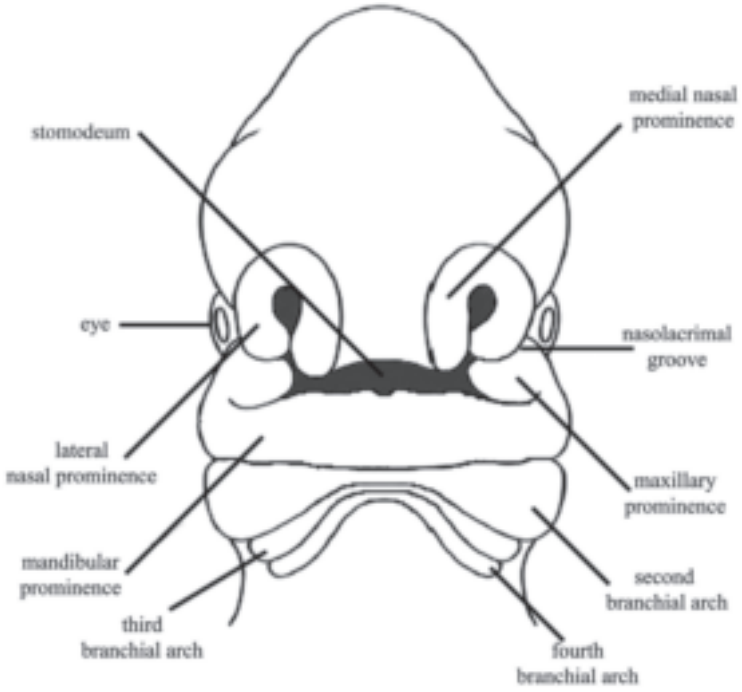

Figure 1 Frontal view of embry at six and half weeks' gestation

In the seventh week of gestation growth toward the midline commences. The medial nasal prominences fuse in the midline to form the central part (crest and tip) of the nose. The medial nasal prominences grow further downwards to form the philtrum and fuse with the maxillary processes to form the upper lip. Although the mandibular prominences merged already in the sixth week, the maxillary prominences merge with the medial part of the nasal placodes in the ninth week. When the prominences of the first branchial arches are fused the nose is more an indentation (produced by the nasal pits) than a protrusion. When the nose develops the nostrils are initially anteverted and the bridge of the nose is shallow. When the bridge of the nose elevates the deep indentation between the forehead and nose disappears. The relative flat nose and the small mandible are characteristics of the prenatal period. The relative smallness of the prenatal face is a result of rudimentary upper and lower jaws, the small size of the nasal cavities and sinuses and the unerupted primary teeth.

Growth and development of the face is further dominated by proportional changes and changes in relative position of facial elements, until long after birth[5-7].

Palate[32-34]

Palatogenesis occurs between eight and twelve weeks' gestation. The primary palate is derived from the wedge shaped intermaxillary prominence that is formed by the two medial nasal prominences. It contains a labial, upper jaw and palatal component. The triangular primary palate forms the anterior part of the palate and will contain the four incisor teeth.

The secondary palate is derived from two shelf-like outgrowths on the internal part of the maxillary prominence. The initial growth is directed obliquely downwards. During the ninth week the shelves ascend to a horizontal position above the tongue.

The shelves fuse anteriorly with the primary palate. The incisive foramen is located in the middle on the boundary between the primary and secondary palates. The primary palate fuses from the back to the front and the secondary palate fuses from the front to the back.

As the palatine shelves merge the nasal septum grows downwards to fuse with the cephalic side of the newly formed palate.

Eyes[35-37]

The eye development appears at the beginning of the sixth week of gestation with grooves on either side of the forebrain. The components of the eye are derived from several different sources: the neuro-ectoderm (retina, posterior layers of the iris and the optic nerve), the mesoderm (fibrous and vascular coat of the eye, choroid, sclerae and corneal endothelium) and surface ectoderm (lens and corneal epithelium).

Striking is the change in relative position of the eyes. In the sixth week the eyes are located on either side of the head. The angle between the imaginary lines passing through the optical axis of each eye is 180 degrees at six weeks' gestation and decreases to 72 degrees at nine weeks' gestation, which is very close to the 68 degrees in an adult[38].

External ears[37, 39, 40]

The external ear consists of the external acoustic meatus, the external layer of the tympanic membrane and the auricle. The external acoustic meatus develops from the first pharyngeal groove. The external layer of the tympanic membrane develops from the pharyngeal membrane. The auricle develops between the eight and twelfth week, from three mesenchymal proliferations at the dorsal end on either side of the first and second pharyngeal arches, surrounding the first pharyngeal cleft. The earlobe is the last part to develop. Originally the ears lie at the base of the neck in a horizontal position but ascend and rotate as the mandible develops to the level of the eyes in a vertical position.

1.3 UTRASOUND OF THE FETAL FACE; PAST, PRESENT AND FUTURE

A-mode ultrasound scanning

The first prenatal measurement made of a fetus with ultrasound was a measurement of the fetal head. Initially measurements were made 'blindly' using the A-mode scan. The measurement of the biparietal diameter (BPD) was invented by Ian Donald in 1961 and further expanded by James Willocks in 1964[41, 42]. In the same year acrania was diagnosed by ultrasound[43].

B-mode ultrasound scanning

The A-scan method evolved into the combined A- and B- method, described in a landmark publication by Stuart Campbell[44], and clinical applicability was explored[45]. In 1971 Campbell and Newman published normograms for the BPD from the 13th week of gestation and have made BPD measurements a standard tool for the assessment of fetal growth until the present day[46]. The first termination of a pregnancy because of an anencephalic fetus was reported in 1972[47].

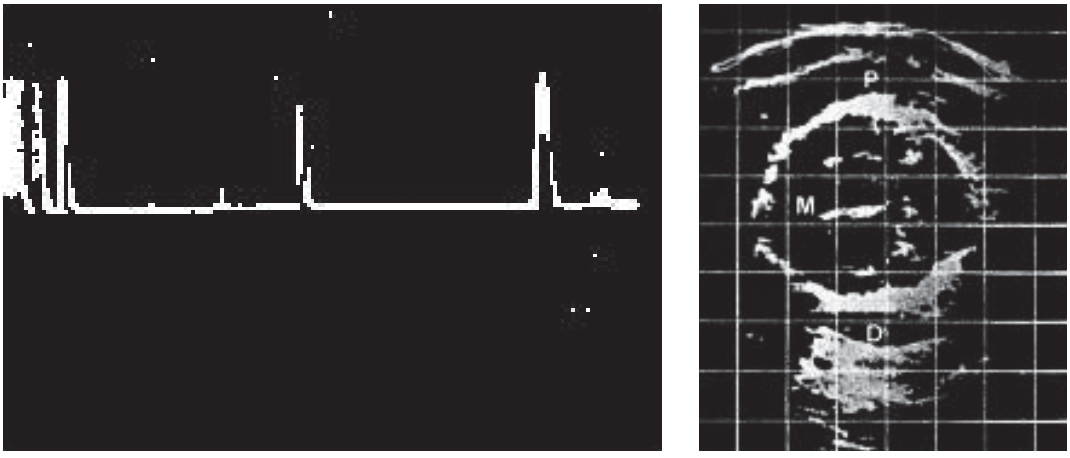

Figure 2 Early A-scan tracing and B-scan image at the level of the BPD

With the development of the technique and equipment, ultrasound was increasingly used[48]. Publications of facial anomalies appeared soon after ultrasonography became part of normal prenatal care in the eighties[21, 22, 49-51]. Most diagnoses were made with qualitative descriptions, however nomograms for orbital diameters were already established in1982[52]. Subsequently, the association between abnormal facial features and genetic syndromes or chromosomal anomalies was noticed and discussed[24, 25, 53-55]. From the early nineties more nomograms of facial structures became available mostly relating to the ear[56, 57,] the mandible[58-60], the palate[61, 62] and the nose[63-65]. An overview is presented in chapter 3 of this thesis. In the Eurofetus study, a large multicentre prospective study performed between 1990-1993 in Europe, including 3686 fetuses with malformations (anomalies of face without serious medical consequences were excluded), the detection rate of nose anomalies, micrognathia/retrognathia, anomalies of the eye and ear were only 1/4, 1/19, 4/18 and 0/18, respectively[66].

Three-dimensional ultrasound scanning

Three-dimensional ultrasound of the fetus was introduced in the late seventies[67] and became a major field of research in obstetrics in the late eighties[68]. It has brought prenatal diagnosis to a new area where the ability to image and analyse complex organs and structures improved enormously.

When, in a general structural survey of the fetus, three-dimensional ultrasound is compared with two-dimensional ultrasound, the new technique proved especially advantageous in demonstrating the fetal face, extremities and surface malformations[11, 69-77]. However, some studies adopt a critical attitude towards the diagnostic capacity of three-dimensional ultrasound when compared to two-dimensional ultrasound[78-80]. When, in targeted ultrasound studies of the fetal face, three-dimensional ultrasound is compared with two-dimensional ultrasound, most authors found that three-dimensional ultrasound has the potential to provide improved visualisation[9-15, 81-84], which is only challenged by Ghi[85].

There were great expectations for the role of 3D ultrasound in the diagnosis of cleft lip and palate[86, 87]. Several techniques have been proposed to improve detection of especially cleft palate[88-91]. 3D ultrasound seems not to improve detection rate of cleft lip and palate but a more precise and reliable diagnosis can be achieved[92, 93].

In two-dimensional ultrasound a single cross sectional plane is imaged at a time. The optimal section through the region of interest is obtained by moving the transducer and changing the angle of insonation by hand. The sonographer has to construct a mental picture of the complex 3D anatomy of the face.

In three-dimensional ultrasound a volume of ultrasound information can be studied rather than a two-dimensional slice of ultrasound information. In three-dimensional ultrasound the exam starts as a two-dimensional ultrasound examination. When the anatomic region of interest is found a box is superimposed over the two-dimensional image. The box outlines the region of interest and is of variable size. During a sweep of the transducer all adjoining two-dimensional section planes within the box are stored. The transducer is usually moved by a motor inside the probe, although more manufactures are developing matrix probes. All stored sectional planes together form a volume. After the volume is digitally stored, the volume can be manipulated in various ways to extract different information from the same dataset. Planes not obtainable by 2D ultrasound can be visualised. Three-dimensional volumes allow for evaluation of the fetal face using for example multiplanar, surface rendering and multislice displays[94].

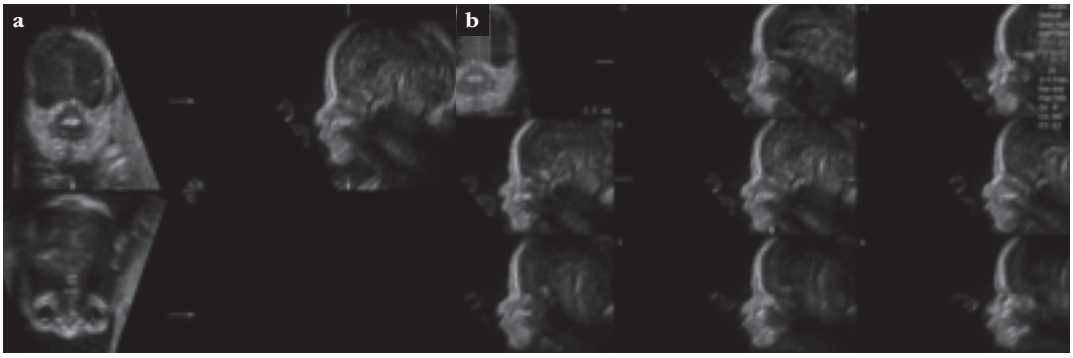

Figure 3 Examples of multiplanar (3A) and TUI (3B) display of the fetal face

When the multiplanar display is used the simultaneous display of the three orthogonal planes allows for correlation between image planes (Figure 3A). The ultrasound volumes of the fetal face can be rotated into a standard symmetrical orientation and reviewed millimetre by millimetre by scrolling through the volumes. The reference dot, which marks the intersection of the three orthogonal planes, is helpful in identifying structures. Accurate topographic depiction of desired image planes is enhanced, which may improve more accurate identification and assessment of landmarks.
TUI (tomography ultrasound imaging) or 'multislice method' demonstrates 2D images that are parallel to each other simultaneously with predefined number and spacing of the slices (Figure 3B). This offers the examiner a more complete picture.

In rendering mode the image includes information from the entire volume in order to obtain a realistic three-dimensional picture (Figure 4). It is possible to turn and rotate the volume and view the volume from various positions. Technical options like the electronic scalpel to remove unwanted structures in front of the face improve the image quality and diagnostic value of ultrasound examinations: the use of the electronic scalpel is reported to be associated with diagnostic improvement in 71.1% of normal cases and in 75.0% in cases with facial pathology[95].

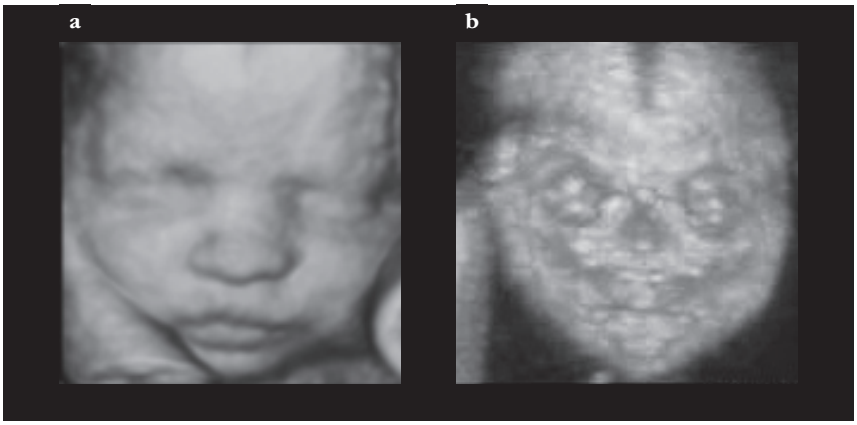

Figure 4 Examples of rendered ultrasound pictures of the face using surface (A) and maximum (B) mode

By choosing various threshold values the rendered volume can be studied in a variety of ways. In the surface view the outer surface of the fetus is highlighted (Figure 4A). The fetus is displayed as a three-dimensional sculpture. By observing the fetal face in rendering mode we will have a general subjective visual impression comparable with the 'gestalt' approach of clinical genetics. Several case-reports describe facial anomalies using rendering mode at different moments during pregnancy[8, 96-102].
In the maximum mode the bones are emphasized. The strongest echoes are kept and the echoes from the soft tissue are eliminated (Figure 4B). This especially allows visualisation of curved skeletal structures like sutures and fontanels of the skull, hard palate and nasal bones[88, 103-109]
The possibility to store 3D ultrasound volumes and edit them off line and start databases with collections of special cases will be an enormous stimulus for further research.

Finally, realistic 3D images may improve communication with the parents or health professionals involved in the management of the pregnancy[9, 86, 110-113].

Enhancement of tissue contrast resolution with CrossXBeam (CRI) and/or Speckle Reduction Imaging (SRI) and techniques like volume contrast imaging (VCI) have further improved image quality.

Four-dimensional ultrasound scanning
Four-dimensional (4D) ultrasound added the fourth dimension 'time' towards the already prevailing 3D ultrasound. This dramatically improved dynamic assessment of the fetal face. Movements of the mouth[114- 116], tongue[82], eyelid[116], lenses[117, 118] and yawning[119-122] can be visualised with 2D, but with the introduction of 4D ultrasound evaluation of facial expression became possible[122-129].

The psychological impact of 3D and 4D ultrasound on the mother, and especially on maternal-fetal bonding became subject of several studies[130-136]. Most studies showed significant increase in maternal fetal bonding after 3D/4D ultrasound. However, the increase was not significant larger after a 3D/4D ultrasound examination than after a 2D ultrasound examination.

The limitations of 3D/4D ultrasound are the same as for 2D ultrasound: high BMI of the mother, oligohydramnios or no pocket of amniotic fluid in front of the face, fetal body parts that obscure visibility or unfavourable fetal position reduce the quality of the image.
In multiplanar mode, the resolution of the calculated plane (generally, a coronal plane depicted in the C box) is usually lower than the resolution of the other two planes, of which the resolution is comparable with the original 2D quality.
The benefits of the traditional 2D ultrasound are well established and proven over the last four decades. 3D/4D ultrasound is seen as a potential new instrument to clarify anatomy and consequently diagnose anomalies. 3D/4D ultrasound has opened a new area in ultrasound with many aspects still to be explored.

1.4 ASSOCIATED ANOMALIES AND GENETIC SYNDROMES OR SEQUENCES

The word 'syndrome' comes from the Greek 'syn'(together) and 'dramein' (to run) and means 'run together'. A syndrome is suspected when a combination of anomalies or dysmorphic features occur together in the same fetus. The more characteristic features are recognized the higher the chance of a syndromal association. Identification of a syndrome is important as it may change the management of pregnancy and perinatal care. Clinical features of genetic syndromes vary between minor, hardly recognisable deformities and severe malformations with profound disability. Life expectation varies between several hours and a normal duration of life. Syndrome identification requires precise knowledge of normal sizes, proportions and dysmorphology for correct classification and diagnosis. Genetic syndromes are a leading cause of infant morbidity and mortality. Incidence figures for genetic syndromes are not ready available. Variability in clinical expression, differences in case definition and inclusion/exclusion criteria account for the wide variation in the reported prevalence rates. However an underlying disorder with a significant genetic component was found in 55% of paediatric hospital admissions in 1978 and in 71% of paediatric hospital admissions in 2004 in the United States[137, 138]. Many syndromes have facial

involvement[23, 139]. This was already noticed in one of the first publications concerning the fetal face[21]. Szigeti correlated prenatal ultrasound diagnosis with perinatal autopsy in fetuses with trisomy 18 and 13 and found that respectively 26% and 77% of the facial abnormalities were detected by ultrasound and concluded that throughout examination of the face may increase detection of these syndromes[140, 141]. The finding of a facial anomaly necessitates a throughout examination of the fetus. In cases with omphalocale and normal karyotype 35-50% has a craniofacial anomaly[142].
The two most common facial abnormalities are facial clefts and micrognathia/retrognathia.

Facial clefts
The incidence of facial cleft in the Netherlands is 1.7-1.8 in 1000 live births[143, 144]. There are about 350 syndromes associated with facial clefting[145, 146, 155].
The incidence of associated structural anomalies, chromosomal aberrations or an underlying genetic syndrome or sequence varies with the anatomical cleft type. Nine studies are summarised in table 1. The percentage isolated cases was highest in the cleft lip group (79-100%) and unanimously 0% in midline and atypical cleft groups. Bilateral clefts (21-45%) had lower percentages isolated cases than unilateral clefts (60-67%). For all types grouped together the incidence of isolated clefts varied between 31 and 71%[147, 148]. Associated anomalies were seen in 95-100% of the cases with chromosomal aberrations[27, 147, 149, 150].

The most frequent associated defect are musculoskeletal anomalies (polydactyly and limb reductions) followed by malformations of the central nervous system and malformations of the cardiovascular system (ventricular and atrial septal defects, tetralogy of Fallot)[147].
Facial cleft were infrequently associated with syndromes or sequences (2-9%)[27, 149]. However, it should be noted that the incidence in reality may be higher due to unidentified syndromes or late expression of characteristic features (e.g. learning difficulties).
The most common syndromes and sequences identified post-partum in cleft patients (however these data also included isolated cleft palate) in the Netherlands between 1997-2007 were Pierre Robin sequence, Van der Woude syndrome, and Stickler syndrome followed by CHARGE association, Ectrodactyly-Ectodermal dysplasia-Cleft syndrome, Goldenhar syndrome, Apert syndrome and Treacher Collins syndrome[151].

Micrognathia / Retrognathia
Micrognathia is a hypoplastic mandible and retrognathia is a posteriorly displaced mandible. Both conditions usually coexist together, although retrognathia can exist without micrognathia. A search in the OMIM website (Online Mendelian Inheritance in Man, a database of human genes and genetic disorders) retrieved 424 hits for 'micrognathia 'and 97 for 'retrognathia'[155]. Frequently only the term micrognathia is used to refer to the combination micrognathia/retrognathia.
Micrognathia has been reported to be a neonatal emergency due to airway obstruction in more than 50 % of the live born children[156]. Micrognathia can be associated with many diseases and syndromes [23, 26, 157]. At autopsy micrognathia has been reported in more than 80% of cases of trisomy 18 and triploidy [23, 158]. Vettraino reports that after neonatal examination, 14 of 15 children, who had isolated micrognathia by prenatal sonogram, were found to have at least one additional abnormality[156].

Table 1 Summary of published data on incidence of associated structural anomalies, chromosomal anomalies or syndromes and isolated cases in facial clefts clustered by anatomical cleft type.

Cleft type	*reference*	*Structural anomaly**		*Chromosomal aberration*		*Syndrome or sequence*		*Isolated*	
CL	Nyberg 1995[149]	1/5	20%	0/5	0%	0/5	0%	4/5	80%
	Bergé 2001[147]	0/3	0%	0/3	0%	0/3	0%	3/3	100%
	Calzolari 2007[148]	261/1993	13%	97/1993	5%	56/1993	3%	1579/1993	79%
	Maarse 2011[154]	2/18	11%	1/18	6%	0/18	0%	15/18	83%
UCL/P	Gillham 2009[153]	13/194	7%	6/194	3%			175/194	90%
UCLP	Nyberg 1995[149]	3/15	20%	3/15	20%	1/15	7%	9/15	60%
	Perotin 2001[150]	7/29	24%	4/29	14%				
	Bergé 2001[147]	4/25	16%	8/25	32%	1/25	4%	16/25	64%
	Maarse 2011[154]	2/18	11%	4/18	22%			12/18	67%
BCL/P	Gillham 2009 [153]	8/44	18%	3/44	7%			33/44	75%
BCLP	Nyberg 1995[149]	5/20	25%	6/20	30%			9/20	45%
	Perotin 2001[150]	13/27	48%						
	Bergé 2001[147]	6/29	21%	17/29	59%	0/29	0%	6/29	21%
	Maarse 2011[154]	1/7	14%	3/7	43%			3/7	43%
U/BCLP	Calzolari 2007[148]	709/3453	21%	358/3453	10%	108/3453	3%	2278/3453	66%
MC	Nyberg 1995[149]	10/21	48%	11/21	52%			0/21	0%
	Bergé 2001[147]	2/11	18%	9/11	82%			0/11	0%
	Gillham 2009[153]**			3**				0/11	0%
	Maarse 2011[154]	1/1	100%	0/1	0%			0/1	0%
AC	Nyberg 1995[149]	4/4	100%	0/4	0%			0/4	0%
	Maarse 2011[154]	0/1	0%	0/1	0%	1/1	100%	0/1	0%
All types grouped together									
	Nyberg 1995[149]	23/65	35%	20/65	31%	1/65	2%	21/65	32%
	Clementi 200[152]	89/553	16%	62/553	11%	36/553	7%	366/553	66%
	Perotin 2001[150]		42%		24%				
	Bergé 2001[147]	12/68	18%	34/68	50%	1/68	2%	21/68	31%
	Chmait 2006[27]	7/45	16%	5/45	11%	4/45	9%	29/45	64%
	Maarse 2011[154]	6/45	13%	8/45	18%	1/45	2%	30/45	67%
	Calzolari 2007[148]	970/5449	18%	455/5449	8%	164/5449	3%	3860/5449	71%
	Offerdal 2008[28]	16/100	16%	8/100	8%	9/100	9%	44/100	44%

*Fetuses with structural anomalies without chromosomal aberrations, syndromes or sequences.
** Karyotype was available for only three fetuses and all 11 fetuses had associated anomalies.
CL, cleft lip; UCL/P, unilateral cleft lip with or without cleft palate; UCLP, unilateral cleft lip and palate; BCL/P, bilateral cleft lip with or without cleft palate; BCLP, bilateral cleft lip and palate; U/BCLP, uni and bilateral cleft lip and palate; MC, midline cleft; AC, atypical cleft.

The associated conditions can be categorized in syndromic conditions primarily involving the mandible (e.g. Pierre Robin sequence, acrofacial dysostosis, orofaciodigital syndromes), skeletal and neuromuscular diseases (e.g. Pena–Shokeir syndrome, multiple pterygium syndrome, achondrogenesis, campomelic dysplasia), chromosomal aberrations (e.g. trisomy 18, trisomy 13, Cri du chat syndrome, Pallister–Killian syndrome) and other non-chromosomal syndromic conditions (e.g. Meckel–Gruber syndrome, Fryns syndrome, Goldenhar syndrome, Peters' plus syndrome)[157].

The incidence of associated conditions in six studies is summarised in table 2. The very low percentage of isolated cases illustrates the severity of this facial anomaly, although it is likely that mild isolated cases escaped identification.

Table 2 Summary of published data on incidence of associated structural anomalies, chromosomal anomalies, skeletal dysplasia or syndromes/sequences and isolated cases in micrognathia.

reference	*Structural anomaly**		*Chromosomal abberation*		*Skeletal or neuromuscular diseases*		*Syndrome or sequence*		*Isolated*	
Nicolaides 1993[159]	10/56	18%	37/56	66%	6/56	11%	2/56	4%	1/56	2%
Turner 1993[24]	1/9	11%	3/9	33%	4/9	44%	1/9	11%	0/9	0%
Bromley 1994[26]	3/20	15%	5/20	25%	4/20	20%	7/20	35%	1/20	5%
Vettraino 2003[156]									1/58	2%
Basburg 2007[160]	7/32	22%	7/32	22%	11/33	33%	7/32	22%	2/32	6%
Paladini 2010[157]			22/50	44%**						

*Fetuses with structural anomalies without chromosomal aberrations, syndromes or sequences, skeletal or neuromuscular disease. **Only chromosomal aberrations were stated.

1.5 CLASSIFICATIONS OF FACIAL ANOMALIES

Facial anomalies are usually named after their location. But sometimes vague descriptions as unusual, coarse or dysmorphic face, not suitable for scientific work or communication, are used. A uniform classification is lacking but a reasonable classification is proposed by Meizner, dividing all facial anomalies in four categories[161]:

1) isolated facial malformations (e.g.retrognathia, facial haemangioma);
2) facial malformation as part of a syndrome (e.g. Nager syndrome, Beckwith-Wiedeman syndrome);
3) facial malformation associated with chromosomal aberrations (e.g. all trisomies);
4) facial malformations resulting from cranial deformities (e.g. craniosynostosis, encephalocele).

It might be useful to add 'facial malformations as part of skeletal or neuromuscular diseases' as a subcategory of main category 2.

1.6 ULTRASONOGRAPHIC APPROACH OF THE FETAL FACE

The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), a scientific organisation that encourages sound clinical practice, teaching and research for diagnostic imaging in women's healthcare, has published guidelines for performance of the routine mid-trimester fetal ultrasound scan. According to the ISUOG minimum evaluation of the fetal face should include an attempt to visualize the upper lip for possible cleft lip anomaly. If technically feasible, other facial features that can be assessed include the facial profile, orbits, nose and nostrils[162]. Many countries have developed local guidelines for the routine mid-trimester scan. In The Netherlands the Dutch Society for Obstetrics and Gynecology (Nederlandse Vereniging voor Obstetrie en Gynaecology, NVOG) has made assessment of the profile, eyes and lips mandatory[163]. The mid-sagittal (profile) plane, the anterior coronal (nose-mouth) plane and coronal plane (orbits) plane are usually sufficient to visualize these structures in a screening setting with 2D ultrasound[15].

In high risk pregnancies, referred to a tertiary center, the ultrasound examination is not a screening tool but a diagnostic examination. When anomalies are encountered an attempt has to be made to achieve a diagnosis. In this situation, there are no restrictions imposed in respect of the planes or techniques to be used. The examination usually starts with a subjective evaluation using 2D ultrasound. A systematic approach to the examination of the fetal face should include sagittal, axial, and coronal planes[15, 24, 51, 85, 164, 165]. In the mid-sagittal plane the profile contains a lot of information; the forehead, nasal bones, prenasal thickness, soft tissue of the nose, philtrum, the tongue, palatal bone, vomer, lower lip and chin can be observed. Also the oropharynx with the uvula (equal sign) can be informative and indicate the existence of retrognathia or cleft palate[166]. The equal sign can also be detected in the axial or coronal plane[166]. In the paramedian sagittal planes the orbits with the lenses and the ears can be visualised. Of the coronal planes is the nose-mouth plane especially helpful in evaluation of the nose (tip, alae nasi and nostrils), upper lip and mouth. Slightly posterior moving of the transducers allows for visualization of the maxilla, both eyelids and orbits with lenses. Serial axial images are particularly useful to analyse the maxilla and mandible with the tooth buds, but also to view the orbits with lenses, ears, palate, lips and tongue. Three-dimensional ultrasound is usually the next step. The fetal face is among the organs that can be particularly well evaluated with three-dimensional ultrasound[9-15, 81-84]. Three-dimensional multiplanar mode can be helpful in obtaining the exact planes and improves the spatial orientation[15, 16]. With rendering mode not only anomalies like clefts or tumours can be visualised but the overall 'gestalt' of the face can be assessed, offering the possibility to suspect dysmorphologies. The rendering mode is also helpful in assessing micropthalmia, ear anomalies, cleft palate, sutures and fontanelles [88, 92, 167-172].

The suspected anomalies can be validated by objective measures of the craniofacial features at a single point in time as well over time. In chapter 3 an overview is presented of published objective measures of facial features arranged by site of appearance. Finally the facial examinations should be combined with additional findings such as associated anomalies, poly- or oligohydramnion, growth, information obtained from invasive procedures and family history in order to achieve a diagnosis.

1.7 PSYCHOLOGICAL IMPACT OF THE PRENATAL DETECTION OF A FACIAL ANOMALY

The birth of a child with a facial anomaly can be traumatic for parents when they are not prepared. This may have impact on the first hours after birth, when parental bonding should peak[173]. The prenatal recognition of a facial anomaly will evokes various strong emotions like stress, guilt, fear and anger, but prenatal diagnosis with counselling also gives parent time to process these feelings and accept the child at birth[19, 20, 174, 175]. The process of mourning for the loss of the expected normal-looking child can start before the child is born.

Facial clefts can be diagnosed with ultrasound and are the most common facial anomaly. This gives researchers the opportunity to evaluate the reaction of parents to the prenatal diagnosis of this anomaly. Studies of parents pregnant with a child prenatally diagnosed with a facial cleft showed that prenatal diagnosis when combined with adequate counselling made psychological coping easier and improved neonatal care in 85-100%[18, 20, 174-176]. Although it is described that 3D ultrasound provides a better understanding of the malformation and thereby facilitating

counselling and acceptance of the malformation, there is no convincing evidence yet that 3D ultrasound eases the psychological process that parents have to go through after the prenatal diagnosis of a facial anomaly[9, 110, 111, 177, 178].

For the parents the three-dimensional ultrasound opens a new window to their unborn child. Three- and four dimensional imaging is usually considered as an exciting positive technique but care has to be taken of all potential harms and benefits before this window can be confidently opened.

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CHAPTER 2

Overview

2.1 INTRODUCTION

In this chapter an overview of the (English) literature is presented, concerning ultrasound of the fetal face, arranged by site of appearance and with special emphasis on objective measurements.

2.2 FOREHEAD, SUTURES AND FONTANELLES

Although the forehead, fontanelles and sutures are part of the neurocranium and not the viscerocranium (facial bones), they will be briefly discussed here since the neuro- and viscerocranium are anatomically closely interwoven. The forehead, for example, is an important component in the evaluation of the fetal profile. In addition, anomalies of the neurocranium like craniosynostosis, macrocephaly or microcephaly can influence the shape of the profile and the face (Jones 97, Bernstein 96, Delahaye 03, Baumeister 04, Malinger 11).

Bossing and sloping foreheads

Bossing and sloping foreheads are markers for very serious underlying conditions. Unfortunately both markers are subtle in the first half of pregnancy, but become increasingly evident during pregnancy (Chevernak 87, Bromley 95, Pooh 99, Malinger 02, Schwärzler 03). Frontal bossing occurs in more than 50 syndromes, like craniosynostosis syndromes and skeletal dysplasia's (Jones 97). Malinger found frontal bossing in 4 of 16 cases with macrocephaly (HC>2SD) and associated findings (Malinger 11). Sloping forehead is usually a sign of a developing microcephaly, frequently accompanied by neurodevelopmental delay (Persutte 98, den Hollander 00). Only one study evaluated quantitatively the forehead between 16 and 36 weeks by measuring in 146 normal fetuses a semi-circular area delimited by a line (through the apex of the philtrum and the nasion) and the frontal skin. A second order polynomial growth for length, height and area was found and these were above the 95th percentile in one achondroplastic fetus. The ratio forehead height/ forehead length was constant throughout gestation with a mean of 0.33 (+ 0.027, range 0.26-0.42) (Sivan 97) (Table 2.2).

One of the clear advantages of 3D-dimensional ultrasound is that it offers the possibility to assess sutures and fontanels of the convex cranium much more clearly than 2D ultrasound. Reports confirming the significance of 3D ultrasound (Pretorius 94, Ginath 04, Dikkeboom 04, Faro 05, Chaoui 05) and case reports using 3D ultrasound were published (Esser 05, Faro 06, Roderique 05).

Most sutures and fontanelles could be visualised with 3D ultrasound. When using transvaginal ultrasound between 15-16 week'gestation 3D ultrasound seems especially superior in demonstrating the sagittal suture (Ginath 04). The coronal suture and posterior fontanelle were the hardest to visualise with 3D ultrasound and visualization became more difficult with increasing gestational age (Dikkeboom 04).

Paladini described a method with 3D ultrasound for correct visualisation of the anterior fontanelle and reported about the normal development (Paladini 08). The actual size of the anterior fontanelle increases during gestation while its size in relation to the volume of the head diminished (Table 2.2). From postnatal studies it is known that anterior fontanelle abnormalities are present in many genetic and non-genetic conditions (Jones 97, Kiesler 03). Likewise Paladini found deviating fontanelle dimensions (18 enlarged and two reduced) in 20 of the 47 fetuses with abnormalities, particularly in those with syndromes and skeletal abnormalities, hydrocephalus,

cardiac overload and other CNS lesions (Paladini 08). The same author assessed the anterior fontanelle in second trimester trisomy 21 fetuses en found a significant increase of dimensions (except for the laterolateral diameter) in trisomy 21 fetuses (Paladini 07).
Faro described the morphology of the frontal bones and metopic suture between 9–34 weeks of gestation using 3D ultrasound (Faro 05). At 9 weeks, small ossification centers were visible and by 11 weeks the frontal bones appeared as 'thick eyebrows'. In the second trimester the metopic suture became delineated and closure starts at 32 weeks moving upwards from the glabella. Chaoui reports about four patterns of abnormality in the metopic suture in association with fetal malformations during the second and third trimesters of pregnancy: delayed closue, premature closure, a U-shaped open suture and the presence of additional bone between the frontal bones (Chaoui 05). Faro investigated the development of the frontal bones and metopic suture in normal fetuses and fetuses with holoprosencephaly at 11 + 0 to 13 + 6 weeks of gestation. Holoprosencephaly is associated with an accelerated development of the frontal bones and premature closure of the metopic suture (Faro 06) (table 2.2.). The development of the frontal bones and metopic suture is normal in trisomy 21 fetuses between 11 and 13+6 weeks' gestation (Faro 06).

Table 2.2 Summary of publications on objective measurements related to the forehead

author (year)	*method**	*measure*	*GA (weeks)*	*N*	*relation with GA*
Forehead					
Sivan (1997)	3D multiplanar abd	FL FH FA FH/FL	16-38	130	FL = −40.631 + 3.826 × GA − 0.066 × GA², r² = 0.866 FH = −20.477 + 2.132 × GA − 0.032 × GA², r² = 0.941 FA = −6.112 + 0.498 × GA − 0.006 × GA², r² = 0.939 FH/FL = 0.33 + 0.027, range 0.26–0.42, constant throughout gestation
Faro (2006)	3D multiplanar abd/vag	FL smallest width of metopic suture	11-13	200	FL = 0.023 × CRL − 0.125, r = 0.788, P<0.0001 metopic suture width = 1.5 mm, r = 0.076, P = 0.282
Anterior fontanelle					
Paladini (2008)	3D rendering abd/vag	FAPD FLLD Perimeter Area	12-38	78	FAPD = −18.25 + 3.87 × GA − 0.7 × GA², r² = 0.336, P<0.001 FLLD = 16.05 + 0.36 × GA, r² = 0.175, r² = 0.175, P<0.001 Perimeter = −4.04 + 1 × GA, r² = 0.366, P<0.001 Area = 1.92 + 0.05 x GA − 0.2 × GA², r² = 0.091, P<0.001

*, method included dimensionality and abdominal or vaginal approach; 3D, measurements performed with three-dimensional ultrasound; abd, abdominal; vag, vaginal; GA, gestational age; FL, forehead length; FH, forehead height; FA, forehead area; FADP, fontanelle anteroposterior diameter: FLLD, fontanelle laterolateral diameter.

Forehead in open spina bifida

Recently it has been demonstrated that in fetuses with open spina bifida at 11 +0 to 13+ 6 weeks, caudal displacement of the forehead relative to the position of the anterior end of the maxilla results in a decreased frontomaxillary facial (FMF) angle (Lachmann 10, Acuna 11).

Miscellaneous
In a case report the presence of prefrontal oedema and subsequent 3D ultrasound (showing the classical postnatal profile, with the phenotypic aspect of a 'Greek warrior helmet') led to the diagnosis of Wolf-Hirschhorn syndrome (4p- deletion) (Levaillant 05).

2.3 EYES

The hypoechoic eyeballs surrounded by the bony orbit are very easy to recognize with ultrasound, therefore it is not surprising that normal values have already been published in the early eighties. Normal values of ocular diameter, interocular distance and binocular distances were established by both Mayden (related to DBP) and Jeanty (related to gestational age) in 1982 with the aim to diagnose hypertelorism, hypotelorism and micropthalmos (Mayden 82, Jeanty 82). Case reports of prenatal diagnosis of ocular anomalies were published soon after (Lev-Gur 82, Feldman 85, Elejalde 85, Crowe 86).
It is generally known by ultrasonographers that the distance between the orbits is about the same as the diameter of one orbit, a facial proportion anecdotally even described by Leonardo da Vinci as being ideal (Farkas 87).
Assessment of the orbits is included in the routine mid-trimester fetal ultrasound scans when technically feasible (Salomo 11). Ocular anomalies are often associated with other malformations especially of the central nervous system (Benacerraf 84, Birnholz 85, Bronstein 91, Trout 94, Achiron 95, Mashiach 04, Green 05). Asymmetry is not uncommon for eye anomalies. In Goldenhar syndrome (Oculoauricuclovertebral spectrum) unilaterality is a typical finding (Martinelli 04).

Orbits
Fetal orbital measurements were reported both in early and late gestation using both transvaginal and transabdominal ultrasound. An overview is presented in Table 2.3. In figure 2.3 the relationship between binocular diameter and gestational age of some studies is presented. Initially normal values of interocular, binocular and ocular distances were published, (Mayden 1982, Jeanty 1982, Jeanty 1984, Birnholz 1985, de Elejalde 85, Tongsong 92, Brons 88, Trout 1994, Piantelli 94, Goldstein 1998, Jacquemyn 00, Rosati 02, Guariglia 02, Dilmen 02, Green 05, Sukonpan 08), followed by normal values of orbital circumference, orbital area (Achiron 95, Goldstein 98, Dilmen 02, Sukonpan 08) and the anterior and posterior chamber length (Achiron 00). The axial ocular growth is reported by Achiron, which may be important for families at risk for infantile glaucoma or persistent hyperplastic primary vitreous (Achiron 00). Values of fetal eyeball volume with 3D ultrasound were determined by Odeh (Odeh 09). This may be helpful in the diagnosis of micropthalmia when the diagnosis is not clear and obvious using 2D ultrasound. Birnholz stated that a diameter of 15 mm or more excludes micropthalmia (Birnholz 88).

Kfir evaluated OD as a potential marker for alcohol-affected fetuses and found OD significantly smaller in the alcohol-exposed group in the third trimester relative to comparison fetuses (Kfir 09). Rosati assessed whether first trimester inter- and binocular distances can be used as screening tools for aneuploidy fetuses. Their data suggests that ocular biometry may be useful for trisomy 13. The measurements for cases with trisomy 21 (n = 36), Turner syndrome (n = 1), Klinefelter syndrome (n = 1), trisomy 18 (n = 3) and unbalanced anomalies (n = 2) were within the normal range (Rosati 03). Green also found ocular distances of 2 first trimester trisomy 21 cases

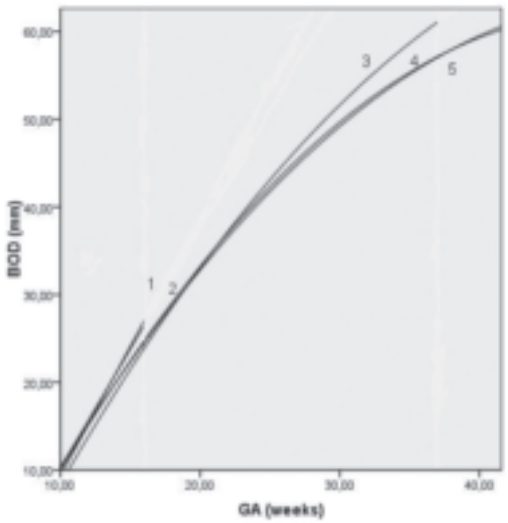

Figure 2.3 Relationships between binocular distance (BOD) and gestational age (GA) in the studies of Rosatie (1), Guarglia (2), Trout (3), Brons (4) and Jeanty (5).

and 1 trisomy 18 case within the normal range (Green 05). Similarly Achiron found normal orbital measurements in 2 trisomy 21 cases and 1 Turner syndrome case in a study performed after 12 weeks (Achiron 95). Only Birnholz found in one case with trisomy 21 in the mid second trimester, a slight delay in growth of the vitreous volume. However, in this case trisomy 21 was accompanied by mild ventriculomegaly and delayed corpus callosum development (Birnholz 85).
A few studies were conducted to compare orbital measurements between populations. Tongsong found a BOD growth pattern in a Thai population that agreed relatively well with those of western studies (Tongsong 92). Jacquemyn found a small, but statistically significant difference for the fetal binocular distance between fetuses of Moroccan origin versus those of native Belgian or those of Turkish origin (Jacquemyn 00). Merz published tables of orbital measurements of a German population and Roth found that previous published tables are well-suited to the French population (Merz 95, Roth 99).

Anopthalmia
The clinical distinction between real anopthalmia and severe micropthalmia is difficult and pathological examination is usually necessary to make the correct diagnosis. Real anopthalmia is probably a lethal condition as severe malformations of the forebrain accompany this anomaly. The antenatal diagnosis of anopthalmia is made using 2D and 3D ultrasound (Lee 95, Wu 00, Mashiach 04) and first trimester diagnosis of anopthalmia is also possible (Duyos 11). However one must beware of false negatives because anopthalmia may sometimes be secondary to degenerative processes that occur in middle or late gestation (Brohnstein 91).
When the fetal head position is unfavorable 3D may be superior to 2D ultrasound for diagnosing anopthalmia; volume determination, visualisation of sunken eye lids, or the use of the reversed face view may be helpful in these cases (Lee 95, Odeh 09, Campbell 03, Wong 08).

Lenses
In the hypoechoic eyeballs the lenses can be identified as white circles. Normal ranges of lens diameter, circumference and area were established (Acharon 95, Goldstein 98, Sukonpan 08, Dilmen 02). Relationships between the ratio's lens/orbital diameter, lens/orbital circumference and lens/orbital area and gestational age showed that growth of the orbit exceeds growth of the lens (Goldstein 98). Interlens distance and BOD/ILD ratio were published by Kivilevitch (Kivilevitch 10). Achiron used transvaginal ultrasound and was able to visualise the lens from 12 week's gestation (Achiron 95).
Visualisation of both lenses may not only be important for the detection of hypo- and hyper telorism, micro- or anopthalmia but also may lead to identification of strabismus, ectopia lentis or cataract (Kivilevitch 10).
Case reports of cataract (opacity of the lens) are published, usually as part of a syndrome, following an infectious disease or in cases with a positive family history (Bronstein 91, Monteagudo 96, Drydale 97, Pedreira 99, Leonard 09).
Eye movements (rapid or slow), first described in 1981 by both Bots and Birnholz, recognised by movements of the lens, can be visualized after 14-16 weeks' gestation (Bots 81, Birnholz 81, Elejalde 85, Inoue 86, Hosimoto 89 & 90).

Eyelids
Although eyelids are visible on prenatal ultrasound eyelid anomalies are uncommon and infrequently reported. Birnholz could visualise the eyelid form 14-16 weeks' gestation in nearly all cases. Opening of the eyelids is seen with increasing frequency after 26 weeks' gestation (Birnholz 81, Birnholz 83, Elejalde 85). A blink response to vibroacoustic stimulation could be elicited after 24-25 weeks and was consistently present after 28 weeks' gestation (Birnholz 83).
Mielke describes a technique for assessment of the fetal palpebral fissure slant. In the frontal view of the face the inferior angle between the palpebral fissure and the midline was constant between 14 and 36 weeks' gestation with a mean of 89 degrees (range 87-90 degree (Mielke 97).
Cryptopthalmos is the fusion of the eyelids. It is frequently associated with microphtalmia and often part of the Fraser syndrome. Prenatal diagnosis of this anomaly is described in a case report (Berg 05).

Hyaloid artery
The hyaloid artery is a transient fetal vessel, visible as a continuous echogenic line between the posterior wall of the orbit and the posterior border of the lens. In the first trimester low peak systolic flow (4cm/sec) can be detected in this artery (Achiron 95). The conversion of the primary vitreous to the secondary vitreous begins in the second month and is completed near term, which is accompanied by degeneration of the hyaloid artery. Achiron and Birnholz describe ultrasonographic regression of the hyaloid artery between 18 and 29 weeks' gestation (Birnholz 85, Achiron 00). Insufficient regression of the hyaloid artery is a pathological finding (Spaggiari 12). This finding can be associated with cataract but is more often associated with persistent hyperplastic primary vitreous (PHPV) and may be seen in genetic disorders like Walker-Warburg syndrome or trisomy 13 (Achiron 95, Katorza 08, Yazicioglu 10, Spaggiari 12). Prenatal diagnoses of PHPV have been published: an irregular hyperechogenic mass extended from the posterior surface of the lens to the posterior wall of the eye is described in these cases (Mahieu-Caputi 03, Yazicioglu 10). Birnholz concluded that delayed regression of the hyaloid artery may occur with trisomy 21 syndrome and other forms of retarded brain development (Birnholz 88).

Dacryocystocele
As a result of delayed canalisation of the distal end of the nasolacrimal duct and an uncommon valve mechanism at the cranial end, the lacrimal sac expands and is visible as a hypoechogenic mass. A dacryocystoceel is usually about 10 mm, located near the nasal canthus and only described in the second half of pregnancy. Differential diagnosis includes encephalocele, haemangioma, lymphangioma, teratoma, glioma, rhabdomyosarcoma and neurofibromatosis. These conditions can easily be differentiated by echotexture, size, localisation, colour-Doppler and time of appearance (de Jong-Pleij 04, Sharony 99). Canalisation of the nasolacrimal pathway solves the problem, which even may occur before birth (de Jong-Pleij 04, Gutierrez 04). A dacryocystocele may be part of numerous syndromes but often is an isolated finding. Bilateral dacryocystoceles have been described (Goldberg 00, Rustico 04). Several case reports with 2D or 3D ultrasound are published since 1987 (Davis 87, Sharony 99, de Jong-Pleij 04, Gutierrez 04).

Miscellaneous
Bault used 3D ultrasound for visualisation of the retina and was able to demonstrate a retinal coloboma (Bault 08, Bault 09). Mahieu-Caputo described retinal detachment at 34 weeks' gestation in a case with Walker-warburg syndrome (Mahiue-Caputo 03).
Birnholz defined the optic nerve as hypoechoic band in the retrobulbair fat, in 1985. Recently Haratz proposed fetal optic nerve sheath measurements as a non-invasive tool for assessment of increased intracranial pressure (Birnholz 85, Haratz 11).
A hyperechogenic pattern of the anterior chamber with a central defect is described in a case with Peter-plus symdrome. In Peter-plus syndrome dysgenesis of the anterior segment results in typical ocular anomalies like corneal opacity and strands running from the iris and lens to the central posterior cornea (Boog 05).

2.4 EXTERNAL EARS

Ear anomalies are frequently encountered in syndromes (Jones 97).Yet the fetal ears have received little attention in prenatal ultrasound, although 3D ultrasound has renewed interest in the external ear. A retrospective analysis of 16 698 fetuses between 2000-2005 in Sweden revealed that no ear malformations were detected on routine ultrasound, although the prevalence of minor ear anomalies was 2.4 per 1000 and of mayor ear (presented in combination with eye, face and neck) malformations 0.3 per 1000 (Romosan 09). Autopsy on 274 second trimester abortions of fetuses with malformations revealed that none of the 4 ears anomalies were detected by ultrasound examination in a tertiary referral center (Kaasen 06).
When ears are surrounded by amniotic fluid they are quite easy to identify. Hence case reports describing ear anomalies are published since the eighties, first with 2D ultrasound (Hill 87, Köble 02, Martinelli 04) followed by case reports using 3D ultrasound (Tanaka 02, Hsu 02, Volpe 04, Johnson 05, Molina 08, Martino 09, Chaoui 11) It must be noted that the ear anomalies were not isolated in most case reports.
Yang showed in a second and third trimester study that the visualisation rate in the transverse view at cervical vertebra level and the parasagittal view was significantly higher than in the transverse view at the mandible level or in the coronal view. The best time for fetal external ear observation was in the same study between 17–24 6/7 weeks gestation (Yang 10). The ears are likely to image very well in the first trimester, when the amount of amniotic fluid is relatively large.

Table 2.3 Summary of publications on objective measurements related to the eye

author (year)	*method**	*measure*	*GA weeks*	*N Population*	*relation with GA (if not available, another parameter is set out)*
ORBIT					
Jeanty (1982)	2D abd axial	OD IOD BOD	12-42	188	OD = 1.257 GA – 0.014 × GA² – 9.316, r = 0.93 IOD = 0.473 × GA + 3.303, r = 0.8 BOD = 3.345 × GA – 0.034 × GA² – 20.085, r = 0.95
Mayden (1982)	2D abd coronal/ axial	IOD BOD	12-40	180	IOD = -2.961 + 0.455 × DBP(mm) – 0.002 × DBP(mm)², r = 0.761 BOD = –4.128 + 0.978 × DBP(mm) – 0.003 DBP(mm)², r = 0.927
Jeanty (1984)	2D abd axial	BOD	10-40	177	GA = 1.526 + 0.595 × BOD(mm) – (6.205e – 6) × BOD(mm)²
Birnholz (1985)	2D abd axial/coronal/ sagittal	OD	12-41	157	various linear relations within 4 week blocks, with growth spurts between 16-20, 28-32 and after 37 weeks
De Elejalde (1985)	2D abd coronal/ axial	IOD BOD	10-40	1108	3rd, 5th, 10th, 25th, 50th, 75th 90th 95th, 97th centiles for GA are given related to IOD and BOD
Tongsong (1992)	2D abd axial	BOD	14-40	555 Thai	Predicted mean BOD for each gestational week is given
Brons (1988)	2D abd axial	OD IOD BOD	12-40	63 Dutch	10th, 50th and 90th percentile for OD, IOD and BOD are given related to GA
Trout (1994)	2D abd axial	IOD BOD	12-37	422 high risk	IOD = –4.14 + 0.94 × GA – 0.007 × GA², r² = 0.84, P<0.001 BOD = –22.17 + 3.36 × GA – 0.03 GA², r = 0.96, P<0.001
Piantelli (1994)	2D abd Plane were eyes are symmetrical	BOD	7-40	72	GA = 1.53 + 1.24 × BOD –0.02 × BOD² + 0.00033 BOD³, r = 0.81, P<0.001
Achiron (1995)	2D vag/abd axial	OC	12-37	450	linear relationship, r² = 0.79, P<0.0001 Predicted mean for gestational age is given
Goldstein (1998)	2D vag/abd coronal/ axial	OD OC OA	14-36	349	OD = –0.66 + 0.5 × GA, r = 0.94, P<0.0001 OC = –2.1 + 1.5 × GA, r = 0.94, P< 0.0001 OA = –98.1 + 8.3 × GA, r = 0.94, P<,0.0001
Jacquemyn (2000)	2D abd axial	BOD	18-40	202 Belgian Turkisch 44 Maroccan	BOD = –15 + 40 × GA – 4.9 × GA² BOD = –14 + 40 × GA – 4.9 × GA²
Achiron (2000)	2D vag/abd axial	AOL	14-38	231	AOD = –0.32 + 0.47 × GA, r = 0.924, P<0.0001
Dilmen (2002)	2D vag/abd coronal/ axial	OD OC OA	15-40	335	OD = 0.36 + 0.46 × GA, r² = 0.92, P<0.0001 OC = 1.15 + 1.43 × GA, r² = 0.92, P<0.0001 OA = -100.13 + 8.73 × GA, r² = 0.95, P<0.0001
Rosatie (2002)	2D vag axial	OD IOD BOD	11-16	2717	OD = –7.395 + 0.142 × GA, r² = 0.821, P<0 0001. IOD = –8.085 + 0.168 × GA, r² = 0.846, P<0.0001 BOD = –20.129 + 0.421 × GA, r² = 0.813, P<0.0001

author (year)	*method**	*measure*	*GA weeks*	*N Population*	*relation with GA (if not available, another parameter is set out)*
Guariglia (2002)	2D vag axial	OD IOD BOD	10-16	923	OD = 0.132 × GA – 6.435, r^2 = 0.79 IOD = 0.153 × GA – 6.73, r^2 = 0.82 BOD = 0.387 × GA – 16.85, r^2 = 0.80
Green (2005)	coronal	OD IOD OD/IOD	11-14	301	OD: linear, r^2 = 0.52, P<0.01 IOD: linear, r^2 = 0.40, P<0.01 OD/IOD = constant through gestation, r^2 = 0.00, P<0.01
Sukonpan (2008)	2D abd coronal/ axial	OD OC OA	15-40	595 Thai	OD = 0.46 + 0.431 × GA, r^2 = 0.96, P<0.0001 OC = 1.942 + 1.379 × GA, r^2 = 0.97, P<0.0001 OA = -98.678 + 8.493 × GA, r^2 = 0.98, P<0.0001
Odeh (2009)	3D vag/abd	volume	14-40	203	right eye: r = 0.946, P<0.001 left eye: r = 0.945, P<0.001 both: increased from 0.12 to 2.63 ml mean eyeball volume for each gestational age is given
EYE CHAMBERS					
Achiron (2000)	2D vag/abd axial	ACD PCD	14-38	231	ACD = 0.47 + 0.14 × GA, r = 0.784, P<0.0001 PCD = –0.68 + 0.33 × GA., r = 0.929, P<0.0001
PALPBRAL FISSURE					
Mielke (1997)	2D abd coronal	PFS	14-36	70	Inferior angle between palpebral fissure and midline: 89º (r, 87º-90º), constant throughout gestation
LENS					
Achiron (1995)	2D vag/abd	LC	12-37	450	linear relationship, r^2 = 0.88, P<0.001 Predicted mean for gestational age is given
Goldstein (1998)	2D vag/abd coronal/ axial	LD LC LA	14-36	349	LD = 0.88 + 1.4 × GA, r = 0.89, P<0.0001 LD/OD = 0.53 – 0.05 × GA, r = 0.55, P<0.0001 LC = 2.78 + 0.4 × GA, r = 0.89, P<0.0001 LC/OC = 0.54 – 0.05 × GA, r = 0.57, P<0.0001 LA = –7.95 + 1.0 × GA, r = 0.89, P<0.0001 LA/OA = 0.3 – 0.04 × GA, r = 0.57, P<0.0001
Dilmer (2002)	2D vag/abd coronal/ axial	LD LC LA	15-40	335	LD = 1.57 + 0.12 × GA r^2 = 0.89, P<0.001 LC = 1.92 + 0.38 × GA, r^2 = 0.89, P<0.001 LA = –5.17 + 0.89 × GA, r^2 = 0.90, P<0.001
Sukonpan (2008)	2D coronal	LD LC LA	15-40	595 Thai	LD = 1.246 + 0.116 × GA, r^2 = 0.89, P<0.0001 LC = 3.989 + 0.494 GA, r^2 = 0.93, P<0.0001 LA = –6.694 + 0.922 × GA, r^2 = 0.95, P<0.0001
Kivilevitch (2010)	2D oblique anterior coronal	ILD BOD/ILD	12-37	377	ILD = –27.287 + 3.782 × GA – 0.078 × GA^2 + 0.001 × GA^3; r^2 = 0.969 BOD / ILD ratio = 1.5 (+ 0.08) constant throughout gestation (P>0.05)

*, method included dimensionality, abdominal or vaginal approach and plane used for measurement, when stated; 2D, measurements performed with two-dimensional ultrasound; 3D, measurements performed with three-dimensional ultrasound; abd, abdominal; vag, vaginal; ID, interocular distance; BOD, biocular distance; OD, ocular diameter; DBP, distancia biparietalis; AOL, axial ocular length; ACD, anterior ocular chamber depth (posterior aspect of lens-inner border eyelid); POC, posterior ocular chamber depth (posterior edge of bony orbit-posterior aspect of lens); VC, vitreous circumference; LC, lens circumference; LD, lens diameter; LA, lens area; ILD interlens distance; BOD/ILD, biocular distance/interlens distance ratio; GA, gestational age; w, weeks; ethnicity is mentioned when specifically stated.

Anomalies of the ear can be categorised as aberrant:

- size
- location
- rotation
- shape

and miscellaneous anomalies like:

- pre-auricular skin tags
- pre-auricular pits
- asymmetry
- earlobe creases

Ear size

Auricular biometry (length and width) during the second and third trimester was published with 2D ultrasound (Birnholz 88, Shimizu 92, Lettieri 93, Awwad 94, Chitkara 00, Yeo 03). A first trimester study was published in 2003 (Sacchini 03). 3D ultrasound based reference ranges also appeared (Chang 00, Roelofsma 07, Hatanka 11). They are presented in Table 2.4 and Figure 2.4. All studies except two (Yeo 03, Roelofsema 07) found linear growth of ear length and width with gestational age. The width to length ratio is stable from 18 weeks on with a mean of 65.4% (SD, 8.43%) (Shimizu 92). This is also described in a postmortem study (Gill 94). 2D and 3D ultrasound derived measurements seem to give similar results (Hatanaka 10) (Figure 2.4).

Several sonographic studies have examined the potential value of measuring fetal ear length at 14–36 weeks of gestation in prenatal screening for trisomy 21 and report contradictory results, with sensitivities from 26 to 78% and false-positive rates of 1.2–8.0% (Letteiri 93, Awwad 94, Shimzu 97, Chang 00, Chitkara 02). One first trimester study concluded that the degree of deviation from normal is too small for ear length measurement to be useful in screening for trisomy 21 (Sacchini 03).

Ear location, rotation and shape

Detailed descriptions with objective measures or markers for location and shape of the external ear are lacking. As a result, the diagnoses are made subjectively. Location, rotation and shape of the external ear can be examined with 2D ultrasounds, however 3D rendered views offer a much clearer image (Birnholz 83, Shih 98, Magione 03).
Several case reports descriping low set ears are published (Hill 87, Hsu 02, Reus 11). Cases of otocephaly in which the ears are fused beneath the maxilla (the mandible is lacking) are published using 2D or 3D ultrasound (Cayes 85, Chaoui 11). Birnholz describes with 2D ultrasound the ridge type in relation to gestational age and found the mature type 3 only beyond 33 weeks (Birnholz 1983). Recently, proposals to analyse quantitative fetal ear rotation with 3D ultrasound are published (Hatanka 11, Ginseng 11).

Table 2.4 Summary of publications on objective measures related to the ear

author (year)	*method**	*measure*	*GA (weeks)*	*N*	*relation with GA (if not available, another parameter is set out)*
Birnholz (1988)	2D sagittal	EL	15-42	180	EL = 1.1011 × GA − 9.5089, r^2 = 0.962
Shimizu (1992)	2D sagittal	EL EW ER	18-42	124	Linear, r = 0.956, P ,0.0001 EW Linear, r = 0.898, P ,0.001 ER Stable at 65.39 ± 8.43%, r = 0.046, P = 0.605 Scatterplots with percentile line are provided
Lettieri (1993)	2D coronal	EL	14-25	452	EL = 1.161 × GA − 9.731, r = 0.84, P ,0.001
Awwad (1994)	2D coronal	EL	20-28	408	EL = -6.000 + 1.075 × GA
Chitkara (2000)	2D	EL	15-40	2583	EL = 1.076 × GA − 7.308, r = 0.96, P<0.0001 r = 0.96, P = 0.0001
Yeo (2003)	2D sagittal or coronal	EL	14-41	447	EL = -9.458 + 0.964 × GA + 0.024 × GA^2 − 0.0005 × GA^3, r^2 = 0.96, P<0.001
Chang (2000)	3D	EL EW EA	17-41	122	EL = 1.752 × GA − 0.016 × GA^2 −10.765, r = 0.881 EW = 0.398 × GA − 0.989, r = 0.848 EA = 0.171 × GA − 2.239, r = 0.890
Roelofsema (2007)	3D multiplanar mode sagittal	EL	18-34	494	EL = 14.40 + 1.310 × (GA −20) −0.0158 × $(GA -20)^2$
Hatanka (2011)	3D rendering mode sagittal	EL	19-24	114	EL = exp(1.215 × (GA − 8.692) r^2 = 0.423
Sacchini (2003)	2D coronal	EL	11-14	450	EL = 0.095 + 0.081 × CRL r = 0.76, P < 0.0001

*, method included dimensionality and plane used for measurement, when stated; 2D, measurements performed with two-dimensional ultrasound; 3D, measurements performed with three-dimensional ultrasound; abd, abdominal; vag, vaginaal; GA, gestational age; EL, ear length; EW, ear width; ER, ear ratio.

Miscellaneous

Pre-auricular skin tags are published in several case reports, usually as part of a malformation syndrome (Volpe 04, Martinell 04, Molina 08). Asymmetry is not uncommon (Shih 98, Tanaka 02, Martinelli 04, Martino 09). Shih describes asymmetry in 3 of the 18 fetuses with anomalous ears (Shih 98). Oedematous external ears are reported in fetuses with severe hydrops (Birnhoz 83, Shih 98).

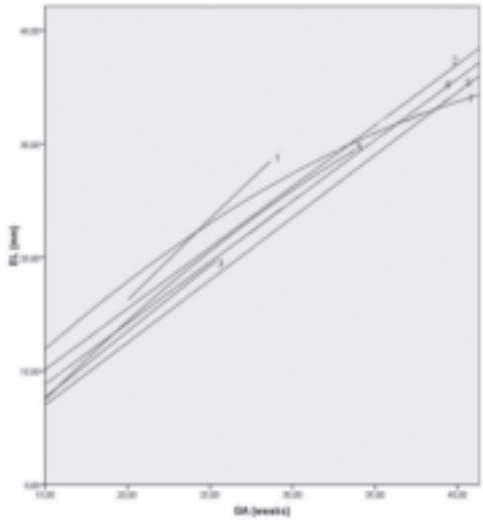

Figure 2.4 Relationships between ear length (EL) and gestational age (GA) in the studies of Awwad (1), Yeo (2), Lettieri (3), Chitkara (4), Birnholz (5), Roelfsema (6) and Chang (7). Roelfsema and Chang used 3D ultrasound.

2.5 NOSE

The nose with its central position probably decisively influences the visual impression of the face. The nose can easily be identified from 11 weeks' gestation (Christ 83). Protocols for prenatal screening contain no specific search for nose anomalies. Most publication describing nose anomalies are case reports or series, reporting fronto-nasal dysplasia (Shipp 02, Sleurs 04, Tonni 06, Guigue 11), maxillonasal dysplasia (Cook 00, Cuillier 05) oculoauriculofrontonasal syndrome (Johnson 05), total arhinia (Cusick 00), split nose (Blaas 02) or tumours (Biasio 06, Beckman 10). Nose anomalies are frequently encountered in holoprosencephaly (Blaas 02).
Bronstein described the prenatal detection of 16 nasal abnormalities out of 25114 ultrasound examinations (75% low risk, 25% high risk) preformed to screen for fetal anomalies between 12 and 27 weeks' gestation. Four cases (25%) were isolated and 6 cases (40%) were diagnosed with an abnormal karyotype (3 trisomy 18, 1 tripoidy, 1 trisomy 21, 1 tetrasomy 12p) (Bronstein 98). Nicolaides found an abnormal karyotype in 6 of 19 cases (32%) with nasal hypoplasia, proboscis or single nostril (Nicolaides 93).
Reports of biometry of the nose, all measuring nasal width, with 2D ultrasound were published in 1997 and 1998 (Pinette 97, Goldstein 97, Ben-Ami 98) and with 3D ultrasound in 2007 (Roelfsema 07)(Table 2.5). Pinette suggested that nasal width may be useful to identify trisomy 21. However as nasal width is postnatally not significantly wider in trisomy 21 than average (Allanson 93) this marker was questioned (Allanson 98). The ratio of nasal width over nasal bone length calculated by Goynummer between 14-39 weeks' gestation and stable at 1.618 (SD, 0.07) might be more useful in pregnancies at risk for anomalies like chromosomal anomalies (Goynummer 11).

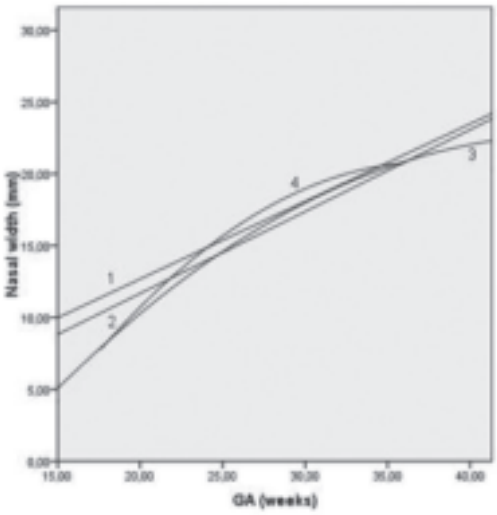

Figure 2.5 Relationships between nasal width and gestational age (GA) in the studies of Ben Ami (1), Goldstein (2), Pinette (3) and Roelfsema (4). Only Roelfsema used 3D ultrasound.

Vicario and Öztük evaluated the nasal root by establishing the normal range of the angle between the nasal bone and the frontal bone in the mid-sagittal plane as an aid to diagnose depressed nasal root (Vicario 10, Öztuk 11). Vicario found an increase of the angle from 119.80º to 125.85º between CRL 45 and 84 mm. Öztürk found a stable angle of 128º (range, 110º-143º) between 18-21 weeks' gestation (Table 2.5).

Nasal bones

The nasal bones have received a lot of attention and there is overwhelming evidence that absent or hypoplastic nasal bones are strong markers for trisomy 21. Excellent reviews have been published by Sonek in 2003 and Shank in 2009, therefor only a short summary is presented here (Sonek 03, Shank 09).

Guise was in 1995 the first to construct normal ranges for the length of the nasal bones in a Caucasian population between 14 and 34 weeks' gestation (Guise 95). Cicero laid the foundations for the use of the nasal bones in first trimester screening in 2001 by describing an association between absent nasal bones and trisomy 21 between 11 and 14 weeks' gestation (Cicero 01). Literature has accumulated and showed that examination of the nasal bones is useful in screening for trisomy 21 in high (Otano 02, Cicero 03) or low risk first trimester populations (Zoppi 03, Orlandi 03, Viora 03).

Second trimester nasal bone hypoplasia or absence was first noticed in three trisomy 21 fetuses in one of the first publications dealing with the nasal bones (Sonek 02). Many studies confirming the benefit of nasal bone assessment in the second trimester followed. Next to nasal bone absence (Vintzileos 03) hypoplasia of the nasal bone became a promising tool in the second trimester risk assessments for trisomy 21 (Cicero 03, Bromley 02, Bunduki 03). Studies have defined nasal bone hypoplasia variously (Cusick 07, Sonek 07): firstly by using a single measurement cut-off like 2.5 mm (Cicero 03) or a percentile (5th or 2.5th) (Bunduki 03), secondly by using ratio's like

BPD/NBL ratio (Bromley 02, Odibo 04)) or PT/NBL ratio (Maymon 05) or thirdly by MoM values (Odibo 07, Odibo 08, Maymon 05, Gianferrari 07).
Three-dimensional ultrasound studies using maximal mode rendering or multiplanar mode indicated that discrepancy between left and right nasal bones and differentiating between absent or hypoplastic nasal bones is better facilitated with 3D ultrasound (Rake 04, Concalves 04, Peralta 05, Benoit 05). Research on advantages and disadvantages of 3D multiplanar mode in generating the exact mid-sagittal plane is still ongoing (Lee 03, Rembouskos 04, Peralta 05, Chen 09, Persico 10). Although as with 2D ultrasound the correct initial insonation angle is essential to obtain a good 3D image quality (Rembouskos 04) and some authors detected no clear advantages of 3D multiplanar mode over 2D ultrasound (Chen 09), the multiplanar mode gives us insight into the effect of deviating planes on the measurements (Lee 03, Chen 09, Persico 10) and the need to standardise the measurement planes.

Nostrils
Goldstein established nostril distance between 14-40 weeks and found a linear relationship with gestational age (Goldstein 97) (Table 2.5). Although aberrant nostrils are part of many syndromes (Jones 97, Sleurs 04) prenatal identification is scarcely described. Perhaps because they are usually part of a serious malformation syndrome like holoprosencephaly (Blaas 02, Chen 98) or frontonasal dysplasia (Sleurs 04) with other more prominent anomalies leading to the diagnosis. Case reports describing a single nostril (Nicolaides 93, Chen 98, Blaas 02, Johnson 05) or narrow nostrils (Lepinard 00, Hsu 02) are published.

2.6 MOUTH

Minimum evaluation of the fetal face should include an attempt to visualise the upper lip for possible cleft lip anomaly (Salomo 2011, Rotten 04). In 1981 Christ was the first to report the detection of a cleft lip by ultrasound (Christ 81). Recognition of the upper lip and mouth are best achieved using a slight oblique coronal plane touching the nose mouth and chin. Maarse conducted a systematic review of the literature to identify all representative studies reporting on the accuracy of prenatal transabdominal sonographic detection of cleft lip and palate during the second trimester (14–28 weeks) of pregnancy (Maarse 10). The accuracy of 2D ultrasound in detecting CL ± P in low risk populations demonstrates a wide variety in diagnostic accuracy with detection rates between 9% and 50%. In high-risk populations detection rates of CL ± P using 3D ultrasound in tertiary care centers were mostly between 60% and 100%. Pretorius compare 2D and 3D sonographic images of the fetal face to determine whether 3D ultrasound can improve visualization an found that abnormal lips were seen on both 2D and 3D sonograms; however, 3D images of cleft lip were easier to understand for both the family and clinical colleagues (Pretorius 95). Also Maarse concludes that 3D ultrasound can provide a more precise image of the defect, allowing parents to produce realistic expectations (Maarse 10).
Vimercati constructed a standard mouth length chart by calculating week-specific means with centiles in the second and third trimester (Table 2.6) (Vimercati 06).
Case reports are published describing microstomia in agnathia (Yang 03) and otocephaly (Lin 98), microstomia with 'whistling' mouth in Freeman-Sheldon syndrome (Vimercati 06), thick lips in Noonan and Costello syndrome (Levaillant 06, Bakker 11), tent-shaped mouth as presenting symptom of congenital myotonic dystrophy (Mashiach 02), continuous open mouth as a marker for skin diseases, like restrictive dermopathy (Stege 97, Mulder 01) or Pena-Shokier phenotype

Table 2.5 Summary of publications on objective measures related to the nose

author (year)	*method**	*measure*	*GA (weeks)*	*N Population*	*relation with GA (if not available, another parameter is set out)*
Nasal width					
Pinette (1997)	2D abd	NW	14-41	782	NW = −16,097 + 1,684 × GA + −0,018 × GA², r = 0.912, P = 0.002
Goldstein (1997)	2D abd/vag	NW	14-40	302	NW = 0.27 + 0.57 × GA, r = 0.88, P < 0.0001
Ben Ami (1998)	2D abd	NW	15-42	229	NW = 1.876 + 0.54 × GA, r = 0.847, P < 0.001
Roelfsema (2007)	3D multiplan mode abd	NW	18-34	494	NW = 10.72 × 1.153 × (GA−20) + 0.0329 × (GA−20)²
Goy-nummer (2011)	2D abd	NBL/NW	14-39	619	NBL/NW 1.618 (SD, 0.07), constant throughout gestation
Angle between frontal and nasal bones					
Vicario (2010)	2D abd	frontonasal angle (FNA)	11-13+6	400	FNA = 112.83 × 0.155 CRL : increases from 119.80° at CRL 45mm to 125.85° at CRL 84mm.
Öztürk (2011)	2D abd	nasofrontal angle (NFA)	18-21	195	Mean: 143° (SD, 6.6°), range 110°-128°, constant between 18-21 weeks' of gestation
Nostrils					
Goldstein (1997)	2D abd/vag	NoD	14-40	302	Nod = 2.77 + 0.15 × GA, r = 0.54, P<0.0001

*, method included dimensionality and abdominal or vaginal approach used for measurement; 2D, measurements performed with two-dimensional ultrasound; 3D, measurements performed with three-dimensional ultrasound; abd, abdominal; vag, vaginaal; GA, gestational age; NW, nasal width; NBL, nasal bone length; NoD, nostril distance;

(Tongsong 00), large continuous fish-like open mouth in congenital ichthyosis (Meizner 92, Bongain 02, Bargul 11, Tourette 12), and tumors arising from the oral cavity like epignathus (Chevernak 84), epulis (Kim 06), ranula (Fernandez 98, Onderoglu 03) or fibrovascular hamartoma (Coombs 11).
Bronshtein decribes a mustache-like structure on the upper lip in seven fetuses between 14-16 weeks' gestation. The 'mustache' disappeared later in gestation and no anomalies of the upper lip were detected after birth (Bronshtein 98).

Philtrum
Two studies generated normograms of philtrum length (Figure 2.6) (Sivan 97, Gull 05). Abnormal philtrum lengths are part of many syndromes (Jones 97.) Case reports describing a long philtrum are published for Brachmann- de Lange syndrome (Boog 99), Peter-plus syndroom (Boog 05) and Femoral Hypoplasia Unusual Facies syndrome (Woosuk 11). Short philtrum is described in 4p-deletion (Levaillant 05), congenital ichthyosis ((Tourette 12) and a bulging philtrum in Cri-du-Chat syndrome (Sonnier 11).

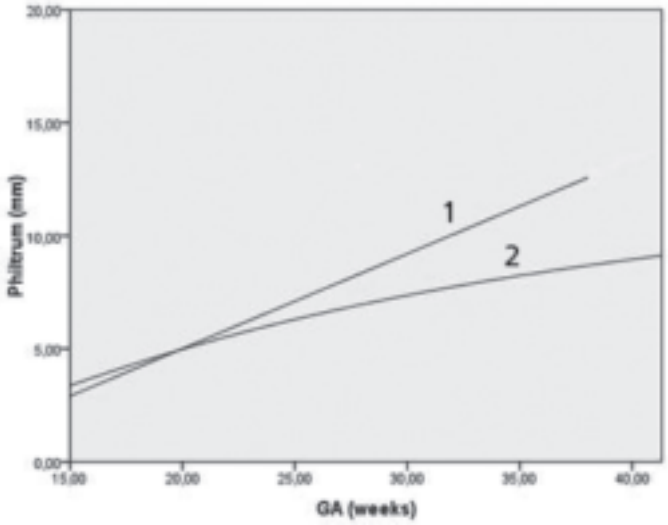

Figure 2.6 Relationships between philtrum length and gestational age (GA) in the studies of Sivan (1) and Gull (2).

Tongue

Achiron established nomograms for tongue circumference and identified cases with microglossia (partial trisomy 1) and macroglossia (trisomy 21) (Achiron 97). Bronshtein constructed nomograms for lingual width and identified a small tongue in three cases with micrognathia. In 5 cases with trisomy 21, 4 with trisomy 13, 3 with trisomy 18, 3 with Turner syndrome and 4 with cleft palate the lingual widths were within the normal range (Bronshtein 98). Macroglossia, subjectively diagnosed as a resting tongue protruding beyond the alveolar ridge (Weissman 95), is a feature in Beckwith-Wiedemann syndrome (Lodeiro 89, Williams 05) and trisomy 21 (Nicolaides 92 & 93, Achiron 97, Weisman 95, Hansman 04, Offerdal 08). Macroglossia can be an isolated sonographic feature (trisomy 21) (Weissman 95, Achiron 97), while microglossia is likely combined with other more striking facial nomalies (Achiron 97, Bronhstein 98, Colombani 06).
A bifid tongue or lingual tumors are rare anomalies, but are described in a case report (Paladini 98, Vincent-Rohfritsch 12).

2.7 MAXILLA

The two main anomalies affecting the maxilla are clefts, with possible protrusion of the premaxilla and hypoplasia, which in contrast yields a flat profile. Although in literature much attention is paid to facial clefts (usually related to sensitivity and specificity of ultrasound examinations), most studies use subjective evaluation. A few studies provide objective parameters (Table 2.7.a). Maxillary nomograms with the aim to detect the midfacial hypoplasia in trisomy 21 cases followed. A nomogram of the maxillary bone length from13 to 40 weeks' gestation is provided by Goldstein (Goldstein 05). In the profile view the length of the rod like maxillary bone was measured. In a comparative study of 23 normal fetuses and 17 trisomy 21 fetuses, with nasal

Table 2.6 Summary of publications on objective measurements related to the mouth

author (year)	*method**	*measure*	*GA (weeks)*	*N Population*	*relation with GA (if not available, another parameter is set out)*
Lip width					
Vimercati (2006)	2D abd coronal	Lip width	15-38	371	Quadratic relation with GA Week-specific means with centiles are given.
Philtrum					
Sivan (1997)	2D abd mid-sagittal	philtrum	16-38	200 African-American	Philtrum = −3.4 + 0.42 × GA, r^2 = 0.87
Gull (2005)	2D abd/vag mid-sagittal	philtrum	13-42	153	Philtrum = e×p (2.779 − 23.477/GA), r^2 = 85.3%, P<0.0001
Tongue					
Achiron (1997)	2D abd/vag axial	tongue circucmference	14-26	120	Circumference (mm) = −23.9 + 3.75 × GA, r^2 = 0.95, P<0.0001 Week-specific means are given
Bronshtein (1998)	2D vag axial	Ligual width	13-18	80	Width = −1.4 + 0.15 × GA, r^2 = 0.83

*, method included dimensionality, abdominal or vaginal approach and plane used for measurement; 2D, measurements performed with two-dimensional ultrasound; 3D, measurements performed with three-dimensional ultrasound; abd, abdominal; vag, vaginaal; GA, gestational age; ethnicity is mentioned when specifically stated and not Caucasian.

bones, Bergann assessed with 3D ultrasound the angle formed by the two maxillary bones at the level of the frontal process in the transverse plane between 18 and 28 weeks' gestation. The mean maxillary angle corrected for gestational age in normal fetuses was 3.24 (SD: ±0.67). The maxillary angle corrected for gestational age in trisomy 21 fetuses was significantly larger: 3.82 (SD: ±0.66) (Bergann 06). Two studies describe the maxillary length or depth between 11 and 13+6 weeks in order to detect the flat face of trisomy 21. (Cicero 04, Dagklis 06). Cicero, measuring with 2D ultrasound in the mid-sagittal plane, found that the maxillary length in trisomy 21 fetuses was significantly shorter than normal by 0.7 mm. However, there was a significant association between maxillary bone length and NT, and in fetuses with absent nasal bone the maxilla was shorter than in those with present nasal bone. Also Dagklis, measuring with 3D ultrasound in the axial plane, found in the trisomy 21 fetuses a significantly smaller depth (mean difference = −0.3 mm, P < 0.001) but concluded that measuring the maxillary depth is probably not useful in identifying trisomy 21, because the value was below the 5th centile of the normal range in only 10% of fetuses with trisomy 21.

Roelfsema assessed, next to the length and curvature of the maxilla, the amount of maxillary protrusion by measuring the angle between the sella-nasion and nasion-anterior rim of maxilla and found a stable angle of 81.08º (95% CI, 80.34º-81.82º) between 18 and 34 weeks' gestation (Roelfsema 06).

Table 2.7a Summary of publications on objective measurements related to the maxilla

author (year)	*method**	*measure*	*GA (weeks)*	*N Population*	*relation with GA (if not available, another parameter is set out)*
Goldstein (1999)	2D abd/vag axial	alveolar ridge width	14-32	323	AR width = −0.37 + 0.101 GA, r = 0.916, P< 0.0001 Scatterplot and table with mean and percentiles at each gestational age are provided
Sherer (2004)	2D abd axial	hard palate	15-41	602	HP width = −0.736 + 0.114 × GA − 0.001 × GA² HP length = −0.820 + 0.118 × GA − 0.001 × GA² HP area = −2.401 + 0.171 × GA + 0.001 × GA² Scatterplots and tables with mean and percentile at each gestational week are provided
Goldstein (2005)		max. length	13-40	327	Max. length = 7.78 + 0.18 × GA, r = 0.645; P < .0001
Bergann (2006)	3D	max. angle		23 nl 17 tri 21	Mean angle: Nl : 3.24° (SD: ±0.67°) Tri 21: 3.82° (SD: ±0.66°) (significant larger)
Cicero (2004)	2D abd sagittal		11-14	839 nl 88 tri 21	Max. length = 0.708 + 0.090 × CRL, r = 0.784; P < 0.0001; maxillary length increased significantly with CRL from 4.8 mm at a CRL of 45 mm to 8.3 mm at a CRL of 84 mm, scatterplot is provided
Dagklis (2006)	3D abd axial	max. depth	11 13+6	862 nl 80 tri 21	Increased linearly with CRL from 3.1 mm at a CRL of 45 mm to 4.8 mm at a CRL of 84 mm Tri 21:on average 0,3 mm shorter (P<0.001)
Roelfsema	3D abd sagittal/ axiaal	max protrusion max length max curvature	18-34	126	Protrusion = 81.08° stable during gestation Length = 19.33 + 1.373 × (GA −20) − 0.021 × GA(−20)² Curvature = 86.46 + 5.93 × (GA −20) − 0.039 × GA(−20)²

*, method included dimensionality, abdominal or vaginal approach and plane used for measurement; 2D, measurements performed with two-dimensional ultrasound; 3D, measurements performed with three-dimensional ultrasound; abd, abdominal; vag, vaginaal; GA, gestational age; max, maxilla(ry); wk, weeks; nl, normal fetuses; tri 21, fetuses with trisomy 21.

FMF angle

The frontomaxillary facial (FMF) angle, defined as the angle between the upper surface of the palate and the frontal bone in a midsagittal view of the fetal face, was introduced in 2007 by Sonek (Sonek 07). The FMF angle does not quantify midfacial hypoplasia by directly measuring the maxilla but by quantifying the location of the front of the maxilla in relation to the forehead. Many publications on the FMF angle followed (Table 2.7.b) and the FMF angle is nowadays, a valuable and useful addition in the first trimester screening for trisomy 21.
Recently it is demonstrated that in fetuses with open spina bifida at 11 +0 to 13+ 6 weeks' gestation the frontomaxillary facial angle is decreased and this measurement may also be useful in early screening for this abnormality (see Chapter 3.2) (Lachmann 10, Acuna 11).

Table 2.7b Summary of most important publications on the FMF angle

author (year)	*objective*	*D & GA (wk)*	*N*	*Corr*	*Mean FMF Normal fetuses*	*Mean FMF Abnormal fetuses*	*conclusion*	*remarks*
FMF and trisomy 21								
Sonek (2007)	FMF in tri 21	3D 11-13+6	300 nl 100 tri 21	(-) CRL (-) NB (-) NT	78,1° range75, 4-104	88,7° range 75,4-104	-FMF sign. larger in tri 21 -FMF may be useful in screening for tri 21 between 11-13+6 wk	feasibility measuring FMF demonstated
Borenstein (2007)	normal range	3D 11-13+6	500 nl	(+↓) CRL (-) serum (-)NT	84,3° at CRL45 76,5° at CRL84	-	-FMF decrease with CRL -no association with NT or serum -FMF is reproducible -2D/3D results similar	FMF in 20% not measurable < 20 min→ FMF unlikely incorporated in 1e trim screening
Plasencia (2007)	reproducibilty	3D 11-13+6	50 nl 50 tri 21	-	78° range 68-88	90° range 77-102	FMF measurement is highly reproducible	landmarks midsag plane: zygomatic process, nose tip
Plasencia (2007)	acquisition plan	3D 11-13+6	103 nl	-	79° range 74-85	--	acquisition plane determines success of FMFmeasurement	
Sonek (2007)	FMF in tri 21	2D 14-23	100 nl 34 tri 21	(+↓) GA (-) NB	-	-	-FMF in 2e trimester is sign. larger in tri 21 -FMF in 2e trimester likely useful in screening tri 21	FMFskin: detection 10% higher
Molina (2008)	FMF in tri 21	3D 16-24	150 nl 23 tri 21	(-)GA	83,9° range 76,9-90,2°	89,4° range 83,1-95,6°	-FMF in 2e trimester is sign. larger in tri 21 -FMF in 2e trim likely sensitive method screening tr 21	-first ray of FMF on palate instead of vomer -angle is higher when NB is absent
Borenstein (2008)	-relation FMF-serum -performance	3D 11-13+6	782 nl 108 tri 21	(+↓) CRL (-) serum (-) NT	83.5° CRL 45 76.4 ° CRL 84		FMF improves performance 1e trim screening	

Odibo (2009)	relation FMF-NB	2D 16-22	201 nl 22 tri 21				the combination resulted in a minimal but nonsignificant improvement in performance	
Alphonso (2010)	comparison 2D-3D	2D/3D 11-13+6	251 nl				FMF is with 3D sign. smaller than with 2D, mean difference is 0.89º	
FMF and tri 13, tri 18								
Borenstein (2007)	FMF in tri 13	3D 11-13+6	500 nl 23 tri 13		see Borenstein 2007		FMF in tri 13 is only sign. increased when associated with holoprosencephalie	
Borenstein (2007)	FMF and MMF in tri 18	3D 11-13+6	200 nl 36 tri 18	FMF& MMF (+↓) CRL	-see Borenstein 2007 -ratio FMF/ MMF 0,74 -MMF 114.5º CRL 45 103.1º CRL 84		FMF is sign. increased and MMF is sign. decreased in tri 18	FMF likely incorporated in 1e trim screening
FMF and open spina bifida								
Lachmann (2010)	FMF in OSB	2D 11-13+6	100 nl 20 OSB		84.0º CRL 45 76.5º CRL 84	9.9º lower than in controls and below the 5th centile in 90%	FMF may be useful in early screening for OSB	
Acuna (2011)	FMF in SB	2D 11-13+6	242 nl 5 SB		90.0º CRL 45 85.9º CRL 84	4 cases below 25 th percentile	FMF might be useful for first trimester SB screening	

FMF, frontomaxillary facial angle; D, dimensionality; 2D, measurements performed with two-dimensional ultrasound; 3D, measurements performed with three-dimensional ultrasound; GA, gestational age; Corr, correlation; (+), significant positively correlated with; (+↓), significant inversely correlated with;(-), no significant correlation with; CRL, crown rump length in mm; NB, nasal bone; NT, nuchal translucency; serum, ßHCG,PAPP-A; MMF,mandibulomaxillary facial angle; tri, trisomy; (O)SB, (open) spina bifida.

2.8 MANDIBLE

The mandible has received relatively much attention as retrognathia is a frequently occurring and serious anomaly (Table 2.8) (Vettraino 03, Paladini 10, Luedders 11).
The first who provided prenatally objective measurements of the mandible was Otto in 1991, followed by Chitty in 1993 (Otto 91, Chitty 93). Both authors measured one ramus of the mandible in an axial scan plane parallel to the mandible from the symphysis mentis to the temperomandibular joint.
Three authors, Watson, Paladini and Zalel use the same plane to measure mandibular depth and width. (Watson 93, Paladini 99, Zalel 06) The width of the mandible is the transverse inner-to-inner distancebetween the rami of the mandible. The depth of the mandible is the anteroposterior distance from the symphysis mentis to the line used for the width measurement. The width was greater than the depth in all cases with faster growth in transverse direction (width) than anteroposterior direction (depth) in all three studies. Paladini introduced the jaw index: anteroposterior diameter/ BPD x 100. He prospectively tested the jaw index in 198 malformed fetuses and compared the results with subjective evaluation. The jaw index showed greater diagnostic accuracy: using a cutoff value of 23, the jaw index had a sensitivity of 100% and a specificity of 98.1%. He also found that in 11 cases with proven micrognathia the anteroposterior growth was more impaired than the transverse growth (Paladini 99). Zalel introduced the mandibular ratio (MR): anteroposterior diameter of the mandible / transverse diameter of the mandible. MR showed a negative linear correlation with gestatonal age (Zalel 06).
Nomograms of the distance between the mandibular angles in the coronal plane were established by Tsai with 3D-ultrasound in Chinese fetuses. This measurement was named mandibular body length (MBL). The ratio BPD / MBL was negatively related to gestational age, meaning the chin grows wider with advancing gestational age, confirming the subjective impression that facial features change from a reverse triangular shape to an oval or square shape during pregnancy (Tsai 04).
In the sagittal plane linear measurements of the fetal chin were provided by Sivan and Gull (Sivan 97, Gull 05). Chin length was measured between the lower lip and the apex of the chin (Sivan 97) or the edge of the skin under the mandibular tip (Gull 05). Gull found a linear growth function through gestation while in Sivans study the curve flattened slightly.
In the latest studies angular measurements in the midsagittal plane are used to define the relative position of the mandible. Rotten uses the inferior facial angle (IFA) defined as the angle formed by the line orthogonal to the vertical part of the forehead at the level of the synostosis of the nasal bones and the line joining the tip of the mentum and the anterior border of the more protruding lip (Rotten 02). This angle was constant from 18 to 28 gestational weeks. The mean IFA was 65.5° (SD 8.13°). In 12 pathological fetuses (Pierre Robin n=8, Treacher Collins n=3, acrofaciale dysostosis n=1) the IFA was smaller than the mean minus 2 standard deviations. Palit describes the frontal naso-mental angle between 18 and 35 weeks. The frontal nasomental angle is defined by one line from the prominent bony part of the forehead to the nasal tip and a second line from the most anterior poin of the soft tissue of the mandible and the tip of the nose. This angle was also constant with a mean of 146.74° (SD 2.7°). In four cases with Pierre Robin syndrome the frontal naso-mental angle was below the 5th percentile (Palit 07). Both Rotten and Palit use soft tissue markers.

Roelfsema assessed, in addition to length and curvature of the mandible, the amount of mandibular protrusion, by measuring the angle between the sella-nasion and nasion-anterior rim of mandible and found a stable angle of 67.25º (95% CI, 66.65º-67.86º) between 18 and 34 weeks' gestation (Roelfsema 06).
Herman used 3D rendered images between 11 and 26 weeks' gestation to assess normative data of several mandibular dimensions: base length, ramus height, total length, mandibular angle (angle between base length and ramus height) and mandibular index (ramus height / base length)
The presence or absence ('mandibular gap') of the mandible in the retronasal triangle view (coronal plane of the face in which the primary palate and the frontal processes of the maxilla are visualised simultaneously) is recently described as a promising new marker to diagnose retrognathia in the first trimester. The mandibular gap was absent and replaced by a bony structure representing the receding chin in cases with retrognathia (Sepulveda 12).

Table 2.8 Summary of publications on objective measurements related to the mandible

author (year)	*method**	*GA (wk)*	*measure*	*N Population*	*relation with GA (if not available, another parameter is set out)*
Otto (1991)	2D axial	14-39	-length of ramus (temperomandibular joint – symphysis mentis)	134	Length = $-2.41 + 0.297 \times GA - 0.003 \times GA^2$, $r^2 = 0.960$ Scatterplot and table with mean and 95% prediction limits at each GA are provided
Chitty (1993)	2D Axial	12-27	-length of ramus (proximal end of ramus– symphysis mentis)	184 Western-european Afro-Caribbean	Length = $-46.516 \times 15.735 \times \sqrt{GA}$ Scatterplot and table with mean and percentiles at each GA are provided
Watson (1993)	2D axial	14-40	-Mand depth (MD) (inner surface of jaw –line used for MW) -Mand width (MW) (inner to inner, on line just touching hypopharynx)	204	$r^2 = 0.95$, $P < 0.0001$ $r^2 = 0.94$, $P < 0.0001$ Table with mean (SD) at each GA is provided
Sivan (1997)	2D sagittal	16-38	-Chin length (CL) (lower lip - apex chin)	200 African-American	$CL = -6.5 + 0.7 \times GA$, $r^2 = 0.91$ Graph with mean (2 SD) and table with mean (range) for GA at two weeks intervals are provided

Paladini (1997)	2D axial	12-37	-Mand depth (MD) (symphysis mentis to line used for MW) -Mand width (MW) (between bases of two rami) -Jaw index: (MD/DBPx100)	262	MD : lineair, $r^2 = 0.822$ MW : lineair, $r^2 = 0.868$ Scatterplots with mean and 95% CI are provided Jaw index : mean = 32.2 (CI, 31.6, 32.8 ; SD, 4.9; range 21-51) 5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, 95^{th} percentile : 24.0, 26.0, 29.4, 32.3, 34.8, 37.9, 41.0 respectively
Rotten (2002)	3D multiplan sagittal/ axial	18-28	-Mand width (MD) -Max width (MX) (MD and MX measured 10 mm posterior to anterior osseous border) -MD/MX ratio -Inferior facial angle (IFA) (line orthogonal to forehead–line joining mentum and most protrusive lip)	371	MD = 0.74 × GA + 7.76, $r^2 = 0.206$, $P < 0.0001$ MX = 0.75 × GA + 7.41, $r^2 = 0.106$, $P < 0.0001$ MD/MX = 1.017 (SD, 0.116), –2SD is 0.785 IFA = 65.5 (8.13)°, –2SD is 49.2° Scatterplots with mean and 95% prediction limits are provided
Tsai (2004)	3D rendering coronal	15-35	-Mand body length (distance between mandibular angles) -Chin width index: (DBP/ mand body length)	183 Chinese	Mand body length: pos. correlation with GA, $r^2 = 0.857$ Chin width index: neg. correlation with GA, $r^2 = 0.343$ Scatterplots with mean and 95% CI are provided
Gull (2005)	2D sagittal	13-42	-Chin length (tip of lower lip – edge of skin under mandible)	153	Chin length = exp(3.792 –28.043/GA, $r^2 = 0.89$, $P<0.0001$ Scatterplot with mean, 5^{th} and 95^{th} percentiles are provide
Zalel (2006)	2D axial	11-31	-Mand length (ML) -Mand width (MW) (both inner-inner) -Mand ratio: (ML/MW)	490	Tables with mean (±1SD and 2SD) of ML and MW are provided ML/MW = 1.776 – 0.011 × GA, $r^2 = 0.05$, negative correlation wth GA, (1.5 at 20 wk)
Roelfsema (2007)	3D multiplan sagittal/ axial	18-34	-Mand protrusion (MP) (line sella nasion – nasion anterior rim mand) -Mand length (ML) (frontal rim mand –last tooth bud) -Mand curvature (MC) (curvature tragus–gnathion x2)	126	MP = 67.25° (95% CI, 66.65–67.86 °), stable during gestation ML = 15.58 + 1.154 × (GA-20) – 0.010 × $(GA-20)^2$ MC = 80.96 + 5.470 × (GA-20) Scatterplots with mean and percentiles are provided

Palit (2008)	2D sagittal	18-35	-Fronto-naso-mental angle (line prominent part bony forehead and nosetip– line prominent part soft tissue chin and nosetip)	81	mean 146.74° (SD, 2.7²), 5th and 95th percentile are 142° and 151°
Hermann (2010)	3D rendering sagittal	11-26	-Base length (BL) (prognathion-posterior mand line point) -Ramus height (RH) (posterior mand line point-condylion) -Total length (TL) (condylion-prognathion) -Mand angle (MA) (angle between BL-RH) -Mand index (MI) (RH/BL)	54	BL increases form 5.2 mm at 11 wk with 1.2 mm/wk RH increased from 2.7 mm at 11 wk with 0.64 mm/wk TL increased from 7.7 mm at 11 wk with 1.7 mm/wk MA decreased from 149° at 11 wk with 0.9°/wk MI was stable at 0.53–0.55 Scatterplots with mean, CI and, prediction intervals are provided

*, method included dimensionality and plane used for measurement; 2D, measurements performed with two-dimensional ultrasound; 3D multiplan, measurements performed with multiplanar three-dimensional ultrasound; 3D rendering, measurements performed with three-dimensional rendered images ;abd, abdominal; vag, vaginal; GA, gestational age; wk, weeks; mand, mandibula(r); max, maxilla(ry); SD, standard deviation; CI, confidence intervals; population, ethnicity is mentioned when specifically stated and not Caucasian;

Miscelaneous

Absence of the mandible (agnathia), usualy lethal, can occur alone (Scholl 77, Yang 03) or in combination with other malformations like in otocephaly (Lin 98) or holoprosencephaly (Rolland 91, Ebina 01).

Clefts of the mandible are rare, but a prenatal diagnosis has been described (Vincent-Rohfritsch 12).

2.9 MISCELLANEOUS

Craniofacial variability index

In order to combine several dimensions of the head and neck an attempt was made to apply the craniofacial variability index (CVI) developed by Garn in prenatal ultrasound (Garn 85, Escobar 93, Roelfsema 07). For calculation of the CVI measurements of the head and face are expressed as Z-scores, relative to standards for age and sex. The standard deviation of the set of Z-scores results in the CVI, which indicates the extent to which the craniofacial complex of a fetus is dimensionally more variable than might be expected. The CVI is introduced prenatally in 1993 with 2D ultrasound by Escobar after establishing normal values of 24 measurements (Escobar 88, 90). In 2007 Roelfsema used 3D multiplanar ultrasound to design a CVI based on 16 measurements and applied the CVI in fetuses with isolated or syndromal cleft lip/palate. More abnormal Z-scores and higher CVI's in the syndromal fetuses were found (Roelfsema 07).

Facial width

Abramowicz assessed cheek-to cheek diameters on a coronal view at the level of the nostrils and lips as an index of the amount of adipose tissue (cheek-to-cheek diameter = −0.908 + 0.195 × GA, $r^2 = 0.806$) and found significant smaller or larger diameters in small- or large-for-gestational-age fetuses. Large-for gestational-age fetuses of diabetic mothers exhibited higher cheek-to-cheek/ biparietal diameters than large-for gestational-age fetuses of nondiabetic mothers ((Abramowicz 91, Abramowicz 93).

The bizygomatic and bigonial breadth is assessed in a 3D ultrasound study by Roelfsema: bizygomatic breadth = −30.27 + 2.145 × (GA -20), bigonial breadth = 23.16 + 1.392 × (GA -20) (Roelfsema 07).

Dimensions of the profile

Goldstein determined dimensions of the lower fetal facial profile at 14–33 weeks' gestation (Goldstein 10). The ratio's: distance from the tip of the nose to the mouth/distance from the mouth to the gnathion and distance from the upper philtrum to the mouth/distance from the mouth to the upper concavity of the chin, were constant throughout gestation. There was a significant linear correlation between GA and all distances: tip of the nose - mouth ($r = 0.943$; $P < 0.00001$; $y = -37.98 + 7.54 \times GA$), mouth - gnathion ($r = 0.946$; $P < 0.00001$; $y = -46.34 + 7.95 \times GA$), upper level of the philtrum - mouth ($r = 0.71$; $P < 0.00001$; $y = 0.22 + 3.33 \times GA$) and moutht - concavity of the chin ($r = 0.665$; $P < 0.00001$; $y = 1.65 + 2.95 \times GA$).

Tessier clefts

In a small percentage facial clefts are atypical and and occur in different portions of the face. According to the well-established Tessier's classification, the defects are numbered 0 to 14 and classified based on the anatomical position of the cleft, with the orbit as the primary structure of reference (Tessier 76).The most common atypical facial cleft found at birth is Tessier 7, a lateral cleft positioned on the line between the corner of the mouth and the ear. Several case reports describe this cleft (Presti 04, Pilu 05, Troyano11).

Salivary glands

Odeh measured the fetal parotid and submandibular salivary glands at 14–16 weeks using transvaginal ultrasound (Odeh 10).The median length of the parotid gland was 7.5 (range, 5.5–11.5) mm and that of the submandibular gland was 5.4 (range, 3.7–8.5) mm. A case report describing a tumor of the parotis gland is published (Teoh 05).

Tumours

Of course the face can be the location for all kinds of tumours, like haemangioma lymphangioma or teratoma (Kasima 05, Paladini 05, Hui 08, Kamil 08, Ocaranza 11, Beckdache 11).

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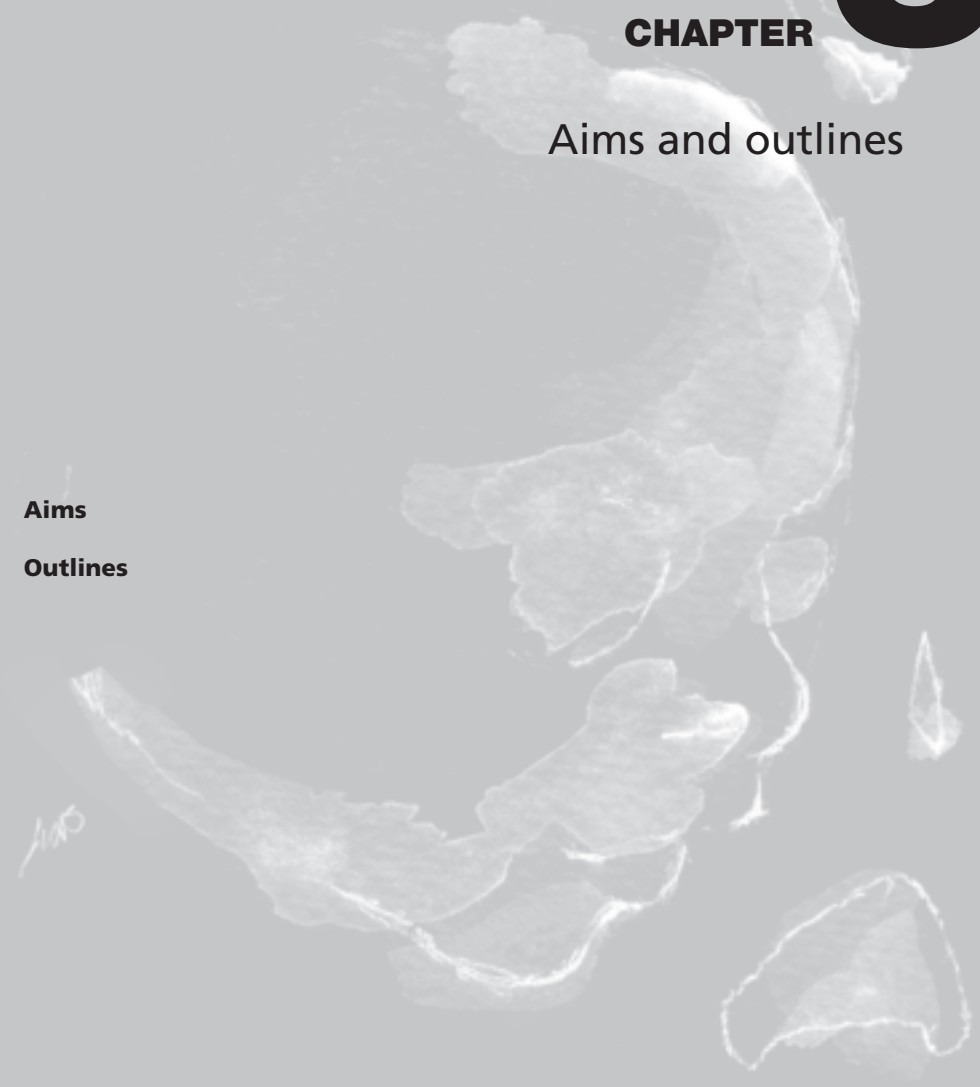
CHAPTER 3

Aims and outlines



3.1 AIMS

The aim of this thesis was to explore various aspects involved with the ultrasound evaluation of the fetal face in the second and third trimester of pregnancy.
These aspects included:

- The study of the additional value of multiplanar three-dimensional (3D) ultrasound next to the traditional two-dimensional (2D) ultrasound, in the evaluation of the fetal profile.
- The search for objective tools to quantify the fetal profile in normal and pathological cases.
- The study of the role of three-dimensional multiplanar ultrasound in improving the measurement of markers for aneuploidies visible in the fetal profile and the evaluation of a new screening tool the nasal bone length/prenasal thickness ratio.
- The investigation of the effect of viewing a 2D or 3D/4D ultrasound image of the fetal face on maternal-fetal bonding and the related opinion of mothers.

3.2 OUTLINES

Part I: ADDITIONAL VALUE OF THREE-DIMENSIONAL MULTIPLANAR ULTRASOUND IN THE EVALUATION OF THE FETAL PROFILE

Chapter 4
In Chapter **4** several clinical applications of 3D multiplanar imaging of the fetal profile are evaluated and compare with 2D ultrasound.

Part II: OBJECTIVE TOOLS TO QUANTIFY THE FETAL PROFILE

Chapter 5, 6 and 7
In Chapter **5** the maxilla-nasion-mandible angle is introduced as a tool to quantify the antero-posterior relationship of the fetal jaw and tested in a group of pathological cases. In Chapter **6** the fetal profile line is introduced and tested in a group of pathological cases. In Chapter **7** the maxilla-nasion-mandible angle and the fetal profile line are applied in fetuses with facial clefts of various severities.

Part III: FACIAL MARKERS FOR TRISOMY 21

Chapter 8 and 9
Chapter 8 and 9 deal with markers for trisomy 21 visible in the fetal profile: the nasal bone length, the prenasal thickness and the frontomaxillary-facial angle.
In chapter **8** the impact of multiplanar 3D ultrasound on imaging and measurability of the markers is explored and in chapter **9** the prenasal thickness: nasal bone length ratio is proposes and tested in normal and trisomy 21 fetuses.

Part IV: EFFECT ON MOTHERS

Chapter 10

Chapter **10** deals with the effect of 3D/4D ultrasound of the fetal face in the third trimester of pregnancy on maternal-fetal bonding and with the reaction of mothers.

A review of literature is presented quantifying the psychological effect of 3D/4D ultrasound on women carrying structurally normal fetuses.

PART I additional value 3D US

CHAPTER 4

Three-dimensional multiplanar ultrasound is a valuable tool in the study of the fetal profile in the second trimester of pregnancy

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ABSTRACT

Objectives

To evaluate the additional value of three-dimensional (3D) multiplanar ultrasound in the examination of the fetal profile.

Methods

Two 3D volumes of the fetal head were obtained from 84 fetuses at 22 to 29 weeks' gestation. The volumes were taken starting at the midsagittal plane with the fetus facing the transducer. The success rate and acquisition time to obtain each volume and display the exact midsagittal plane by 3D multiplanar ultrasound were analyzed. The correction angles from the original two-dimensional (2D) profile view to the exactmidsagittal plane were noted. Of six measurements, related to the fetal nose and jaws, the success rate and the intraobserver reproducibility between the 2D and the 3D multiplanar ultrasound were compared.

Results

In 81 (96.4%) cases we succeeded in obtaining a profile volume, 70% of the volumes being obtained within 10 min. It was possible to define by multiplanar mode the exact midsagittal plane in less than 1 min. The mean rotation necessary to obtain the exact midsagittal plane with 3D multiplanar mode was significantly larger around the y-axis (11.9°) than around the z-axis (4.3°) of the fetus. For between 5 and 12% of the six measurements under investigation it was not possible to obtain values with 2D ultrasound. However, 3D ultrasound made these measurements possible in at least one volume. The intraobserver reproducibility was higher with 3D multiplanar ultrasound than with 2D ultrasound, this difference being statistically significant for five of the six measurements.

Conclusions

3D multiplanar ultrasound improves the topographic depiction of the midsagittal profile view, enables correct measurement of anatomical details and improves intraobserver reproducibility. 3D multiplanar ultrasound is a powerful instrument for investigating the fetal profile.

INTRODUCTION

The specific diagnosis of a fetal facial anomaly is a challenge, even for experienced investigators, but prenatal recognition of a facial anomaly is important because it can lead to the suspicion of genetic disorders such as syndromes or chromosomal abnormalities[1–6]. For more than a decade three-dimensional (3D) ultrasonography has been used as a complementary tool to two-dimensional (2D) ultrasonography for the evaluation of fetal anatomy.
Many studies have investigated the additional value of 3D ultrasound in identifying facial malformations. 3D ultrasound seems to improve ultrasound performance in recognizing facial anomalies[7–14], although this is not unanimously accepted[15]. Most studies involve qualitative methods but a more quantitative approach may be necessary for the detection of minor anomalies of the fetal face.
When searching for facial anomalies, investigation of the fetal profile is a fundamental part of the examination. Many facial anomalies such as retrognathia or a flat face are only recognizable in the profile view. Several authors have mentioned profile-related anomalies that are not visible with 2D ultrasound but that are subsequently diagnosed with 3D ultrasound[9,13,16].
The aim of this study was to evaluate the additional value of 3D ultrasound in the examination of the fetal profile by analyzing the ability to obtain, and the time needed for obtaining, an exact midsagittal profile view by 3D multiplanar ultrasound and the angles necessary to correct the original 2D profile to the exact midsagittal plane. We also compared the success rate in obtaining a set of six predefined profile measurements by 2D and 3D multiplanar ultrasound and tested intraobserver reproducibility.

METHODS

The study was approved by the local ethics committee and all women gave written consent. Study data were obtained from 84 healthy, low-risk, pregnant Caucasian women with a singleton pregnancy. Women were recruited at the time of their dating scan or routine second-trimester anomaly scan. They were asked to attend for an additional examination at between 22 and 29 weeks' gestation. Only non-anomalous fetuses were included. Gestational age was determined from the last menstrual period combined with a first-trimester dating scan. The examinations were carried out transabdominally, using a General Electric Voluson 730 Expert ultrasound system (GE Medical Systems, Zipf, Austria). In the course of the study the 2–5-MHz transducer was replaced by a 4–8-MHz transducer.The ultrasound image of the fetal head was enlarged to at least one third the size of the screen, the render box was placed such that the whole fetal head was included within it and the angle of the volume was adjusted to the size of the fetal head. Volumes were obtained with high-2 or maximum quality depending on the behavioral state of the fetus. A normal frequency range was used in most women, but this was changed to "resolution" or "penetration" in cases of slim or obese women. Each fetus was analyzed only once for the purpose of this study. The time needed to visualize the profile was noted.
The ultrasonographer's first task was to acquire a volume of the fetal head with the fetus facing the transducer in the midsagittal plane. Subsequently a second volume was acquired after the probe had been lifted from the maternal abdomen and put in place again. Special care was taken to avoid movement artifacts. The mother was asked to hold her breath during acquisition when necessary. Biometric measurements, the position of the baby and the amniotic fluid index (AFI)

were noted and a global fetal examination was carried out. When the baby moved to a more favorable position during the scan, additional volumes of the profile were taken. The causes of unsatisfactory 3D volume acquisition were noted. All examinations were carried out by one experienced ultrasonographer (E. J. P.). The volumes were stored on removable digital media for subsequent analysis on 4D View software, version 7.0 (GE Medical Systems).
Six measurements – nose length (NL), nose protrusion (NP), philtrum length (Ph), pronasale-subnasale distance (PS), facial height (FH) and maxilla-nasion-mandible angle (MNM), including bony landmarks when possible – were chosen for this study (Table 1 and Figure 1).

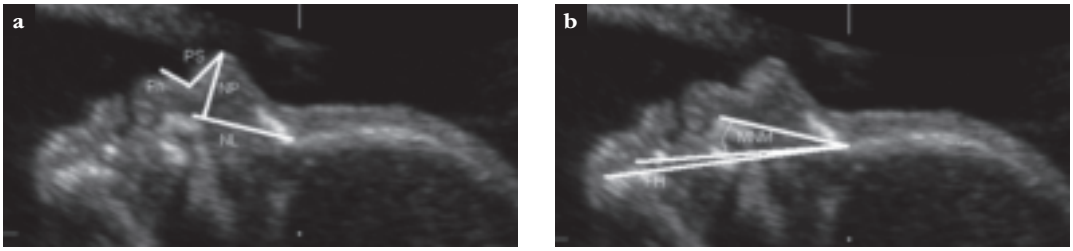

Figure 1 Ultrasound images of the fetal face showing nose length (NL), nose protrusion (NP), philtrum length (Ph) and pronasale-subnasale distance (PS) (a) and facial height (FH) and maxilla-nasion-mandible angle (MNM) (b).

For each fetus the two volumes that were closest to the exact midsagittal plane and that showed the profile landmarks for the measurements mentioned above most clearly, were chosen for analysis. The unprocessed picture in the A-plane represents the original 2D profile (2Dpr). After correcting the A-plane with the multiplanar mode to the exact midsagittal plane, the picture in the A-plane was named the 3D profile (3Dpr). For every volume the amount by which it was necessary to rotate the volume around the y- and z-axes of the fetus, to obtain an exact midsagittal profile in the A-plane, was noted. The angle on the 4D View software changes at fixed steps of 4 or 5° starting with 2° (2°, 6°, 10°, 14°, 19°, 23° etc.). In the unprocessed B-plane of the multiplanar

Table 1 Nomenclature of measurements and landmarks

Measurement	*Abbreviation*	*Description*
Nose length	NL	Distance between nasion* and upper anterior corner of maxilla
Nose protrusion	NP	Distance between pronasale landmark† and line used for nose-length measurement (perpendicular on the NL line)
Pronasale-subnasale distance	PS	Distance between pronasale and subnasale landmarks‡
Philtrum length	Ph	Longest straight distance from the line along the skin from the subnasale landmark to the upper lip
Facial height	FH	Distance from the nasion to the lower anterior corner of the mandible
Maxilla-nasion-mandible angle	MNM	Angle between the lines maxilla-nasion and mandible-nasion. The landmarks on the maxilla and mandible are in the middle of the anterior borders of the jaws

*The nasion landmark is located in the midline, at the intersection of the frontal bones and the nasal bones. †The pronasale landmark is the most protruding point of the apex nasi. ‡The subnasale landmark is located in the midline at the columella base, where the lower border of the nasal septum and the upper lip meet.

view the distance from the tip of the nose to the original plane of acquisition was measured (Figure 2). In the first volume, the six measurements were taken from the profile in the unprocessed A-plane (2Dpr-1). After a minimum of 3 days the six measurements were repeated in the profile in the A-plane that had been multiplanar-mode corrected (3Dpr-1). Again, after a minimum of 3 days, the same procedure was repeated for volume 2 (2Dpr-2 and 3Dpr-2). For all measurements the examiner was blinded to all previous results.

The data were described using percentages and means with range or SD when appropriate. Correlation was determined using Pearson's correlation test. The statistical significance of the difference of the means of two groups was tested with the unpaired Student's *t*-test, and Bland–Altman analysis was used to compare the measurement agreement and bias for paired measurements[17]. Equality of variance was tested by means of Levene's test for this parameter. $P < 0.05$ was considered statistically significant. The data were analyzed using the statistical software SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA) and Excel for Windows 2000.

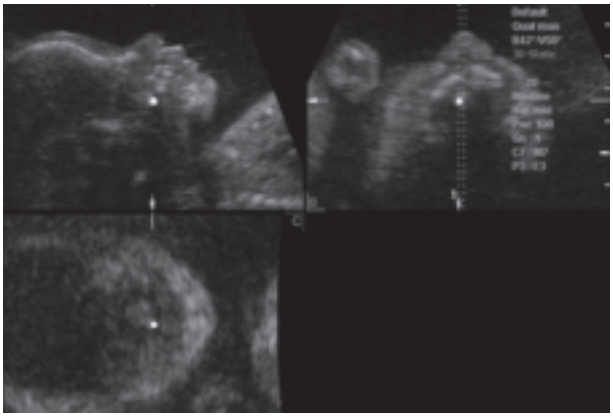

Figure 2 In the unprocessed multiplanar view, the marker dot in the A-plane was moved towards the nose tip. Subsequently the distance between the original plane of acquisition (dashed line through marker dot) and the nose tip (dashed line through nose tip) was measured in the B-plane with the "distance-between-two-lines" option.

RESULTS

In total 84 investigations of fetuses at between 21 + 4 and 28 + 5 weeks' gestation (mean, 25 + 1 weeks) were included in the study. Fifty-two investigations (61.9%) were performed with the 2–5-MHz transducer and 32 (38.1%) with the 4–8-MHz transducer. Mean body mass index of the women before pregnancy was 24.4 (range, 18.2–34.9) kg/m^2. The mean AFI was 18.6 (range, 11.7–25.9). The position of the fetus was cephalic in 64%, breech in 32% and transverse in 4% of the cases. The maximum examination time, including the global fetal examination, was 33 min. In three fetuses (3.6%) no volume could be obtained because the fetus was facing the maternal spine, and in five fetuses (6.0%) only one volume could be obtained; the reasons were fetal position in two and shadows produced by the extremities in three cases. Excessive fetal movements made volume acquisition difficult in 11 cases (13.1%), but it was still possible to acquire the

two volumes in these 11 cases. The time necessary to visualize the profile was recorded on 70 occasions. This was on average 8 min 4 s (range, 2 s to 33 min 4 s). Fifty percent of the profiles were obtained within 3 min and 70 and 90% were obtained within 10 and 22 min, respectively. Volume acquisition time was between 3 and 5 s, depending on the size and on the chosen quality level of the volume recorded. When the profile was evaluated by multiplanar mode, the exact midsagittal plane was found by correlating and rotating the multiplanar views. The time necessary to display the multiplanar view and to adjust for the exact midsagittal profile (3Dpr) was between 15 and 50 s. The rotation necessary to obtain an exact midsagittal profile of the best volume was significantly larger around the y-axis than around the z-axis of the fetus (mean y-axis rotation, 11.9° vs. mean z-axis rotation, 4.3°; $P < 0.001$). The maximum value around the y-axis, which was found in three cases, was 31°. In these three cases the 2D profile was considered inappropriate for analysis. However, 12 of the 18 measurements could be accomplished with 3D multiplanar ultrasound. All other deviations around the y-axis were 27° or less (Figure 3). Around the z-axis the maximum deviation from the exact midsagittal plane was 19°. The mean distance of the tip of the nose to the original unprocessed 2D plane was 1.5 mm (SD 1.3 mm). The mean values of the six measurements taken by 2D or 3D ultrasound were not different and the 2D and 3D values of

Table 2 Measurements obtained by two-dimensional (2D) and three-dimensional (3D) multiplanar ultrasound (both volumes) and their correlation coefficients

Measurement	*2D measurement*	*3D measurement*	*Pearson correlation*	
			r	P
NL (cm)	1.46 (0.17)	1.45 (0.17)	0.83	<0.01
NP (cm)	0.96 (0.12)	0.98 (0.10)	0.81	<0.01
PS (cm)	0.79 (0.13)	0.83 (0.10)	0.68	<0.01
Ph (cm)	0.60 (0.10)	0.59 (0.08)	0.52	<0.01
FH (cm)	3.16 (0.35)	3.21 (0.37)	0.89	<0.01
MNM (°)	14.63 (2.93)	13.73 (2.05)	0.45	<0.01

Measurements are given as mean (SD). FH, facial height; MNM, maxilla–nasion–mandible angle; NL, nose length; NP, nose protrusion; Ph, philtrum length; PS, pronasale–subnasale distance.

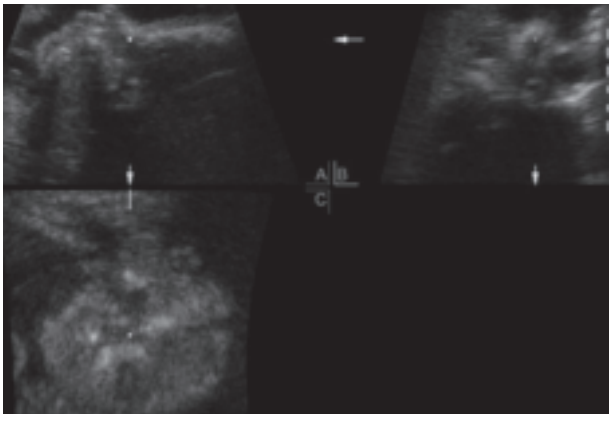

Figure 3 Multiplanar view of a volume with a deviation around the y-axis and z-axis of the fetus of 27° and 3°, respectively.

all six measurements were significantly correlated (Table 2). Of the nose-related measurements (NL, NP, PS and Ph) 4.9, 4.9, 7.4 and 6.2%, respectively, were not definable in both 2D images, yet they were definable and subsequently measurable in at least one volume on 3D ultrasonography. For the mandible-related measurements (FH and MNM) this was the case in 12.4% of cases (Table 3). The results of the Bland–Altman analysis are presented in Table 4. The 95% limits of agreement of the differences of paired 2D and 3D measurements are presented in a box plot (Figure 4). In all measurements intraobserver reproducibility was higher with 3D than with 2D ultrasound. For all measurements the SD of differences between paired measurements was significantly smaller in 3D compared to 2D measurements (Levene $P < 0.01$), except for philtrum length (Levene $P = 0.20$).

Table 3 Number of cases in which two-dimensional sonography could not define landmarks that were visible and measurable on three-dimensional sonography

Measurement	*n (%)*
Nose length	4 (4.9)
Nose protrusion	4 (4.9)
Pronasale–subnasale distance	6 (7.4)
Philtrum length	5 (6.2)
Facial height	10 (12.4)
Maxilla-nasion-mandible angle	10 (12.4)

Table 4 Mean difference and 95% limits of agreement (LOA) with their 95% CIs between paired two- (2D) and three-dimensional (3D) measurements

Measurement	n	*Mean difference*	*Lower LOA (95% CI)*	*Upper LOA (95% CI)*
2D measurements (2Dpr-1 – 2Dpr-2)				
Nose length (mm)	71	0.31	−2.90 (−2.25, −3.55)	3.52 (2.85, 4.15)
Nose protrusion (mm)	71	−0.02	−2.23 (−1.75, −2.64)	2.18 (1.75, 2.65)
Pronasale–subnasale distance (mm)	63	0.21	−1.97 (−1.53, −2.47)	2.39 (1.93, 2.87)
Philtrum (mm)	53	−0.12	−3.05 (−2.39, −3.80)	2.81 (2.09, 3.51)
Facial height (mm)	50	0.66	−4.73 (−3.38, −6.02)	6.04 (4.68, 7.22)
Maxilla–nasion–mandible angle (°)	54	−0.19	−5.85 (−4.52, −7.18)	5.47 (4.14, 6.80)
3D measurements (3Dpr-1 – 3Dpr-2)				
Nose length (mm)	73	0.04	−1.93 (−1.51, −2.29)	2.01 (1.61, 2.39)
Nose protrusion (mm)	73	−0.07	−1.26 (−1.54, −1.06)	1.12 (0.86, 1.33)
Pronasale-subnasale distance (mm)	65	0.01	−1.45 (−1.21, −1.79)	1.46 (1.21, 1.79)
Philtrum (mm)	56	−0.18	−2.10 (−1.65, −2.55)	1.74 (1.25, 2.15)
Facial height (mm)	69	−0.20	−3.63 (−2.88, −4.32)	3.23 (2.49, 3.92)
Maxilla–nasion–mandible angle (°)	68	0.29	−2.92 (−2.26, −3.58)	3.50 (2.84, 4.16)

2Dpr-1 and 2Dpr-2, measurements 1 and 2 (obtained ≥3 days apart) of the 2D profile i.e. the unprocessed A-plane image of the profile; 3Dpr-1 and 3Dpr-2, measurements 1 and 2 (obtained ≥3 days apart) of the 3D profile i.e. the A-plane image of the profile after correction to the precise midsagittal plane.

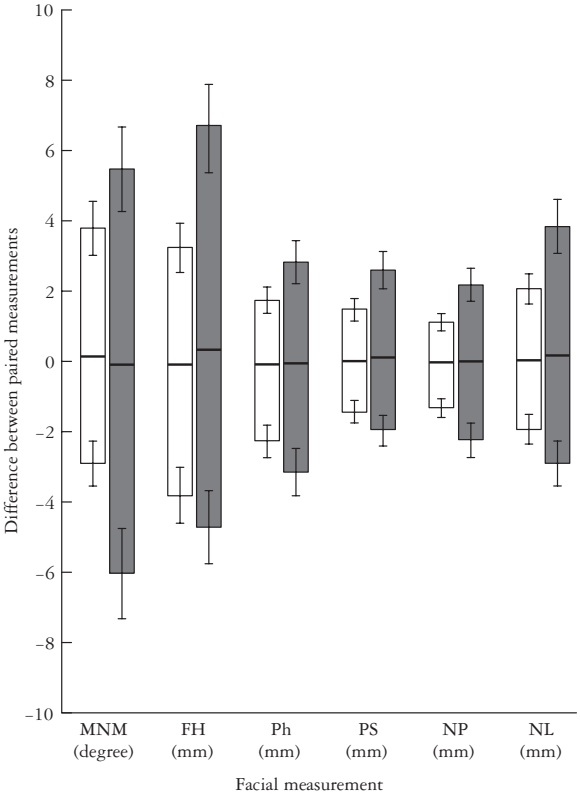

Figure 4 Box plot showing mean difference (black horizontal bars) and 95% limits of agreement (boxes) with their confidence intervals (whiskers), for paired 3D (□) and 2D (■) measurements. FH, facial height; MNM, maxilla–nasion–mandible angle; NL, nose length; NP, nose protrusion; Ph, philtrum length; PS, pronasale–subnasale distance.

DISCUSSION

This study shows that it is possible to acquire a volume starting at the profile view by 3D ultrasound within 10 min in 70% of fetuses at between 22 and 29 weeks' gestation. Thereafter, by multiplanar mode it is possible to define in less than 1 min the exact midsagittal profile. It also shows that reproducibility in profile measurements is higher when 3D ultrasound is used than when 2D ultrasound is used.

The profile view plays a key role in the examination of the fetal face. It is therefore important to obtain a correct midsagittal view. In this study the use of 3D ultrasound revealed the magnitude of inaccuracy inherent in attempts to define a correct midsagittal profile view by 2D ultrasound. Awareness of these inaccuracies can improve 2D and consequently 3D acquisition of a correct profile view.

Evaluation of the fetal profile in an incorrect midsagittal plane can lead to diagnostic inaccuracies. Pretorius *et al.*[16], for instance, described a case in which micrognathia was not diagnosed by 2D ultrasound but was subsequently recognized on 3D ultrasound. Similarly Dyson *et al.*[9] reported

that four out of five micrognathia cases were only recognized on 3D ultrasound and that 3D images were helpful in all cases of anomalies only detectable on the basis of an abnormal profile. 3D multiplanar ultrasound can also be of help in conclusively diagnosing a flat profile[13]. Identification of the precise midsagittal profile plane enables measurements to be obtained that can help in recognizing subtle facial anomalies. Even measurements of nasal bone length, used as a second-trimestermarker for Down syndrome, may be significantly inaccurate, unless obtained from a perfect midsagittal profile plane.

In an attempt to obtain the fetal profile the nose will most likely be used as a landmark around which the ultrasonographer adjusts the scanning plane by rotating around the y- and z-axes of the fetus, in search of the true midsagittal plane. In our study the mean distance of the tip of the nose to the original plane of acquisition was 1.5 mm. This is very small compared with the total nose width, which grows from 14 to 18 mm between 22 and 29 weeks' gestation[18]. This supports the idea that the tip of the nose can indeed be used as an accurate landmark when searching for the profile. We found that the deviation around the y-axis was significantly larger than around the z-axis. This is in agreement with the finding of Merz *et al.*[8], who studied with 3D multiplanar ultrasound the profile view of 125 fetuses at between 9 and 37 weeks' gestation and found that the mean deviation of a volume from the exact midsagittal plane was larger around the y-axis (12.6°) than around the z-axis (7.8°).

When only 2D ultrasound is available, special care should be taken to align the profile correctly around the y-axis. To do this, midline structures in the middle or in the back of the head (hard palate, corpus callosum, cerebellar vermis) are necessary in order to define the correct midsagittal plane. Facial bones produce shadows, therefore the transfrontal view, in which the frontal suture serves as an acoustic window, facilitates the identification of midline structures, and thus may be very helpful for standardizing the scanning plan. This approach can be successfully used, at least until 32 weeks' gestation, after which the frontal bones start to fuse[19,20].

Between 5 and 12% of the measurements could not be performed in this study with 2D ultrasound, owing to poor definition of the landmarks, whereas 3D ultrasound clearly improved definition and measurability. Mandible-related measurements like FH and MNM seem to benefit especially from 3D ultrasound. This can be explained by the fact that the mandible is relatively far away from the nose and therefore easily affected by even small deviations from the midsagittal plane. This should be kept in mind when evaluating the mandible in cases where retrognathia needs to be confirmed or excluded.

When performing ultrasound measurements one would like to know how closely these measurements reflect *in-vivo* dimensions. This is however impossible. In fact even direct measurements performed after birth or at pathological studies will be affected by alterations following the process of birth or fixation treatments. We have therefore to rely upon indirect measurements, but it seems important to use the most reproducible methods to decrease measurements errors. In this study we have demonstrated that 3D techniques improve intraobserver reproducibility.

A single experienced ultrasonographer was involved in this study. As shown in the study by Wah *et al.*[21], operator experience is of great influence on the ability to find the exact midsagittal plane. The additional value of 3D multiplanar ultrasound will therefore be even greater for less experienced ultrasonographers.

In this study we assumed that the original A-plane in the 3D multiplanar acquisition is comparable with 2D ultrasound. This is confirmed by a study of Viñals *et al.*[22] on the transfrontal view of the cerebrum. In this study the quality and detailed visualization of structures were comparable

between 2D ultrasound and the A-plane of the 3D multiplanar acquisition when the 3D volume acquisition was started in the same plane as the 2D picture. The design of our study made it possible to directly evaluate the additional value of 3D multiplanar ultrasound. To push the "3D button", instead of the "freeze button", and adjust the planes on the multiplanar view adds only about a minute to the examination time but guarantees that the true profile view is examined.

In this study we did not specify the pre-acquisition insonation angle around the fetal x-axis, as for example is required for the measurement of nasal bone length[23]. The use of a specific pre-acquisition angle of insonation, adjusted to the measurement of interest, may further increase the reproducibility of the measurements for 2D and 3D ultrasound. The present study, however, was not designed to test the clinical value of the six measurements in differentiating normal from pathological cases.

Facial anomalies are usually diagnosed late in pregnancy, unless they are associated with other anomalies or with a positive family history[5,15,24,25]. The continuing technical advances in 3D ultrasound and the development of normative measurements enable a quantitative approach. This opens the possibility of diagnosing isolated or minor forms of facial anomalies during the second trimester of pregnancy or even earlier, such as the identification of the flat face of trisomy 21 fetuses in the first trimester of pregnancy[26].

In conclusion, 3D multiplanar ultrasound is a powerful instrument for investigating the facial profile, capable of improving the accurate topographic depiction of the midsagittal profile view, the likelihood that a structure is measurable and the precision of facial profile measurements. 3D multiplanar ultrasound therefore has the potential to refine the diagnosis of facial profile anomalies or dysmorphisms, which often are a key sign for syndrome recognition and diagnosis.

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PART II objective tools

CHAPTER 5

Maxilla–nasion–mandible angle: a new method to assess profile anomalies in pregnancy

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ABSTRACT

Objectives

To collect normative data and test the feasibility and reproducibility of measurement of the maxilla–nasion–mandible (MNM) angle between 16 and 36 weeks' gestation and its diagnostic ability in a group of pathological cases.

Methods

The MNM angle is defined as the angle between the intersection of the maxilla–nasion and mandible–nasion lines in the exact mid-sagittal plane.
After assessing reproducibility, the MNM angle was measured in 3D volumes in 241 fetuses cross-sectionally and in 11 fetuses longitudinally. The MNM angle was then tested in 18 pathological cases with facial malformations or syndromes with specific facial features.

Results

The MNM angle could be measured in 92.3% of normal fetuses. Intra- and interobserver intraclass correlation coefficient (ICC) variability was 0.92 and 0.81, respectively. The difference between paired measurements performed by one or two observers was less than 2.5° and 3.6°, respectively in 95% of the cases. The mean MNM angle was 13.5° and did not change significantly during pregnancy ($r = -0.08$, $P = 0.25$). The MNM angle was above the 95th centile in all cases of retrognathia and maxillary alveolar ridge interruption. The MNM angle was below the 5th centile in Apert syndrome, thanatophoric dysplasia and in two of the three Down syndrome cases.

Conclusions

The feasibility and reproducibility of measurement of the MNM angle is good. The MNM angle can be used to evaluate the convexity of the fetal profile by enabling an objective assessment of the anteroposterior relationship of the jaws and it may therefore be of help in the diagnosis of retrognathia, maxillary alveolar ridge interruption and flat profile.

INTRODUCTION

Important information can be drawn from examination of the fetal profile. As opposed to the adult profile, which is flat, the fetal profile is characterized by a convex form, profoundly influenced by the position of the jaws. Conditions such as retrognathia of the mandible, maxillary hypoplasia or maxillary alveolar ridge interruption can all influence the convexity of the profile. These features are frequently encountered in genetic disorders such as chromosomal abnormalities or syndromes[1]. Jaw abnormalities may also be associated with swallowing disorders that may cause polyhydramnios and may affect breathing or feeding after birth[2,3]. Later in life, jaw abnormalities can result in speech, mastication or orthodontic problems and may cause variable degrees of psychological problems[3].

Evaluation of the fetal profile is currently largely dependent on subjective visual interpretation. However, for a correct diagnosis of profile abnormalities it is important to rely upon normative measurements providing standards for classification, documentation, follow-up and comparison. Previously, we have demonstrated that 3D ultrasound is an essential tool for definition of the exact mid-sagittal profile view[4]. However, an easy and objective method to assess jaw position at prenatal ultrasound is still lacking. This method should be simple and reproducible, with easy to identify superficial landmarks that are not hampered by shadowing of bony structures, and without the need for reference lines or specific insonation angles.

Of all the measurements proposed in the literature, the cephalometric point A–nasion–point B (ANB) angle (nasion is the most anterior point at the intersection of the frontal and nasal bones), used by Riedel to assess the jaw relationship for orthodontic diagnosis, prognosis and treatment planning in 1952, appears promising for application during prenatal ultrasound examination (Figure 1)[5].

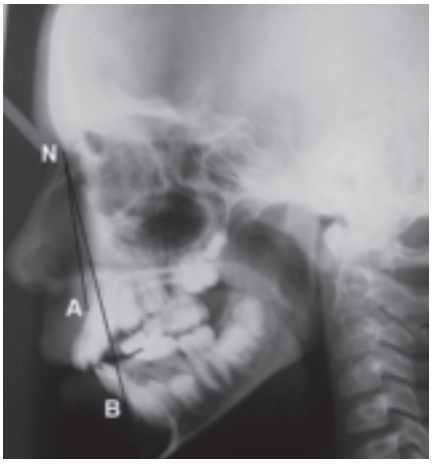

Figure 1 Point A–nasion–Point B (ANB) angle measurement on a cephalogram of an adult. The ANB angle is the angle between the lines Point A–nasion and Point B–nasion. Point A is the innermost point on the curvature of the anterior aspect of the maxilla. Point B is the innermost point on the curvature of the anterior aspect of the mandible. N is the nasion, the most anterior point at the intersection of the frontal and nasal bones.

In the present study, we collected normative data and determined whether a prenatal version of the ANB angle, renamed the maxilla–nasion–mandible angle (MNM angle), could be a useful tool to establish, by means of 3D ultrasound, the convexity of the profile in the second and third trimesters of pregnancy (Figure 2). We also tested the MNM angle in pathological cases.

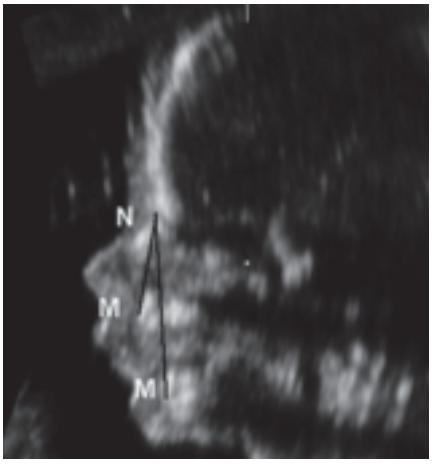

Figure 2 Maxilla–nasion–mandible (MNM) angle measurement on a prenatal ultrasound image. The MNM angle is the angle between the lines maxilla–nasion and mandible–nasion in the exact mid-sagittal plane. The landmarks on the maxilla (upper M) and mandible (lower M) are in the middle of the anterior borders of the jaws. N is the nasion, the most anterior point at the intersection of the frontal and nasal bones.

PATIENTS AND METHODS

The study was approved by the local ethics committee and all women gave written consent. Study data were obtained from 261, nonsmoking, healthy, low-risk, pregnant Caucasian women with a singleton and uncomplicated pregnancy. Women were recruited at the time of the dating scan or routine second-trimester anomaly scan. They were asked to attend an additional examination at between 16 and 36 weeks' gestation. In addition, 11 healthy Caucasian employees of our hospital attended every 4 weeks, starting at 16 weeks' gestation, for a longitudinal study. Only non-anomalous fetuses were included. Gestational age was determined from the last menstrual period and by a first-trimester dating scan. The examinations were carried out transabdominally, using a Voluson 730 Expert ultrasound system (GE Medical Systems, Zipf, Austria). In the course of the study, the 2–5-MHz transducer was replaced by a 4–8-MHz transducer.
When the fetus was facing the transducer with closed mouth, 3D volumes of the fetal head were acquired, starting at the mid-sagittal plane. An attempt was made to start at the exact mid-sagittal plane, without a specific insonation angle around the x-axis of the fetus. The ultrasound image of the fetal head was enlarged to at least one third the size of the screen, the render box was placed such that the whole fetal head was included within it and the angle of the volume was adjusted to the size of the fetal head. Volumes were obtained with high-2 or maximum quality depending on the behavioral state of the fetus. A normal frequency range was used in most women, but

this was changed to 'resolution' or 'penetration' in case of a slim or obese woman. Except in the longitudinal group, each fetus was investigated only once for the purpose of this study. An attempt was made to collect at least two volumes per investigation.
All examinations were carried out by one experienced ultrasonographer (E.J.P.). The volumes were stored on removable digital media for subsequent analysis on 4D View software version 7.0 (GE Medical Systems). With the multiplanar mode the exact mid-sagittal plane was depicted. The MNM angle was then defined as the angle between the lines maxilla–nasion and mandible–nasion in the exact median plane (Figure 2). The nasion is defined as the most anterior point at the intersection of the frontal and nasal bones. Jaw landmarks were defined as the middle points of the anterior borders of the maxilla and mandible. Calipers were placed on the outermost borders of the bone.
When there was a gap between the nasal and frontal bones, the landmark nasion was at the point of intersection between the lines tangential to the nasal bone and tangential to the lower part of the frontal bone.
When there was a wide metopic suture, the echogenic line representing the future frontal bone was used. When necessary, the marker dot in the B-plane of themultiplanar view was used to identify landmarks on the maxilla or mandible (Figure 3).

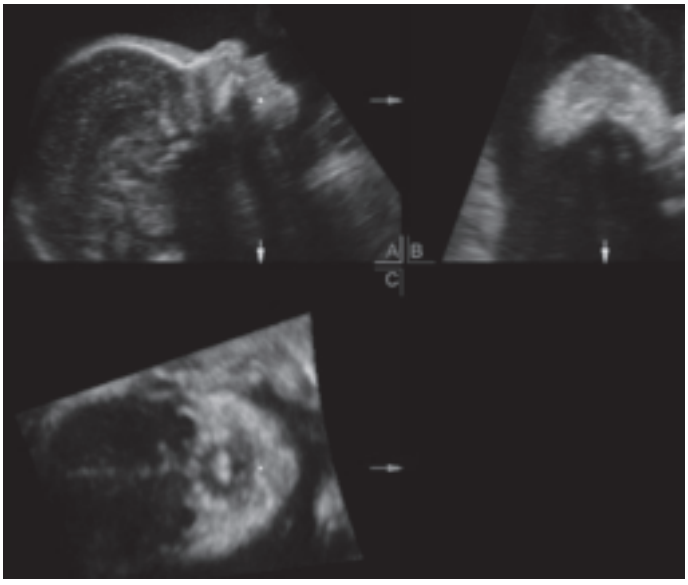

Figure 3 Multiplanar view showing identification of the landmark used for the mandible (i.e. the middle point of the anterior border) with marker dot in the B-plane

Intra- and interobserver variability was assessed by intraclass correlation coefficient (ICC) and Bland–Altman analysis[6] on paired volumes, acquired using the 4–8-MHz transducer, of 20 patients chosen at random at different gestational ages, with at least 3 days between the two assessments. In 18 fetuses, the MNM angle was measured on stored 3D volumes after a facial anomaly or syndrome with specific facial features was suspected at ultrasound investigation and before the final diagnosis had been made (by genetic investigation or postpartum examination).

Data were analyzed using the statistical software SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA) and Excel for Windows 2000. Means with ranges or SD were calculated when appropriate. Correlation was determined by Pearson's correlation test. The statistical significance of the difference of the means of two groups was tested with the unpaired Student's t-test. To compare means on the same subjects over time, the paired t-test was used. $P < 0.05$ was considered statistically significant.

RESULTS

The cross-sectional study group included 261 fetuses. In two fetuses, an anomaly was diagnosed: one was excluded from the study (spina bifida) and the other was moved to the pathological group (facial cleft). In 16 fetuses (6.1%), no volume could be obtained because the fetus was facing the maternal spine (15 cases) or had an unfavorable position combined with shadows produced by the arms (one case). These cases were equally distributed over both trimesters: seven in the second trimester, nine in the third trimester. One case was excluded after analysis because of uncertainty over mouth closure. Another was excluded because extreme flexion of the head prevented identification of the mandibular landmark. The MNM angle was thus measured in 241 normal fetuses (92.3%). Fifty-two investigations (22%) were performed with the 2–5-MHz transducer and 189 investigations (78%) with the 4–8-MHz transducer. Mean BMI of the women before pregnancy was 23.7 (range, 17.4–36.2). The mean amniotic fluid index was 17.0 (range, 7.3–28.3). The presentation of the fetus was cephalic in 67%, breech in 28% and transverse in 5%. The mean birth weight of the babies was 3473 g (range, 1160–4885 g), with 89% of the babies between the 5th and 95th centile. Fifty-four percent of the babies were boys and 46% were girls. The MNM angle measurements, with corresponding gestational ages, used to assess intra- and interobserver variability are shown in Table S1. The intra- and interobserver ICC variability was 0.92 and 0.81, respectively. For paired measurements performed by one observer, the mean difference and 95% limits of agreement (with their 95% CI) were −0.05° (−2.50° (−3.44° to −1.54°) to 2.40° (1.44° −3.34°)). For paired measurements performed by two different observers, the respective valueswere −0.15° (−3.57° (−4.89° to −2.25°) to 3.27° (1.94–4.59°)) (Figure 4).
The mean MNM angle of the study population (241 fetuses) was 13.53° (95% CI, 13.28–13.78°; range, 8.96–19.58°). No correlation between gestational age and the MNM angle could be demonstrated (Pearson r = −0.08, P = 0.25). The 5th and 95th centiles were 10.39° and 16.91°, respectively (Figure 5). There was no difference between the MNM angle in boys (mean: 13.45°) and girls (mean: 13.59°) (Student's *t*-test P = 0.68).
The MNM angles of the longitudinal study group are presented in Figure 6 (mean MNM angle: 13.81° (range, 10.61–16.81°)). The first and last measurements of the longitudinal group were not significantly different (paired *t*-test P = 0.52).

Pathological cases
The pathological group consisted of eight cases in which retrognathia was suspected (CHARGE association, two cases of trisomy 18, campomelic dysplasia, Cri du chat syndrome, Goldenhar syndrome, Goldenhar syndrome with VACTERL association and Pierre–Robin syndrome), three cases with suspicion of a flat profile (Apert syndrome and two cases of thanatophoric dysplasia type 1, without cloverleaf skull), three cases of trisomy 21 and four cases of facial clefts of variable severity. The results are presented in Figure 7 and Table 1.

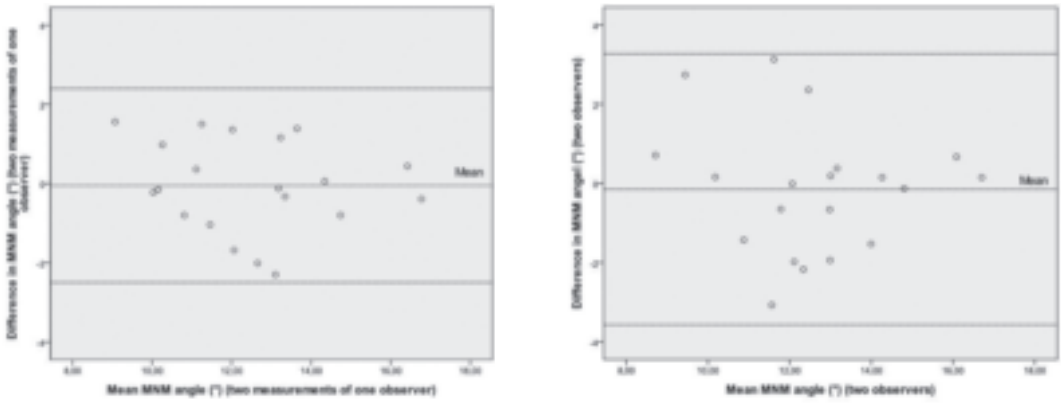

Figure 4 Bland–Altman plots showing mean difference and 95% limits of agreement between paired measurements of the maxilla–nasion–mandible (MNM) angle by (a) the same observer (intraobserver) and (b) two different observers (interobserver).

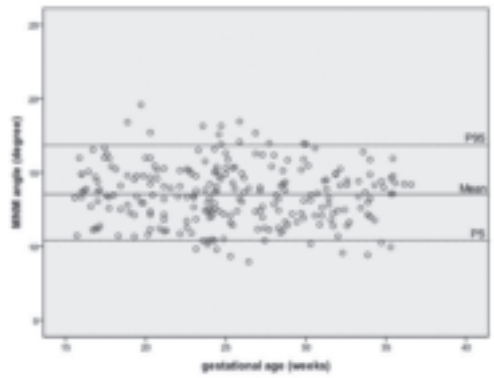

Figure 5 Scatterplot of maxilla–nasion–mandible (MNM) angle against gestational age in 241 healthy fetuses, with mean (———) and 5th and 95th centiles (- - - -).

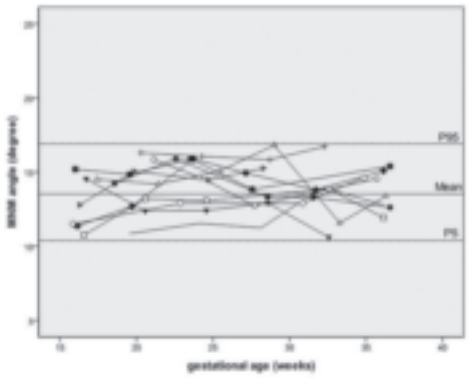

Figure 6 Serial maxilla–nasion–mandible (MNM) angle measurements in 11 healthy fetuses between 16 and 36 weeks'gestation, showing mean (———) and 5th and 95th centiles (- - - -) of the normal cross-sectional population.

In all six cases with postnatally confirmed retrognathia, the MNM angle was above the 95th centile. The MNM angle was normal in the two cases without retrognathia. The MNM angle was below the 5th centile in Apert syndrome, in both cases of thanatophoric dysplasia and in two of the three trisomy 21 cases. In all three cases of bi- or unilateral interruption of the alveolar ridge, the MNM angle was above the 95th centile. The MNM angle was normal in the case with unilateral cleft lip and palate but intact alveolar ridge. In the case of cleft lip detected in the study group, the subtle interruption of the alveolar ridge was only identified after the enlarged MNM angle (17.9°) prompted a careful reexamination of the volumes (Figure 8).

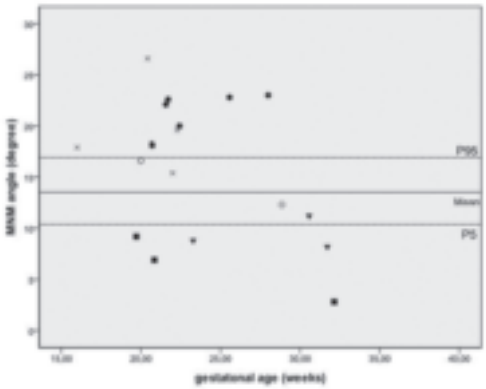

Figure 7 Maxilla–nasion–mandible (MNM) angle measurements in 18 pathological cases plotted against gestational age, with mean (———) and 5th and 95th centiles (- - - -) for normal fetuses. Pathological cases included: Apert syndrome and thanatophoric dysplasia (■); trisomy 21 (▼); facial clefts (×); cases with retrognathia (trisomy 18, campomelic dysplasia, Cri-du-chat syndrome, Goldenhar syndrome, Goldenhar syndrome with VACTERL and Pierre–Robin syndrome) (●); cases without retrognathia (CHARGE association, trisomy 18) (O).

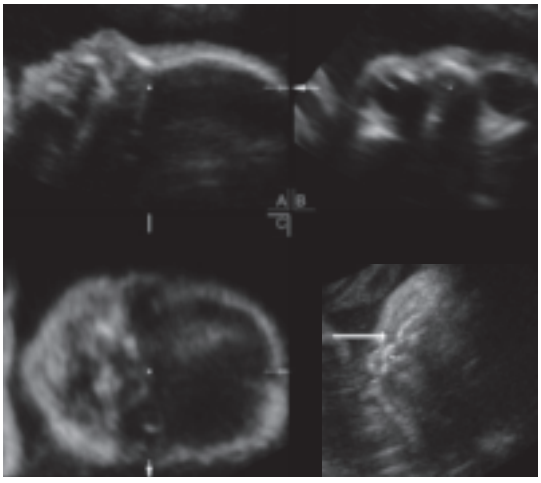

Figure 8 Fetal profile that was subjectively interpreted as normal, shown in multiplanar mode. A small interruption in the alveolar ridge is shown in the axial plane (arrow). This was only noticed after the enlarged maxilla–nasion–mandible angle (17.9°) had alerted the investigator.

Table 1 Summary of pathological cases with maxilla–nasion–mandible (MNM) angle measurements

Abnormality	*Genetic confirmation*	*GA (weeks)*	*MNM angle (°)*	*MNM angle classification*	*Retrognathia**	*Cleft alveolus**	*Other facial anomalies seen with ultrasound*
Thanatophoric dysplasia type I	Yes	19 + 5	9.2	<P5	No	No	Frontal bossing
Thanatophoric dysplasia type I	Yes	20 + 6	6.9	<P5	No	No	Frontal bossing
Apert syndrome	Yes	32 + 1	2.8	<P5	No	No	Frontal bossing
CHARGE association	Yes	28 + 6	12.3	P5–P95	No	No	Hemifacial microsomia, unilateral microphthalmia
Trisomy 18	Yes	20 + 0	16.6	P5–P95	No	No	Small nose
Trisomy 18	Yes	22 + 3	20.0	>P95	Yes	No	—
Campomelic dysplasia	Yes	20 + 5	18.1	>P95	Yes	No	—
Cri du chat syndrome	Yes	28 + 0	23.0	>P95	Yes	No	—
Goldenhar syndrome	No	21 + 4	22.1	>P95	Yes	No	Hemifacial microsomia, unilateral microphthalmia
Goldenhar syndrome + VACTERL	No	21 + 5	22.6	>P95	Yes	No	Hemifacial microsomia
Pierre–Robin syndrome	No	25 + 4	22.8	>P95	Yes	No	—
Trisomy 21	Yes	31 + 5	8.2	<P5	No	No	—
Trisomy 21	Yes	23 + 2	8.8	<P5	No	No	—
Trisomy 21	Yes	30 + 4	11.2	P5–P95	No	No	—
Bi. cleft lip/alveolus and palate (isolated)	No	16 + 0	17.9	>P95	No	Bi.	—
Bi. cleft lip/alveolus and palate (trisomy 13)	Yes	20 + 3	26.6	>P95	No	Bi.	—
Uni. cleft lip/alveolus (isolated)	No	22 + 2	19.6	>P95	No	Uni.	—
Uni. cleft lip and palate (VCF syndrome)	Yes	22 + 0	15.4	P5–P95	No	No	—

*Confirmed after birth. Bi., bilateral; GA, gestational age; P, percentile; Uni., unilateral; VCF, velocardiofacial.

DISCUSSION

This study proposes measurement of the MNM angle as a new method enabling an objective assessment of fetal jaw abnormalities in the second and third trimesters. The mean angle remains constant at 13.5° and measurements can easily be performed using 3D ultrasound, with good intra- and interobserver reproducibility.

3D ultrasound improves accuracy[4]. Ultrasonographers should be aware of this when using 2D ultrasound. No specific preacquisition insonation angle around the fetal x-axis is required. However, the accuracy of the measurements probably increases when an insonation angle perpendicular to the profile plane is used.

Because racial variations in craniofacial morphology are reflected in a different configuration of alveolar and dental areas, an ethnic variation in the angle is expected[7,8]. Future studies should therefore investigate the angle in non-Caucasian fetuses also. The MNM angle appears not to be affected by fetal gender, confirming the findings of a postmortem study[9].

Several second- and third-trimester jaw measurements have been proposed, such as length of mandibular ramus[10,11], transverse mandibular diameter[12–16], anteroposterior mandibular diameter[12,13,16], maxillary length[17] and maxillary width[14], as well as ratios such as anteroposterior mandibular diameter/biparietal diameter (BPD) ×100[13], mandibular width/maxillary width[14], BPD/transverse mandibular diameter[15] and transverse/anteroposterior mandibular diameter[16]. These measurements have seldom been used clinically. One explanation could be that they require visualization of the fetal face in the axial or coronal plane, which are not routinely used[10–17]. Moreover, difficulty in identifying landmarks located more posteriorly in the head, and therefore more affected by shadowing, may hamper application of these measurements[10–14,16,17].

In this 3D ultrasound study, measurement of theMNM angle was successful whenever the fetus was facing the transducer. Measurement failed in one case in which extreme flexion of the head prevented visualization of the mandibular landmark. When the nasal bone is absent the lowest anterior edge of the frontal bone can be used as a reference point, as for prenasal thickness measurement[18]. Because the frontal bones develop independently of the nasal bones, the lowest anterior edge of the frontal bone is not influenced by nasal bone hypoplasia and it is therefore an acceptable alternative for the nasion in such cases[19].

The MNM angle can be derived from two gestational age-independent angular measurements proposed by Roelfsema *et al*.[20]. The difference between their mean mandibular and maxillary protrusion is 13.8°, which is very close to the 13.5° reported in this study. Two other studies, aimed at improving the diagnosis of retrognathia in the second and third trimesters of pregnancy, also found constant values in angular measurements in the profile view[14,21]. A limitation of these studies is that the forehead was used as a reference point, implying that malformations like bossing or sloping forehead will influence these measurements. Moreover, both studies used superficial skin landmarks, difficult to identify when there is not sufficient amniotic fluid surrounding the face, and possibly influenced by facial expression.

During fetal life, the maxilla, anatomically fused with the cranium, is pushed forward by the progressive brain development, while the cranial base flattens. This implies that it is difficult for the mandible, only connected to the skull through the temporomandibular joint and muscles, to catch up withmaxillary growth[22]. Postnatally, facial growth predominates over brain growth and the functional development of chewing and speech further stimulate growth of the mandible[23].

This catch-up growth of the mandible results in a change in profile during adolescence from convex to flat. The ANB angle becomes, on average, 2.8° in adulthood[7].
When the MNM angle is small, the profile is flat (Figure 9a–c). This can be the result of maxillary hypoplasia or forward displacement of the mandible; the latter is a rare finding in prenatal life. When the MNM angle is abnormally large, the fetal profile is exaggeratedly convex (Figure 9d–f). The mandible is then moved backwards or the maxilla forwards, as shown by retrognathia and facial cleft cases. When an abnormally large MNM angle is encountered, an alveolar ridge interruption or retrognathia is likely. When the MNM angle is negative the profile is concave. This is described postnatally in non-syndromic healthy Caucasian adults, but prenatally this is an extremely rare finding. Owing to the by nature convex fetal profile, this is clearly pathological and will be easy to recognize.

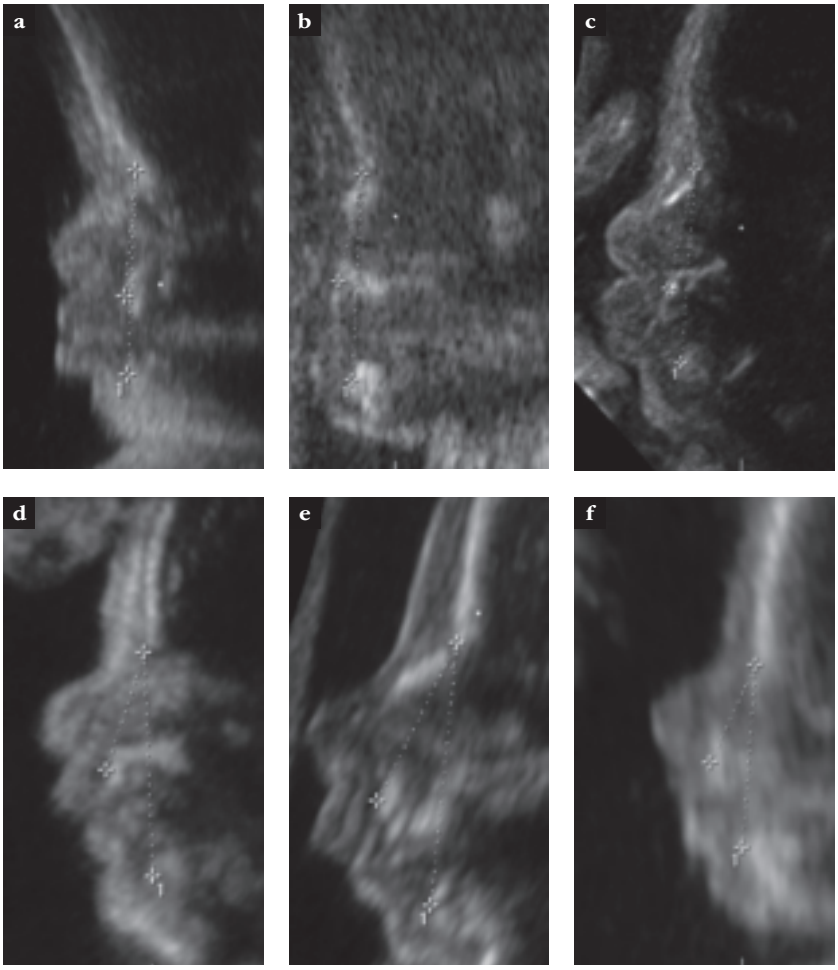

Figure 9 Examples of abnormally small (a–c) and large (d–f) maxilla–nasion–mandible (MNM) angles: (a) Apert syndrome (MNM: 2.8°); (b) thanatophoric dysplasia (MNM: 9.2°); (c) trisomy 21 (MNM: 8.8°); (d) Cri-du-chat syndrome (MNM: 23.0°); (e) Goldenhar syndrome (MNM: 22.6°); (f) alveolar ridge interruption (MNM: 19.6°).

The position of the nasion influences the MNM angle, but the nasion is probably not easily influenced by facial malformations. Backwards or downwards displacement of the nasion should theoretically increase the MNM angle. Nevertheless, both cases of thanatophoric dysplasia, a syndrome known to be associated with small facies and a low nasal bridge, had an abnormally small MNM angle, indicating a flat profile. Further studies are necessary to detect how, for example, midfacial hypoplasia influences the position of the nasion and possibly the MNM angle. In all six cases with postnatally confirmed retrognathia, the MNM angle was above the 95th centile. Therefore, the MNM angle seems to be an objective method to confirm the subjective suspicion of retrognathia at prenatal ultrasound. Because the anterior border of the mandible is used as landmark in the MNM angle, this may imply that, technically, only retrognathia and not micrognathia could be identified. However, in 11 fetuses with micrognathia, Paladini *et al*.[13] observed that in this condition the growth deficit is more evident in the sagittal plane than in the coronal plane, implying that micrognathia is often also accompanied by retrognathia. In the facial cleft cases, the MNM angle was above the 95th centile only when the alveolar ridge was not intact, indicating that the MNM angle may be helpful in identifying small alveolar ridge interruptions. The MNM angle may be of diagnostic value in recognizing premaxillary protrusion, recently described as a prognostic factor for lethal aneuploidies associated with bilateral cleft lip and palate[24]. In the Apert syndrome case, a syndrome characterized by a flat face, the MNM angle was below the 5th centile. Interestingly, the MNM angle was also small in two of the three trisomy 21 cases. However, larger series are needed to establish the exact clinical value of the MNM angle in diagnosing specific facial abnormalities.

In conclusion, the MNM angle is a promising tool to establish the convexity of the fetal profile by enabling an objective assessment of the anteroposterior relationship of the jaws. This method has the potential of assisting in the prenatal recognition and classification of abnormal profile findings.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information is published in the online version of the article:

Table S1 Maxilla–nasion–mandible (MNM) angle measurements used for assessing intra- and interobserver variability, arranged from lowest to highest gestational age.

Gestational age (weeks)	*Observer 1 First measurement (degree)*	*Observer 1 Second Measurement (degree)*	*Observer 2 First Measurement (degree)*
22 4/7	11.21	10.41	8.07
22 5/7	15.14	14.34	14.87
22 6/7	13.24	13.12	10.05
23	12.65	13.81	14.76
23 1/7	14.25	11.95	12.91
23 6/7	10.14	9.92	13.1
24 2/7	13.66	11.65	13.31
25 2/7	8.29	9.85	8.36
27 1/7	12.95	14.34	11.28
27 2/7	16.20	16.64	15.75
27 5/7	16.97	16.58	16.63
27 5/7	10.93	11.29	13.1
27 6/7	12.90	11.22	12.07
28 2/7	10.50	12.00	13.42
28 4/7	13.51	13.18	12.97
28 5/7	14.31	14.37	14.19
28 6/7	11.98	10.94	12.11
30 2/7	10.23	10.08	11.59
34	11.34	12.70	13.96
34 5/7	9.77	10.75	10.10
Mean (SD) range	12.51 (2.25) 8.29-16.97	12.46 (2.06) 9.85-16.64	12.63 (2.26) 8.07-16.63

CHAPTER 6

The fetal profile line; a proposal for a sonographic reference line to classify forehead and mandible anomalies in the second and third trimester of pregnancy

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ABSTRACT

Objectives

To test the fetal profile (FP) line, defined as the line that passes through the anterior border of the mandible and the nasion, as a reference line for forehead and mandible anomalies.

Methods

Volumes of 248 normal and 24 pathological fetuses (16–36 and 19–37 weeks' gestation, respectively) were analysed retrospectively. When the FP line passes anteriorly, across or posteriorly to the frontal bone, this was defined as 'negative', 'zero' or 'positive', respectively. When the FP line was positive the distance (F distance) between the FP line and the frontal bone was measured.

Results

No cases with a negative FP line were found in the normal fetuses. Before 27 weeks' gestation the FP line was always 'zero' except in one case. After 27 weeks' gestation the FP line was 'positive' in up to 25% (F distance (mean, range): 2.8, 2.1–3.6mm). The FP line correctly identified 13 cases with retrognathia, 5 cases with frontal bossing and 3 cases with a sloping forehead.

Conclusion

Although large prospective studies are needed, the FP line may be a useful tool to detect second trimester profile anomalies such as retrognathia, sloping forehead and frontal bossing with the possibility of quantifying the latter.

INTRODUCTION

Of all ultrasound images, the fetal face and especially the profile is highly appreciated by parents and frequently sought after by sonographers. Many abnormalities of the profile such as retrognathia, bossing or sloping forehead are associated with a wide range of genetic conditions and syndromes[1–5]. When multiple anomalies or markers are present, the recognition of specific features typical of a syndrome can be of crucial importance for optimal parental counselling and for further management of the pregnancy.

Although it is to be expected that the experienced sonographer will notice facial dysmorphisms, less experienced sonographers may benefit from objective measurements. Furthermore, the use of objective measurements creates the opportunity to document, communicate, compare, classify and follow-up findings.

The fetal profile is a tremendous source of information and therefore attempts should be made to find a simple approach capable of translating the information it contains into simple lines and measurements. This may seem a challenge, owing to the complex curved nature of the fetal profile. The aim of the present study was to develop and evaluate an easily applicable line, which we named the fetal profile (FP) line, as a potential new reference to identify and quantify forehead and mandible anomalies (Figure 1). The FP line was applied to three-dimensional volumes of normal second and third trimester fetuses (cross-sectionally and longitudinally). We also tested the proposed FP line retrospectively in pathological cases.

MATERIAL AND METHODS

The study was approved by the local ethics committee and all participants gave written consent. Study data were obtained from 272 (261 for cross-sectional and 11 for longitudinal study), nonsmoking, healthy, low-risk, pregnant Caucasian women with a singleton and uncomplicated pregnancy. Women were recruited at the time of the dating or routine second-trimester anomaly scan. They were asked to attend an additional examination between 16 and 36 weeks' gestation. Eleven healthy Caucasian employees of our hospital attended every 4 weeks, starting at 16 weeks' gestation, for a longitudinal study. Fetuses were excluded when a structural anomaly was found on ultrasound. Gestational age was determined from the last menstrual period and by a first trimester dating scan.

The examinations were carried out transabdominally, using a General Electric Voluson 730 Expert ultrasound system (GE Medical Systems, Kretz Ultrasound, Zipf, Austria) equipped with a 2 to 5MHz or 4 to 8MHz abdominal transducer.

When the fetus was facing the transducer with closed mouth, at least two volumes of the fetal head were acquired, starting at the midsagittal plane. The ultrasound image of the fetal head was enlarged to at least one third the size of the screen, the render box was positioned to include the whole fetal head and the angles of the volume were adjusted to the size of the fetal head. Volumes were obtained with high-2 or maximum quality depending on the behavioural state of the fetus. A normal frequency range was used in most women, but this was changed to 'resolution' or 'penetration' in case of a slim or obese woman. Except in the longitudinal group, each fetus was investigated only once for the purpose of this study.

All examinations were carried out by one experienced sonographer (EJP). The volumes were stored on removable digital media for subsequent analysis on 4D View software version 10.2 (GE

Medical Systems, Kretz Ultrasound, Zipf, Austria). With the multiplanar mode the exact midsagittal plane was depicted as follows: initially the multiplanar images were rotated to obtain symmetrical views of the orbits. The reference dot was then placed at equal distance from the inner border of the orbits in the axial and coronal images, resulting in the exact midsagittal image in the original profile view.
The FP line was defined as the line that passes through the middle point of the anterior border of the mandible and the nasion (Figure 1). The nasion is the most anterior point at the intersection of the frontal and nasal bones.

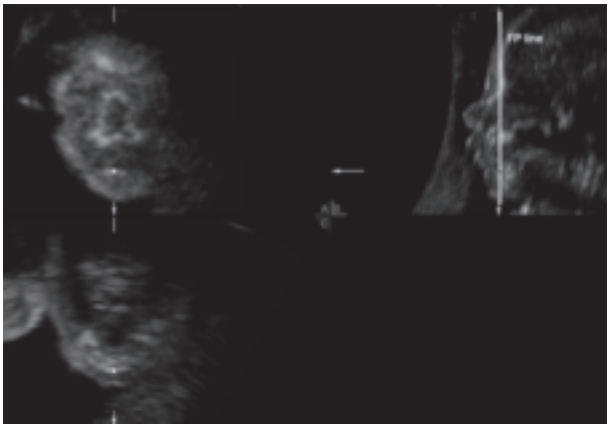

Figure 1 Multiplanar view of a normal fetus showing the fetal profile (FP) line in box B and identification of the landmark used for the mandible (i.e. the middle point of the anterior border) with marker dot in the C-box

When necessary the marker dot in the C-box was used to identify the landmark on the mandible (Figure 1). Volume contrast imaging was used where necessary to improve the image quality.
When the FP line passed the frontal bone anteriorly its position was called 'negative' (Figures 2 (as) and (ar)). When the FP line passed lengthwise through the frontal bone, this was called 'zero' (Figure 2(b)) and the length of the FP line passing through the frontal bone was measured. When the FP line passed the frontal bone posteriorly, its position was called 'positive' and the largest distance (F distance) from the FP line to the outer border of the frontal bone could be measured (Figure 2(c)). The F distance was measured perpendicular on the FP line.
Intraobserver and interobserver variability of the F distance was assessed by the intraclass correlation coefficient (ICC) on paired volumes acquired by the 4 to 8MHz transducer from 15 patients with at least 3 days between the two assessments.
Subsequently, the FP line was tested retrospectively on stored three-dimensional volumes of fetuses that were suspected to have a facial anomaly or syndrome with specific facial features. All children born in this group were evaluated by an experienced neonatologist and when necessary by geneticists and dysmorphologists at a university centre.
Data were analysed using the statistical software SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA) and Microsoft Excel for Windows 2010. Means with ranges or percentage were calculated. Fisher's exact test was used to compare groups. $P \leq 0.05$ was considered statistically significant.

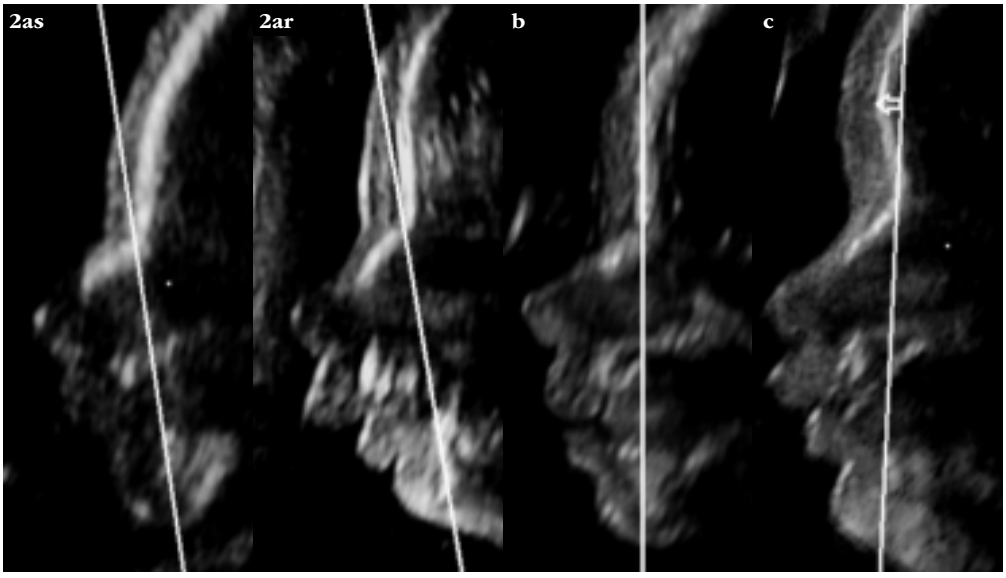

Figure 2 Ultrasound pictures showing examples of the 3 types FP lines. (as) and (ar), FP line is negative; (b) FP line is zero; (c) FP line is positive. Arrowindicates F distance. Fetus in picture (as) had a sloping forehead (case with trisomy 13), fetus in picture (ar) has retrognathia (case with Pierre Robin sequence), the other two fetuses are normal (case (b) at 25weeks gestational age and case (c) at 32weeks gestational age)

RESULTS

The cross-sectional study group included 261 fetuses. Two fetuses were excluded because an anomaly was diagnosed (spina bifida and facial cleft). In 16 fetuses no volume could be obtained because the fetus had an unfavourable position. Six cases were excluded from analysis because of uncertainty over mouth closure (one case), because extreme flexion of the head prevented identification of the mandibular landmark (one case) and because the forehead was not clearly visible (four cases). The FP line was tested in 237 fetuses crosssectionally
and in 11 fetuses longitudinally. Forty-nine investigations (20%) were performed with the 2 to 5MHz transducer and 199 investigations (80%) with the 4 to 8MHz transducer.
The mean body mass index of the women before pregnancy was 23.7 (range, 17.4–36.2). The mean amniotic fluid index was 17.1 (range, 7.3–28.3). The position of the fetus was cephalic in 67%, breech in 28% and transverse in 5%. The mean birth weight of the babies was 3472 g (range, 1160–4885 g) with 89% of the babies between the 5th and 95th percentile. Of the babies, 53% were boys and 47% girls.
The ICC for the F distance was 0.96 for both intraobserver and interobserver variability.

Cross-sectional group
There were no cases with a negative FP line. The FP line was zero in 222 cases (93.7%). The mean length of the FP line passing through the frontal bone was 15.6mm (range, 5.1–31.6 mm). The FP line was positive in only 15 cases (6.3%); this never occurred before 27 weeks' gestation. The mean F distance was 2.8mm (range, 2.1–3.6 mm). Most commonly seen was an FP line with position zero (>75% for each gestational week). The position of the FP line was not different

between male and female fetuses, nor between fetuses in cephalic and breech or transverse position (P = 0.26 and 1.0, respectively).

Longitudinal group

In all 11 cases, at least four measurements were performed. All the measurements were within the normal range (established in the cross-sectional group) except in one case, where the FP line had already changed to positive already at 20 4/7 weeks' gestation. A normal boy was born in this case. In 7 of the 11 longitudinal cases the FP line remained zero throughout pregnancy. In four cases the FP line changed during pregnancy, these changes were always from zero to positive and never the other way around.

Pathological group

The pathological group consisted of 24 cases. They are summarised in Table 1.

In 16 cases the ultrasound investigation raised the suspicion of retrognathia. In 13 of the 16 cases a negative FP line was found and in each of these cases retrognathia was confirmed after birth (Figure 2(ar)). Three of the 16 cases had a normal FP line position and retrognathia was not confirmed after birth.

In six cases ultrasound examination yielded a suspicion for bossing forehead (case 17–22). In five cases (case 17–21) the FP line was positive with an increased F distance (positive before 27 weeks or more than 3.6mm after 27 weeks). A bossing forehead was confirmed in these five cases. In case 22 the measurements of the femur and humerus were<P3, there was a large amount of amniotic fluid (amniotic fluid index 270mm) and the forehead seemed a little bossing (Figure 2(c)).

The FP line position was normal and a healthy but dysmature child was born.

In two cases with suspicion of microcephaly (case 16, 23) the FP line was negative. Microcephaly was confirmed in both cases. Case 24 was diagnosed with micropthalmia, cerebellar and corpus callosum hypoplasia. The FP line was clearly negative (Figure 2(as)). Head circumference measurement was at the 5th percentile. Trisomy 13 was diagnosed and the pregnancy was terminated.

DISCUSSION

We have described the fetal profile line as a possible tool for identifying profile anomalies.The FP line traces the frontal border of the mandible, the nasion and has, especially before 27 weeks, a stable relationship with the forehead. The FP line is the first objective tool for possible assessment of a sloping forehead. We showed that before 27 weeks the forehead of almost all fetuses is straight and the FP line is aligned with the lower part of the frontal bone for at least 5mm. We suggest that no further measurements are needed when the FP line has position zero. This line should therefore be easy to apply as a screening tool during a second trimester fetal anatomic survey. After 27 weeks the forehead changes to a curved shape with a positive FP line position in up to 25% of the cases. The shape of the forehead is not affected by the sex or the position of the fetus and we assume that the shape is determined by normal genetic anatomic predisposition. Closure of the gap between the frontal bones with delineating of the metopic suture starts at around 16 weeks. At 32 weeks there is apparently closure of the metopic suture.[6] In our series in almost all cases an ossification line was visible, indicating that the ultrasound beam is wider than

Table 1 Summary of pathological cases

Nr	*GA (weeks)*	*FP line* [a]	*Retro-gnathia* [b]	*Bossing forehead* [b]	*Micro-cephaly* [b]	*Postnatal diagnosis*	*Other findings (detected by ultrasound, postpartum evaluation or pathology)*	*Genetic confirmation*
1	37 1/7	0	–	–	–	normal	polyhydramnios	No
2	20	0	–	–	–	trisomy 18	small nose, cleft palate, CDH, AVSD, crossed fingers, rocker-bottom feet	Yes
3	28 6/7	0	–	–	–	CHARGE association	hemifacial microsomia, unilateral micropthalmia, horse-shoe kidney	Yes
4	21 6/7	neg	R	–	–	14q11.2 deletion	hypoplastic aortic arch, LVOTO, peri-membranous VSD	Yes
5	21 4/7	neg	R	–	–	Goldenhar syndrome	hemifacial microsomia, unilateral micropthalmia, unilateral cleft lip, bilateral cleft palate, abnormal ear, heart defect (not specified), hemivertebrae	No
6	25 4/7	neg	R	–	–	Pierre Robin syndrome	cleft palate, malalignement VSD	No
7	26 6/7	neg	R	–	–	Pierre Robin syndrome	cleft palate	No
8	20 5/7	neg	R	–	–	Campomelic dysplasia	characteristic skeletal malformations	Yes
9	21 5/7	neg	R	–	–	trisomy 13	DORV, micropthalmia	Yes
10	19 2/7	neg	R	–	–	del 4q dupl 7q (unbalanced)	Tetralogy of Fallot	Yes
11	22 3/7	neg	R	–	–	trisomy 18	DORV, VSD, strawberry skull, large kidney, crossed fingers, rocker bottomfeet, enlargedCM, polyhydramnios, umbilical cord cyst	Yes
12	21 5/7	neg	R	–	–	retrognathia, VACTERL association	hemivertebrae, small stomach, hydronephrosis	No
13	27	neg	R	–	–	Pierre Robin syndrome	cleft palate, ear tag	No
14	28	neg	R	–	–	Cri-du-chat syndrome D	ORV, VSD, MA, rocker-bottom foot	Yes
15	29	neg	R	–	–	Stickler syndrome	cleft palate	Yes
16	28 3/7	neg	R	–	M	Acrofacial dysostosis	IUGR, cleft palate, VSD, ventricular disproportion (L > R), small stomach, hydronephrosis, club foot, clinodactyly	No
17	19 5/7	3.7*	–	B	–	Thanatophoric dysplasia type 1	characteristic skeletal malformations without cloverleaf skull	Yes
18	20 6/7	5.5*	–	B	–	Thanatophoric dysplasia type 1	characteristic skeletal malformations without cloverleaf skull	Yes
19	21 2/7	6.3*		B	–	Thanatophoric dysplasia type 2	characteristic skeletal malformations with cloverleaf skull	Yes
20	32 1/7	7.4*	–	B	–	Apert syndrome	syndactyly of both hands	Yes
21	24 6/7	4.0*	–	B	–	Gorlin syndrome	unilateral cleft lip and palate	Yes
22	28 6/7	2.4	–	–	–	Normal, severe dysmaturity	femur and humerus < P3	No
23	25 5/7	neg	–	–	M	microcephaly	lissencephaly, CCA, colpocephaly, cerebellar hypoplasia, CDH	No
24	21 4/7	neg	–		–	trisomy 13	micropthalmia, cerebellar and corpus callosum hypoplasia	Yes

Retrognathia was suspected in cases 1 to 15, in case 16, both retrognathia and a forehead anomaly were suspected and in cases 17 to 24 a forehead anomaly was suspected. GA, gestational age in weeks. [a], classification of FP line: 0, FP line passes parallel through the lower part of the frontal bone; neg, FP line passes the frontal bone anteriorly, when the FP line passes the frontal bone posteriorly the F distance was noted in mm. *Enlarged F distance. [b] Confirmed after birth; R, retrognathia; B, frontal bossing; M, microcephaly; –, retrognathia or forehead anomalies absent after birth. CDH, congenital diaphragmatic hernia; AVSD, atrioventricular septum defect; LVOTO, left ventricular outflow tract obstruction; VSD, ventricular septum defect; DORV, double outlet right ventricle; CM, cisterna magna; MA, mitral atresia; IUGR, intra uterine growth retardation; CCA, corpus callosum agenesis.

the metopic suture or sufficient ossification has taken place to depict the bony forehead. In a few cases a thin echogenic line indicated the position of the future bony forehead and could easily be used as a landmark. The landmark on the mandible was sometimes difficult to delineate because of shadowing. With multiplanar mode and the marker dot it was possible to identify this landmark in most cases (Figure 1).

Retrognathia

In retrognathia the FP line is negative, indicating that the FP line is rotated counter clockwise (when the fetus is looking to the left) by the retroposition of the mandible (Figure 2(ar)). The FP line was normal in three cases without retrognathia but with a subjective suspicion for this condition prenatally. Paladini et al. showed in a prospective study that when an objective measurement (jaw index) was used both sensitivity and specificity for the detection of micrognathia increased compared with subjective evaluation[7].

Frontal bossing

When the FP line is positive before 27 weeks or the F distance is larger than 4mm after 27 weeks, the frontal bone is bossing as shown by our five cases. We chose 4mm as the upper limit of normal because the largest F distance in our normal population was 3.6mm. The optimal cut-off point would need to be determined in a larger prospective study. Prognathia of the mandible might also cause an enlarged F distance (clockwise rotation of the FP line). We assume that this is a rather theoretical option. The combination of bossing forehead and retrognathia, may give the impression of a normal FP line; however, the combination of these anomalies is extremely rare and likely to be noticed.

Sloping forehead

In the two cases with confirmed microcephaly the FP line was negative. A fetus at 21weeks with trisomy 13 and a head circumference at the 5th percentile also had a negative FP line (Figure 2(as)). It is tempting to assume that this fetus would have developed microcephaly. However, it may be plausible to state that the negative FP line indicated a sloping forehead meaning a disproportional growth of the skull compared with the face. Therefore, a negative FP line may indicate a sloping forehead as an early symptom of microcephaly. A sloping forehead is frequently seen in microcephaly and has been proposed as a valuable tool to recognise microcephaly; however, appropriate standardisation of this feature is still lacking.[3,4,8,9].

Sonographers should be aware that a negative FP line may indicate a sloping forehead, retrognathia or even both. Additional investigations like neurosonography and measurements like head circumference, frontal lobe length, the MNM-angle or biometry of the mandible will be helpful to identify the underlying pathology.[7,10–14,18] However, we believe that the FP line can be valuable to assist the sonographer in differentiating between a normal or abnormal profile and even has the potential to identify a sloping forehead as amarker for microcephaly at an earlier stage than biometry[9,15,16]. The FP line does not identify nose or maxilla anomalies.

Only second and third trimester fetuses from Caucasian parents were included; therefore, the results cannot be extrapolated to non-Caucasian fetuses or to the first trimester. We expect an increase in false positive cases when the line is applied in two-dimensional profiles with some deviation from the exact midsagittal plane because of the retrognathic appearance of the mandible in these cases. Caution should be used in applying the proposed FP line to profiles acquired by two-dimensional ultrasound.[17]

The FP line was tested retrospectively in fetuses where an anomaly was already suspected. Hence, larger studies are needed to test sensitivity and specificity of the FP line prospectively. To prevent false positives caution should be used in interpreting an abnormal FP line in the absence of other anomalies in low risk fetuses. Referral to a Fetal Medicine Unit with broad extensive experience is indicated in these cases.

In conclusion, we have shown that the FP line passes through the lower part of the forehead in almost all fetuses before 27 weeks. After 27 weeks the forehead develops a more curved appearance in about 25% of the fetuses. The FP line might be a useful tool to detect second trimester profile anomalies such as sloping foreheads, retrognathia and frontal bossing with the possibility of quantifying the latter. A negative FP line or enlarged F distance is suggestive of an abnormal profile and prompts further investigation to clarify the exact nature of this finding. However, findings must be interpreted carefully because larger prospective studies are needed to assess the exact sensitivity and specificity.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Fetal profile anomalies are associated with a wide range of genetic conditions and syndromes.

WHAT DOES THIS STUDY ADD?

- It is likely that the fetal profile line may improve the prenatal detection of retrognathia, sloping foreheads and frontal bossing.
- The fetal profile line is the first objective tool for assessing sloping foreheads and quantifying bossing foreheads.

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CHAPTER 7

Premaxillary protrusion assessment by the maxilla-nasion-mandible angle in fetuses with facial clefts

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ABSTRACT

Objective

To measure the degree of premaxillary protrusion in fetuses with orofacial clefts of various severities.

Methods

The maxilla-nasion-mandible (MNM) angle was measured retrospectively on by multiplanar corrected volumes of fetuses with orofacial clefts and known outcome.

Results

The MNM angle could be measured in 48 fetuses (mean gestational age 23 (range, 18-30) weeks). The mean MNM angle was normal in all 9 cases with cleft lip and intact alveolar ridge (15.2°; range, 12.5°-16.9°). In 24 cases with unilateral complete cleft lip with or without cleft palate (UCL/P) the mean MNM angle was 20.0° (range, 13.3-26.2°), above the 95th percentile in 79% (n=19) and normal in 21% (n=5). In 14 bilateral complete cleft lip and palate (BCL/P) cases the mean MNM angle was 26.5° (range, 19.2°-33.7°) and above the 95th percentile in all cases. There was no difference in MNM angle between isolated clefts and clefts with other anomalies in all groups. In 1 case with a Tessier 4 cleft the MNM angle was above the 95th percentile (25.2°).

Conclusion

The premaxilla tends to protrude in both BCL/P as UCL/P cases. The degree of protrusion, probably caused by several forces, varies greatly, especially in the BCL/P group.

INTRODUCTION

Orofacial clefts represent the most common facial anomaly, affecting about 1-2 per 1.000 live births[1]. Prevalence rates in fetal populations are even higher since cases with lethal malformations are often not included in postnatal studies[2] . Detection of an orofacial cleft is important because the defect is frequently associated with other anomalies and syndromes [3-5]. Nyberg presented a prenatal classification in which the type of cleft correlates with fetal outcome[6]. Recently Gabrielli reported that in case of bilateral cleft lip and palate the presence of a flat profile, as opposed to convex profiles as in case of premaxillary protrusion, increases the risk on lethal aneuploides in particular trisomy 18[7]. (The premaxilla is the bone lying anterior to the incisive foramen of hard palate containing all four upper incisors). Therefore adequate characterisation of the cleft is important not only to counsel parents appropriately on the severity of the defect, the expected surgical treatment and aesthetic outcome, but also on its likely association with chromosomal or syndromal anomalies.
Our group proposed the maxilla-nasion-mandible (MNM) angle as an instrument to measure the convexity of the profile and demonstrated premaxillary protrusion in three of the four cases with an orofacial cleft[8]. All other studies published so far use subjective evaluation of the defect. The aim of this study was to determine the degree of premaxillary protrusion in a larger group of fetuses with orofacial clefts of various severities by the MNM angle.

METHODS

This was a retrospective observational study. Databases of the St. Antonius Hospital, Academical Medical Centre Amsterdam and Universities of Utrecht and Groningen, all referral centres for high risk pregnancies in the Netherlands, were reviewed for cases with diagnosed orofacial clefts where three-dimensional (3D) volumes had been stored. Selection criteria were an adequate visualization of the nasion, anterior borders of maxilla and mandible and complete follow-up. Midline clefts and isolated cleft palates were not included in this study.
When the cleft was limited to the lip with intact alveolar ridge (bony ridge of the maxilla that contains the alveoli of the future teeth) the cases were classified as cleft lip (CL). All other enrolled cases were classified as unilateral cleft lip with or without cleft palate (UCL/P), bilateral cleft lip with or without cleft palate (BCL/P) or atypical cleft (AC).
The MNM angle is an objective method to determine the anteroposterior position of the jaw and is defined as the angle between the lines maxilla-nasion and mandible-nasion in the exact mid sagittal plane[8]. The nasion is defined as the most anterior point at the intersection of the frontal and nasal bones. Jaw landmarks were in the middle points of the anterior borders of the maxilla and mandible. Callipers were placed on the outermost borders of the bone. To obtain an exact mid-sagittal view the axial and coronal images of the multiplanar view were individually rotated to obtain symmetrical views of the orbits. Symmetry of the mandible, but not of the midface, was also used to define the midsagittal plane. When necessary the marker dot in the axial plane was used to identify landmarks on the maxilla or mandible. VCI (volume contrast imaging) was used, when indicated, to improve the image quality.
The mean MNM angle, as established in our previous study, was 13.5º and did not change significantly during pregnancy. Therefore in de present study a MNM angle between the 5th (10.4º) and 95th percentile (16.9º) was considered normal.

Cases with evidenced for retrognathia (established with the inferiorfacial angle[9] and fetal profile line[10]), as a confounding factor for an enlarged MNM angle, were excluded.

Data were analysed by the statistical software package SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA) and Microsoft excel for Windows 2000. Correlation was determined by Pearson's correlation test. The Mann-Whitney U or MANOVA test was used to compare groups. $P < 0.05$ was considered statistically significant.

RESULTS

In 48 of 62 cases, with an orofacial cleft and 3D volumes it was possible to clearly visualize the landmarks for the measurement of the MNM angle (Table 1). Gestational age varied from 18 to 30 weeks. Cases were excluded mainly because the landmarks were unclear or were acquired while the fetus had an open mouth. Only one of two cases with a Tessier cleft type 4[10] was excluded because of evidence of retrognathia.

There were 9 cases with CL (Table 1). In one case, a cleft of the soft palate was observed after birth and later a 22q11 deletion was diagnosed. In the 8 other cases the cleft was isolated (no other anomalies). In two cases a small indentation was visible postnatally in the otherwise intact alveolar ridge. All MNM angles in this group were within the normal range (mean, 15.2°; range, 12.5°-16.9°) (Figure 1). There was no relation between MNM angle and gestational age ($P = 0.30$).

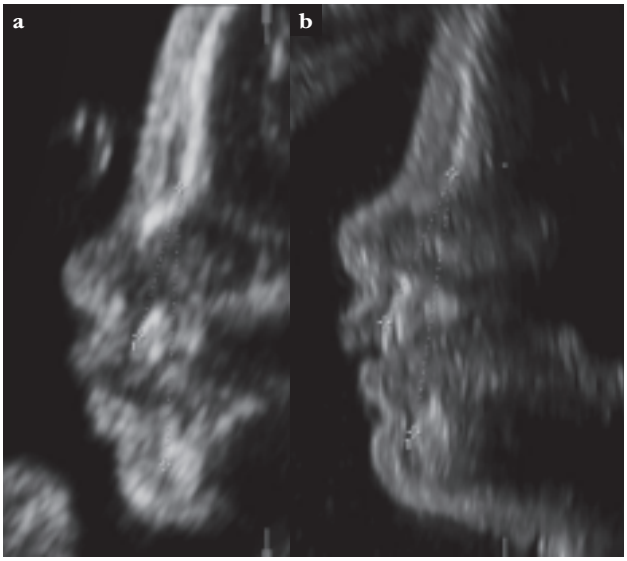

Figure 1 Ultrasound pictures of cases with CL. Case 1 (A) with smallest (12.5°) and case 9 (B) with largest (16.9°) MNM angle in CL group.

There were 24 cases with UCL/P (Table 1). One case was diagnosed with trisomy 21, one with Gorlin syndrome and another case had multiple anomalies. In the remaining 21 cases the cleft was isolated. The MNM angel was normal in 5 cases (21%) and above the 95th centile in 19 cases (79%) (Figure 2). The MNM angle was not different between the isolated cases and cases associated with other anomalies (Mann-Whitney U: P = 0.86) or cases with intact or cleft secondary palate (Mann-Whitney U: P = 0.29). There was no relation between MNM angle and gestational age (P = 0.56).

There were 14 cases with BCL/P (Table 1). In two cases the clefts of the lip were incomplete. Two cases were diagnosed with trisomy 13, one with trisomy 18, one with Bohring-Opitz syndrome, one with Wolf-Hirschhorn syndrome and one case had multiple anomalies. In all 14 cases the MNM angle was above the 95th centile (Figure 3). The two cases with trisomy 13 and the case with multiple anomalies had a large MNM angle of more than 25º (Figure 3B).
The MNM angle was not different between the isolated and not-isolated cases (24.6º and 27.4º respectively, Mann-Whitney U: P = 0.46). There was no relation between MNM angle and gestational age (P = 0.59).

The MNM angle was significantly different between the three groups CL, UCL/P and BCL/P (MANOVA: P<0.001).

In one case with a Tessier 4 cleft[9] the MNM angle was above the 95th percentile (25.2º).

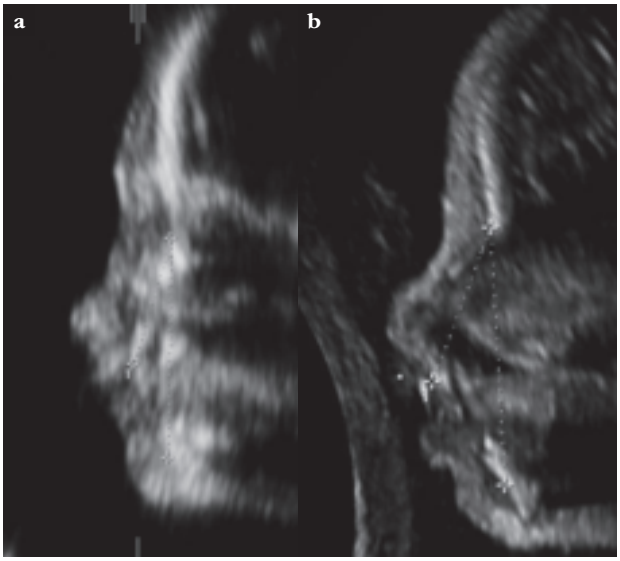

Figure 2 Ultrasound pictures of cases with UCL/P. Case 12 (A) with trisomy 21 and normal (15.0º) MNM angle. Case 33 (B) with isolated UCL/P and largest (26.2º) MNM angle in UCL/P group.

Table 1 Overview of cases clustered by type of cleft and ordered by ascending MNM angle. Reported are gestational ages at moment of ultrasound investigation, MNM angle, integrity of lip, alveolar ridge and palate, karyotype if performed, associated anomalies and final diagnosis.

Type cleft	*Case nr*	*GA (weeks)*	*MNM angle (degree)*	*Lip*	*Alveolar ridge*	*Palate*	*Karyotype*	*Associated anomalies*	*diagnosis*
CL									
	1	23 5/7	12.5	uni	intact	intact	–		isolated
	2	19 5/7	13.4	uni(ic)	intact	intact	nl		isolated
	3	25 2/7	15.1	uni	intact (i)	intact	–		isolated
	4	20	15.4	uni	Intact	cleft (pm)	22q11 del	cardiac anomaly	VCF syndrome
	5	22 5/7	15.7	uni	intact (i)	intact	–		isolated
	6	21 1/7	15.9	uni	intact	intact	–		isolated
	7	29 6/7	15.9	uni	intact	intact	nl		isolated
	8	24 3/7	16.5	uni	intact	intact	–		isolated
	9	27 1/7	16.9	uni	intact	intact	–		isolated
UCL/P									
	10	29 6/7	13.3	uni	uni	cleft	nl		isolated
	11	21	13.9	uni	uni	cleft	nl		isolated
	12	22 3/7	15.0	uni	uni	cleft	trisomy 21	semilobar holoprosencephaly	trisomy 21
	13	23 5/7	15.9	uni	uni	intact	nl		isolated
	14	22	16.4	uni	uni	cleft	nl		isolated
	15	21	17.0	uni	uni	intact	nl		isolated
	16	21	17.2	uni	uni	intact	–		isolated
	17	24 5/7	18.3	uni	uni	cleft	nl		Isolated-
	18	23 6/7	18.8	uni	uni	intact	–		isolated
	19	24 5/7	18.8	uni	uni	cleft	–		isolated
	20	20	19.4	uni	uni	cleft	nl		isolated
	21	20 3/7	20.5	uni	uni	cleft	–		isolated
	22	20	20.8	uni	uni	cleft	nl		Gorlin syndrome
	23	20 5/7	20.9	uni	uni	intact	–		isolated
	24	21 5/7	20.3	uni	uni	cleft	–		isolated
	25	24 3/7	20.6	uni	uni	cleft	nl		isolated
	26	22	21.1	uni	uni	intact	nl		isolated
	27	26	21.8	uni	uni	cleft	nl		isolated
	28	23 5/7	22.1	uni	uni	cleft	bal. transl.	semilobar holoprosencephaly	multiple anomalies
	29	19 6/7	22.5	uni	uni	cleft	nl		isolated
	30	22	22.8	uni	uni	cleft	–		isolated
	31	29 3/7	23.3	uni	uni	cleft	nl		isolated
	32	26 4/7	24.5	uni	uni	cleft	–		isolated
	33	19	26.2	uni	uni	cleft	–		isolated

BCL/P									
	34	20 4/7	19.2	bi	bi	cleft	nl	small nose, abnormal position of hand, clubfoot, hypertelorisme, hypogenesis of corpus callosum	Bohring-Opitz syndrome
	35	19 6/7	20.0	bi(ic)	bi	cleft	–		isolated
	36	27	21.3	bi(ic)	bi	cleft	–		isolated
	37	24 4/7	21.9	bi	bi	cleft	nl		isolated
	38	27 1/7	25.0	bi	bi	cleft	–		isolated
	39	20 4/7	25.9	bi	bi	cleft	trisomy 18	omphalocele, rocker bottom feet cardiac anomaly, hypogenesis of corpus callosum	trisomy 18
	40	20 3/7	26.6	bi	bi	cleft	trisomy 13		trisomy 13
	41	21 4/7	26.6	bi	bi	cleft	nl		isolated
	42	23 4/7	28.1	bi	bi	cleft	–		isolated
	43	25 3/7	30.1	bi	bi	cleft	–		isolated
	44	20 6/7	30.2	bi	bi	cleft	nl	cardiac anomaly	multiple anomalies
	45	21 3/7	30.2	bi	bi	cleft	transloc 3 4	IUGR, brachycephaly, hypertelorisme, diafragmatic hernia,VSD, hypospadia	Wolf-Hirschhorn syndrome
	46	19 5/7	32.5	bi	bi	cleft	–		isolated
	47	19 1/7	33.7	bi	bi	cleft	trisomy 13	semilobar holoprosencephaly, hypogenesis of corpus callosum and cerebellum, ventriculomegaly, clinodactily	trisomy 13
AC									
	48	22 5/7	25.2	Tessier 4			–	ASD	multiple anomalies

CL,cleft lip; UCL/P, unilateral cleft lip and alveolar ridge with or without cleft palate; BCL/P, bilateral cleft lip and alveolar ridge with or without cleft palate; AC, atypical cleft; GA, gestational age; uni, unilateral cleft; bi, bilateral cleft; (i), small indentation on otherwise intact alveolar ridge; pm, palatum molle; (ic), incomplete cleft; bal. transl., balanced translocation; IUGR, intrauterine growth retardation; VSD, ventricular septal defect; ASD, atrial septal defect.

DISCUSSION

We report the MNM angle in 48 orofacial cleft cases and show that premaxillary protrusion is present in 78% of UCL/P cases, in 100% of BCL/P cases and in the only AC case. No premaxillary protrusion was seen in cases with an intact alveolar ridge (Figure 1). An enlarged MNM angle should therefore alert the ultrasonographer for alveolar ridge interruption in cases with a facial cleft where this is not evident.

The use of the MNM angle has enabled prenatal identification of premaxillary protrusion in the midsagittal plane in UCL/P cases. Without an objective measurement premaxillary protrusion may not be obvious (Figure 2B). The tendency of the premaxilla to protrude postnatally in unoperated individuals with UCL/P is described by cephalometric evaluation by several authors[10-13]. The musculus orbicularis oris which pulls the premaxilla to the non-cleft side likely causes ventral rotation and subsequent protrusion in the midsagittal plane of the premaxilla.

An abnormal fetal profile in BCL/P case was already noticed in 1982[14]. Premaxillary protrusion has been reported by Nyberg in 1992 as a sonographic sign of BCL/P[15]. The same author describes in a group of 20 fetuses with BCL/P that 17 had protrusion of the premaxillary component and 3 did not[6]. These 3 fetuses had multiple anomalies and a fatal outcome. The subjectively flattened profile was considered hypoplasia of the midface, as seen in the same study in cases with a midline cleft lip and palate, who also all had a flattened profile and a fatal outcome. Gabrielli found an association between a flattened profile and aneuploidy, especially trisomy 18[7].

In our series, by measuring the position of the premaxilla with the MNM angle, we found a certain degree of protrusion in all cases with BCL/P. This seems to contradict the findings of Nyberg and Gabrielli who describe flattened profiles in some BCL/P cases. However the objective measurement of the anteroposterior position of the bony jaws with 3D ultrasound used in this study cannot be compared with subjective 2D evaluation of the profile, which includes the often altered and underdeveloped soft tissue of the nose, columella and upper lip. Nevertheless a large variation in the position of the premaxillary component is also evident in our series of BCL/P cases, with MNM angles ranging from 19º to 34º (Figure 3).

Postnatally the most striking facial characteristic observed in unoperated patients with BCL/P is the protrusive premaxilla[16-18]. The absence of a lip restraining effect likely contributes to the premaxillary protrusion seen in unoperated BCL/P individuals[10, 19]. However, postnatal groups differ from prenatal groups as postnatally teething, chewing, swallowing, speaking, anterior tongue thrusts to close the cleft and facial growth influences facial morphology.

The finding that not only in all cases with BCL/P the premaxilla is moved forward but also in 77% of the UCL/P and in the AC suggests the existence of forces that pushe/pull the premaxilla forward. Forward growth of the five facial mesenchyme prominences and the forward growing nasal septum in early gestation may act as a primary force, which in case of alveolar ridge disruption causes premaxillary protrusion. The tongue, normally counteracted by the intact alveolar ridge and lips may further push the premaxilla forwards. It is interesting that in the case with trisomy 21 and holoprosencephaly the MNM angle was not enlarged. This may be explained

as well by midfacial hypoplasia, known to be associated with holoprosencephaly and trisomy 21 as by the fact that the tongue in trisomy 21 fetuses is often positioned outside the mouth and hypotonic[20, 21]. The finding that in the only two cases with incomplete BCL/P the MNM angles were marginally increased might be explained by restraining effect from remaining fibres of the musculus orbicularis oris in these cases. Differences in facial morphology between individuals with complete or incomplete clefts are also described in postnatal studies[22].

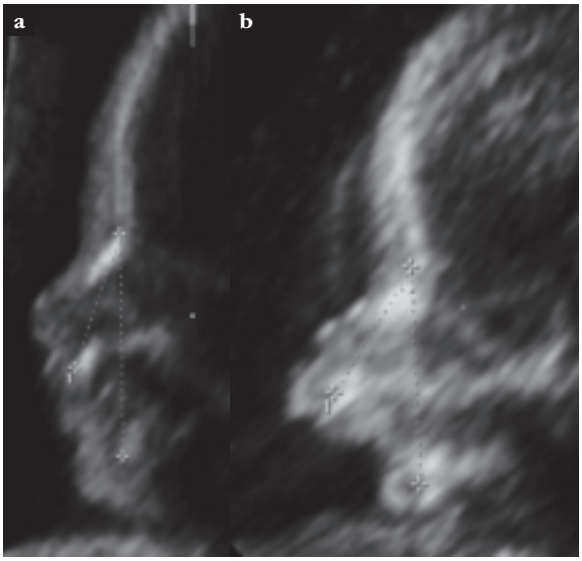

Figure 3 Ultrasound pictures of cases with BCL/P. Case 36 (A) with isolated incomplete BCL/P, the subjective normal profile has a MNM angle above the 95th percentile (21.3°). Caser 47 (B) with trisomy 13 has a large MNM angle (33.7°).

If forward movement of the premaxilla is a consequence of normal fysiological events, the absence of premaxillary protrusion may indicate pathofysiology. This is in accordance with the fatal outcome in BCLP cases without premaxillary protrusion as reported by Nyberg and Gabrielli[6, 7]. However, in our series 4 of the 5 BCLP cases with associated anomalies had a large MNM angle and showed obvious premaxillary protrusion (Figure 3B). Facial clefts can be part of many different kind of syndromes, with each a very heterogenic pathophysiology. The amount of protrusion of the premaxilla will probably be influenced by many different factors, like completeness and size of the cleft(s), muscle function of the lips and tongue and intrinsic growth potential of the midface. Therefore large studies are needed to establish the behaviour of the premaxilla in relation to specific syndromes with a facial cleft.

Limitation of our study is the retrospective design. The fact that MNM angle was measured on previously stored volume may explain why a good measurement could be obtained in 48 out of 62 (77%) cases. This is at variance with a previous prospective study where we showed that a good MNM angle could be measured in 92.3% of the cases.

The ultrasonographer has to be measured aware that also retrognathia increases the MNM angle and the two anomalies may occur together. Additional investigations like measuring the inferior facial angle[9] and Fetal Profile line[10], but also biometry of the mandible and evaluation of the pharyngeal space will be helpful in equivocal cases[23-27]. Previously we showed that 3D ultrasound improves accuracy, therefore caution should be used in applying the MNM angle to profiles acquired by 2D ultrasound[28].

In conclusion, we showed that there is a tendency for a forward displacement of the premaxilla both in cases with a unilateral or bilateral interruption of the alveolar ridge. This finding contributes to our understanding of the pathophysiological events occurring in orofacial clefts. A multitude of factors like muscle activity of the lip and tongue, intrinsic growth potential and completeness of the cleft will probably determine the degree of protrusion of the premaxilla, which varies greatly especially in BCL/P.

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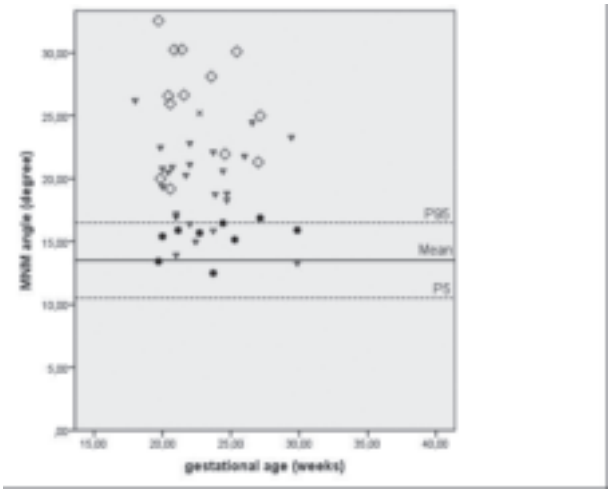
Figure MNM angle in fetuses with an orofacial cleft



Maxilla–nasion–mandible (MNM) angle measurements in 30 fetuses with an orofacial cleft plotted against gestational age, with mean (——) and 5th and 95th centiles (----) for normal fetuses. ●, fetuses with cleft lip but intact alveolar ridge; ∇, fetuses with unilateral cleft lip and alveolar ridge with/without cleft palate ; ◇, fetuses with bilateral cleft lip, alveolar ridge and palate; x, fetus with Tessier cleft type 4.

CHAPTER 8

Three-dimensional ultrasound imaging and measurement of nasal bone length, prenasal thickness and frontomaxillary facial angle in normal second- and third-trimester fetuses

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ABSTRACT

Objectives

To assess the feasibility of nasal bone length (NBL), prenasal thickness (PT) and frontomaxillary facial (FMF) angle measurements performed on the same three–dimensional (3D) multiplanar-corrected profile view in healthy second- and third-trimester fetuses, to create reference ranges and to review published measurement techniques.

Methods

3D volumes of 219 healthy second- and third–trimester fetuses were retrospectively analyzed. The quality of images and measurability of the markers were assessed with 5-point and 3-point scoring systems, respectively. Measurements of NBL (with care to exclude the frontal bone), PT and FMF were obtained in the exact mid-sagittal plane. Reference ranges were constructed based on measurements from images with high-quality (4 or 5 points) and high measurability (2 or 3 points) scores and compared with those in the most relevant published literature.

Results

A high-quality score was assigned to 111 images. Among these, a high measurability score was significantly more often achieved for NBL (98.2%) and PT (97.3%) than for the FMF angle (26.1%) ($P < 0.001$). Both NBL ($NBL = -6.927 + (0.83 \times GA) - (0.01 \times GA^2)$) and PT ($PT = (0.212 \times GA) - 0.873$) (where GA = gestational age) showed growth with gestation, with less pronounced growth for NBL after 28 weeks. Our reference range for the NBL showed a systematically smaller length than those in other two-dimensional (2D) ultrasound–based publications. The FMF angle measurements that we obtained did not show a significant change with GA.

Conclusions

NBL and PT are easily measured using 3D ultrasound whereas FMF angle measurement is more challenging. When it is measured in the exact mid-sagittal plane and care is taken to exclude the frontal bone, measurements of the NBL are systematically smaller than those in previous 2D ultrasound-based publications.

INTRODUCTION

Down syndrome is characterized by specific facial features such as a flat face and a small nose[1]. Continuous technical improvements in ultrasound techniques have enabled optimal visualization of these features which, in turn, have evolved into markers currently used as screening tools for the detection of Down syndrome. First-trimester nasal bone assessment, in combination with nuchal translucency measurements, was the first to be introduced[2], while second-trimester markers have also been proposed[3–5]. Nasal bone length (NBL), prenasal thickness (PT) and the frontomaxillary facial (FMF) angle are three second-trimester markers measurable in the mid-sagittal profile view. Improvements in three-dimensional (3D) ultrasound imaging have increased the accuracy of measurements by standardizing the examination plane through multiplanar correction of the acquired volume. The mid-sagittal plane obtained can differ considerably from the plane judged as mid-sagittal on two-dimensional (2D) ultrasound[6]. This has raised the question of whether the first published reference ranges, based on 2D images, are still valid and how they compare with the new ones obtained by 3D techniques. Reports on the role of 3D ultrasound in obtaining accurate NBL, PT and FMF angle measurements and individual reference ranges for these markers in the second trimester of pregnancy are available[7–10]; however, no study has thus far measured all three markers in the same fetus and extended the normal ranges to the third trimester. Although screening programs for trisomies are offered earlier in pregnancy, late diagnosis of chromosomal anomalies is not uncommon, especially in countries with a low uptake of screening programs. In addition, even when termination of pregnancy is no longer an option, the diagnosis of Down syndrome can be of value in establishing the optimal place of delivery and optimal perinatal management, and in preparing parents for the birth of a Down syndrome baby. The aims of this study were to assess the feasibility of NBL, PT and FMF angle measurements performed on the same 3D-corrected profile view in normal second- and third-trimester fetuses and to create reference ranges for these parameters. Furthermore, differences in definition or measurement techniques in the most relevant published literature on the individual markers were reviewed.

METHODS

The ultrasound unit of the Saint Antonius Hospital in Nieuwegein, The Netherlands, offers routine ultrasound investigation in the second and third trimesters of pregnancy. 3D images of the fetal face were collected cross-sectionally in 219 fetuses from a cohort of nonsmoking, healthy, low-risk Caucasian women with a singleton pregnancy. Only non-anomalous fetuses from uncomplicated pregnancies were included. All images were obtained using a GE Voluson 730 Expert ultrasound system equipped with a RAB2-5L or RAB4-8L probe (GE Medical Systems, Kretz Ultrasound, Zipf, Austria). Volumeswere acquired from fetuses facing the transducer, starting from as close as possible to the exact mid-sagittal profile view during periods of quiescence and with an insonation angle of less than 45°. An attempt was made to collect at least two such volumes per fetus. The volumes were stored on removable digital media for subsequent analysis on 4D View software version 7.0 (GE Medical Systems). These images were retrieved retrospectively for the purpose of this study and the markers measured offline using the multiplanar mode of the 4D View program. The study was approved by the local ethics committee and all women gave written consent. Initially the multiplanar images were magnified to obtain the maximum possible size of

the fetal profile, and the reference dot was positioned in Plane A (Figure 1a, upper left) just below the nasal bone. Planes B and C were then individually rotated to obtain symmetrical views of the orbits. When this multiplanar correction was carried out appropriately, the nasal bones and frontal processes of the maxilla automatically appeared in Plane B as an 'inverted V-shape'. To obtain an exact mid-sagittal view in Plane A, the reference dot was placed in Planes B and C exactly at an equal distance from the inner border of the orbits, at the level of the nasal bone. The adjusted planes, resulting in an exact mid-sagittal view in Plane A, are displayed in Figure 1a. NBL, PT and FMF angle were all measured in the enlarged image in Plane A.

For each fetus, the volume with the best mid-sagittal view was selected. Firstly, all images were corrected by multiplanar mode to the exact mid-sagittal view and scored from 1–5 in terms of quality for contrast and clarity (quality score), 1 being poor and 5 excellent. Specific points of interest were an optimal mid-sagittal view and clear contrast between the fetal profile and surrounding tissue or fluids. Only images with a quality score of 4 or 5 were used for further analysis. Subsequently, in the included images, each individual marker was scored from 1–3 in terms of visualization of landmarks (measurability score), 1 being poor and 3 excellent. Optimal contrast between bony and soft tissue at the location of the landmarks was considered important. Only markers with a measurability score of 2 or 3 were used for further analysis. Each marker was measured three times and the average was taken as the final measurement.

The nasal bone was measured from the nasion to the distal end of the white ossification line (Figure 1b). The nasion was defined as the most anterior point at the junction between the frontal and nasal bones. As the frontal bone extends posteriorly of the nasal bone (Figure 1c), care must be taken to measure the nasal bone starting from the level of the nasion, without including the frontal bone in the measurement, as this would erroneously enlarge the measured NBL (Figure 1d). The PT was measured as the shortest distance between the nasion (same landmark as used for measuring the NBL) and the frontal skin (Figure 1b). In cases in which there was a gap between the nasal and the frontal bones (disjunction), for PT measurement the landmark nasion was set at the point of intersection of two lines drawn tangentially to the nasal bone and to the lower part of the frontal bone, whereas for NBL measurements only the white ossified part of the nasal bone was measured.

The FMF angle was measured according to the different techniques proposed in the literature by various researchers; Sonek *et al*.[5] measured the FMF angle with the first ray drawn from the top edge of the palatal complex (Figure 1e) and the second line to either the frontal bone or the skin anteriorly of the frontal bone. In contrast, Molina *et al*.[7] made a distinction between two structures in the palatal complex: the vomer and the palate (Figure 1f). They placed the first ray along the palate and the second ray along the frontal bone. To determine which of these methodologies for FMF angle measurement was the easier to perform andmore reproducible, we measured the FMF angle in six different ways (Figures 1e and f).

To assess intraobserver variability, all markers were remeasured in the acquired volumes following a 1-week interval. Interobserver variability was assessed by a second sonologist, who repeated the measurements as described above on all markers. Finally, results were compared with the most relevant literature. Data analysis was performed by Microsoft Excel for Windows 2000 (Microsoft Corp., Redmond, WA, USA) and SSPS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Data are presented as mean (SD) or median (range). Bland-Altman analysis was used to describe intra- and interobserver variability. The best-fit polynomial line was used for constructing reference ranges. Differences between observed frequencies were compared by the chi-square test, and $P < 0.05$ was considered to be statistically significant.

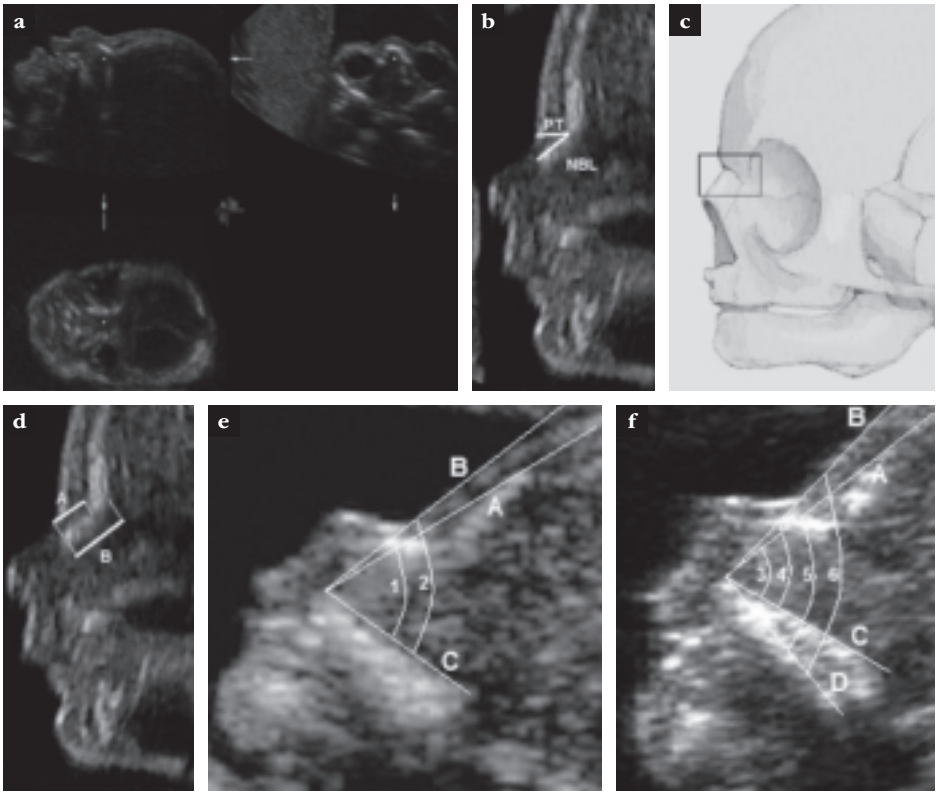

Figure 1 (a) Multiplanar ultrasound image showing the 'inverted V-form' of the nasal bones and frontal processes of the maxilla in Plane B. In Plane A the reference dot was placed just below the nasal bone and in both Planes B and C exactly at equal distances from the inner borders of the orbits. (b) Ultrasound image showing prenasal thickness (PT) and nasal bone length (NBL) measurements. (c) Illustration of the fetal skull: the frontal bone continues posteriorly to the nasal bone. (d) Ultrasound image showing correct NBL measurement (A) and incorrect NBL measurement with inclusion of the frontal bone (B). (e) Ultrasound image of measurement of frontomaxillary facial angles between the frontal bone (A), skin (B) and palatal complex (C). In cases where only the palatal complex was visible (and no distinction was possible between vomer and palate) the first ray was drawn along the upper surface of the palatal complex. The second ray was directed to either the frontal bone (angle 1, complex–bone) or skin (angle 2, complex–skin) at the point of its greatest anterior excursion. In all cases the point of intersection was the upper corner of the anterior aspect of the maxilla. (f) Ultrasound image of measurement of frontomaxillary facial angles between the frontal bone (A), skin (B), vomer (C) and palate (D). In cases where the two structures, vomer and palate, could be identified, the first ray was drawn along the upper surface of the vomer or through the palate. The second ray was directed to either the frontal bone or skin at the point of its greatest anterior excursion. In all cases the point of intersection was the upper corner of the anterior aspect of the maxilla. 3, vomer–bone angle; 4, vomer–skin angle; 5, palate–bone angle; 6, palate–skin angle.

RESULTS

The cross-sectional study group included 219 fetuses at 15–33 weeks' gestation (mean, 23 weeks). In 111 fetuses the mid-sagittal image obtained was given a quality score of 4 or 5. The quality scores of the images from all 219 fetuses and the measurability scores of the 111 highquality images are presented in Table 1. The frequency distribution of the measurability scores of the 111 high quality images was not equal for the three markers (chi-square $P < 0.001$). A measurability score ≥ 2 was obtained in 109 cases for the NBL (98.2%), in 108 cases for the PT (97.3%) and in 29 cases for the FMF angle (26.1%). A measurability score of ≥ 2 was obtained for both NBL and PT measured in the same mid-sagittal profile view in 106 cases (95.5%), for FMF angle and NBL in 26 cases (23.4%) and for FMF angle and PT in 28 cases (25.2%). The angle between the transducer and the nasal bone was less than 45° in all cases.

Table 1 Quality score of 219 images and measurability score of facial markers in 111 images that had a quality score of 4 or 5

		Measurability (n = 111)		
Score	*Quality (n = 219)*	*NBL*	*PT*	*FMF*
1	7	2	3	82
2	47	105	102	28
3	54	4	6	1
4	108	–	–	–
5	3	–	–	–

Data given as number of images. Quality was scored from 1 (poor) to 5 (excellent) for contrast and clarity. Measurability was scored from 1 (poor) to 3 (excellent) in terms of visualization of landmarks. FMF, frontomaxillary facial angle; NBL, nasal bone length; PT prenasal thickness.

The intraobserver 95% limits of agreement were −1.03 to 0.86 mm, −0.61 to 0.76 mm and −8.18 to 5.29°, for NBL, PT and FMF angle, respectively. The respective interobserver 95% limits of agreement were −1.20 to 1.30 mm, −0.52 to 0.69 mm and −6.22 to 8.50° (Table 2).
NBL increased significantly with gestational age (GA), from 3.3 mm at 15 weeks' gestation to 9.6 mm at 33 weeks (linear regression $P < 0.001$). NBL followed a second order polynomial relationship with GA: $NBL = -6.927 + (0.83 \times GA) - (0.01 \times GA^2)$ ($R^2 = 0.78$, $P < 0.001$) (Figure 2). Figure 2 also shows the mean NBL derived from this study compared with the mean published by Sonek *et al.*[11].
PT increased significantly with GA from 2.3 mm at 15 weeks to 6.1 mm at 33 weeks (linear regression $P < 0.001$). A linear relationship with GA was confirmed on polynomial regression: $PT = (0.212 \times GA) - 0.873$ ($R2 = 0.74$, $P < 0.001$) (Figure 3). A comparison between the mean PT derived from this study and mean PT measured by Persico *et al.*[9] is also shown in Figure 3.
The palate and vomer were seen as a palatal complex in 21 out of 29 cases (72.4%), and as two separate structures in eight cases (27.6%). The likelihood of the two being observed as a palatal complex or as two separate structures seemed to be independent of GA. Median GA for visualization as a palatal complex was 19.5 (range, 15.4–28.2) weeks, and for separate structures it was 18.5 (range, 15.6–25.5) weeks. In view of the paucity of FMF angle data, the measurements

of 'complex' angles (angles 1 and 2, Figure 1e) and 'vomer' angles (angles 3 and 4, Figure 1f) were pooled together; given the fact that in both measurements the first ray is placed at the same position, the angles 'complex–bone' and 'vomer–bone' are similar, as are 'complex–skin' and 'vomer–skin'. The difference between FMF angles measured to the skin or to the bone had a constant value of 10° (median 10.0°, range 6.1–14.6°) throughout gestation (Pearson's r = –0.12, P = 0.54), making it unnecessary to use these two different measurement techniques in this study. Consequently, further analysis of FMF angles was performed by analyzing two measurements only: complex/vomer–bone angle (i.e. complex–bone and vomer–bone pooled together) and palate–bone angle (Figure 4). The FMF angles did not change significantly with gestation, with a mean complex/ vomer–bone value of 67.05° (range, 57.85 – 77.78°; SD = 4.34) (P = 0.11). The mean palate–bone angle was 85.08° (range, 80.8 – 94.9°; SD = 5.13) (P = 0.74).
NBL and PT were highly correlated (P < 0.001). Owing to the paucity of FMF angle data, no analysis of correlation was performed between this and any other marker.

DISCUSSION

In this study we present novel reference ranges for NBL and PT measured on multiplanar view-corrected midsagittal plane using 3D volumes of normal second- and third-trimester fetuses. Both NBL and PT showed growth with gestation, with less pronounced growth for NBL after 28 weeks. Good visualization leading to high-quality measurements was achieved significantly more often for NBL and PT than for the FMF angle.
To the best of our knowledge this is the first study using 3D ultrasound to measure all three markers in the same fetus and extending the measurements into the third trimester.
Markers for Down syndrome are mainly studied early in pregnancy. However, uptake of first-trimester screening varies across countries as well as does the rate of late bookers. It is therefore important to have effective Down syndrome markers available for later diagnosis in pregnancy.
The importance of measuring NBL, PT and FMF angle in the exact mid-sagittal view has recently been emphasized in the literature by a study showing that the use of 3D multiplanar mode improves the accuracy of profile measurements[6]. In addition, Persico *et al.*[10] showed that the NBL is overestimated when measured in oblique midsagittal views and underestimated in parasagittal planes.
Although the present study design was retrospective, volumes were rigorously selected in order to obtain optimal measurements. The stored volumes did not always allow optimal visualization of facial structures to enable high-quality measurements. This was dependent on the angle of insonation and fetal position. Although this may seem a limitation of the study, in our opinion it rather reflects a 'real-world' situation where, in a routine clinical setting, volumes are stored during the examination and markers measured retrospectively.
Measurement of the FMF angle was particularly challenging, being judged to be of high quality only in 26% of the cases, in contrast to 98% and 97% for NBL and PT, respectively. This suggests that measurement of the FMF angle is more difficult after the first trimester and probably requires a very specific insonation angle to avoid shadowing by the facial bony structures that hamper good visualization of the thin vomer.
After re-examining the nasal and frontal bones on multiplanar mode-corrected profile view using 3D volumes, we redefined our measurement technique. In the new technique care was taken not to add part of the frontal bone to the measurement of the NBL, as this would erroneously increase the measurement (Figures 1c and d). When in Down syndrome fetuses the nasal bone

is hypoplastic, the nasal and frontal bones are not in contact, but are separated by a gap (nasal bone–frontal bone disjunction). In such cases we used the reconstructed landmark nasion as a starting point for PT measurement, instead of the lowest part of the frontal bone. This landmark may be more difficult to reconstruct in case of absence of the nasal bone in the second and third trimesters of pregnancy. However, later in pregnancy the nasal bone is more commonly hypoplastic rather than absent. We preferred to measure PT from the (landmark) nasion, as this avoids combining bony tissue and skin tissue in the PT measurement. The advantage would be that only the skin is measured, which tends in our opinion to be more edematous in Down syndrome fetuses. However, comparative studies are needed to substantiate this assumption.

It is mandatory to adhere to standardized measurement techniques when using markers for the estimation of Down syndrome risk in order to prevent overestimation or underestimation of the calculated risk. Several measurement techniques for NBL have been described in the literature (Table S1 online)[3,8,10–12]. 2D ultrasound may lead to overestimation of the NBL if this is measured slightly obliquely and/or the measurement erroneously includes part of the frontal bone. This supposition is confirmed by the smallerNBL in our study and in that of Persico *et al.*[10]. Moreover, when our range is compared with the 2D reference range published by Sonek *et al.*[11], the NBL in our study is systematically smaller (by about 1–2 mm) while the means otherwise follow the same trend (Figure 2).

Both Maymon *et al.*[4,13] and Persico *et al.*[9] studied PT in normal fetuses. We chose to compare our results with those of the latter study, as it is recent and based entirely on 3D-corrected images examined offline. While our results show a linear trend of PT with GA, the reference range of Persico *et al.* follows a second-order polynomial trend. Possible explanations for this discrepancy could be that our study has a wider gestational window (15–33 compared with 16–24 weeks) and that we used a different definition of PT in cases of disjunction. Nevertheless it seems unlikely that this different definition could play a major role in explaining the discrepancy between reference ranges, as disjunction was observed in only a very limited number of cases.

For FMF angle measurement we used six different techniques (Figure 1e and f) that have been described previously in the literature. The difference between the FMF angles using a ray towards the frontal bone or the frontal skin showed a non-significant change between 15 and 33 weeks' gestation, with a mean of 10°. We observed that (independently of GA) in our population the vomer and palate were more often seen as one complex than as two separate structures. For these reasons we decided to adopt the combination complex–bone/vomer–bone angle and the palate–bone angle. Of the three facial measurements we found the FMF angle to be the most difficult to visualize and measure.

Table 2 Intra- and interobserver mean differences and 95% limits of agreement (LOA) with 95% CIs between paired measurements of facial markers

	Intraobserver		*Interobserver*	
Measurement	*Mean diff.*	*LOA (95%CI)*	*Mean diff.*	*LOA (95%CI)*
NBL (mm)	−0.08	−1.03 (−0.87, −1.19), 0.86 (0.71, 1.02)	0.05	−1.20 (−0.99, −1.40), 1.30 (1.09, 1.50)
PT (mm)	0.08	−0.61 (−0.49, −0.72), 0.76 (0.65, 0.88)	0.09	−0.52 (−0.62, −0.42), 0.69 (0.59, 0.79)
FMF (°)	−1.45	−8.18 (−5.98, −10.38), 5.29 (3.08, 7.49)	1.14	−6.22 (−3.85, −8.59), 8.50 (6.13, 10.87)

Diff., difference; FMF, frontomaxillary facial angle; NBL, nasal bone length; PT, prenasal thickness.

FMF angle measurement in normal second-trimester fetuses has previously been performed by Sonek *et al*.[5] and Odibo *et al*.[14] using 2D ultrasound and by Molina *et al*.[7] using 3D ultrasound. Consistent with the findings of Molina *et al*. and in contrast to those of Sonek *et al*. and Odibo *et al*., our results show a constant FMF angle measured from the palate and a slight increase in the FMF angle measured from the vomer through gestation (Figure 4), although the latter was not statistically significant, possibly due to the small number of cases.

In conclusion, when measured on 3D volumes, NBL and PT are reproducible markers and easy to measure, whereas the FMF angle is more challenging. In this study we present novel reference ranges for NBL and PT. Both NBL and PT show growth with gestation, with less pronounced growth for the NBL after 28 weeks. Following measurement in the exact mid-sagittal plane and with care taken to exclude the frontal bone, our reference range for the NBL showed a systematically smaller length than those in other publications.

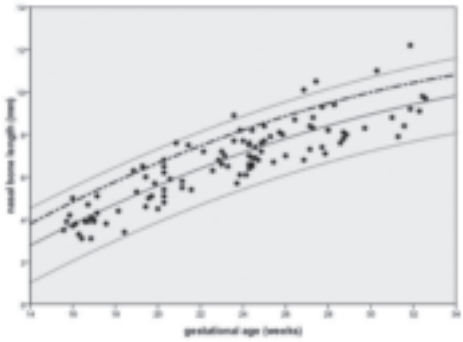

Figure 2 Scatterplot of nasal bone length (NBL) with mean (———) and 5th and 95th percentiles (----) in 109 healthy fetuses, showing mean NBL from reference range of Sonek *et al*.[11] (–·–·–·).

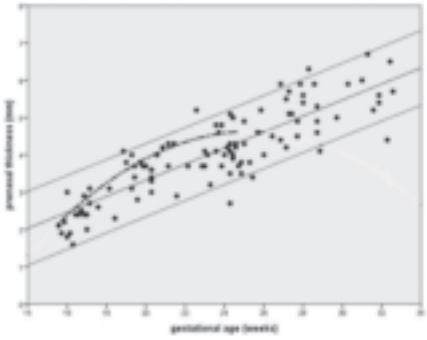

Figure 3 Scatterplot of prenasal thickness (PT) with mean (———) and 5th and 95th percentiles (----) in 108 healthy fetuses, showing mean PT from reference range of Persico *et al*.[9] (–·–·–·).

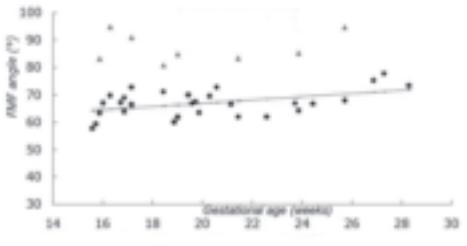

Figure 4 Scatterplots of palate–bone angle measurements (▲) in eight fetuses and of complex/vomer–bone angle measurements (●) with corresponding mean trend in 29 fetuses (P = 0.11).

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information is published in the online version of the article:

Table S1 Overview of definitions used for nasal bone length, prenasal thickness and frontomaxillary facial angle.

Definition of NBL	*Definition of FMF-angle*	*Definition of PT*
Guis, 1995[3]: N = 376, 2D, 14-34 weeks Synostosis has to be visible.	**Sonek, 2007[5]:** N = 100, 2D, 14-24 weeks FMF bone = 'the angle between the top edge of the upper palate and the bony forehead.' FMF skin = 'the top edge of the upper palate and the skin over the forehead.' In the images it can be seen that the vomer can be identified as the 'upper palate'.	**Maymon 2005[4]:** N = 500, 2D, 14-27 weeks Measured from the fronto-nasal angle to the outer part of the closest nasal skin edge.
Sonek, 2003[11]: N = 3537, 2D, 11-40 weeks Identified and measured at the level of the synostosis.	**Molina 2008[7]:** N = 150, 3D, 16-24 weeks FMF angle = 'angle between the palate and frontal bone.' Molina specifically states that, in contrast to Sonek, the FMF angle is measured from the palatine bone.	**Persico 2008[9]:** N = 135, 3D, 16-24 weeks The shortest distance between the anterior edge of the lowest part of the frontal bone (at the junction with the nasal bone when present) and the skin anteriorly.
Bergann, 2006[8]: N = 23, 3D, 18-28 weeks Measured from the base of the nose nearest to the frontal bone, to the farthest extent of ossification.	**Odibo, 2009[14]:** N = 201, 2D, 16-22 weeks Use same measuring technique as Sonek et al. Measuring the skin does not seem to make any difference.	**Vos, 2012:** N = 108, 3D, 15-33 weeks Measured as the shortest distance between the nasion and the frontal skin. When there is a gap between the nasal and the frontal bones, the landmark nasion is at the point of intersection between the lines tangential to the nasal bone and tangential to the lower part of the frontal bone.
Gianferrari, 2007[12]: N = 2515, 2D, 15-24 weeks measured from the base of the nose closest to the frontal bone to the most distal aspect of ossification.	**Vos, 2012:** N = 29, 3D, 25-33 weeks 1. Complex/Vomer-bone angle: angle between vomer or palatal complex and frontal bone. 2. Palate-bone angle: angle between palate and frontal bone.	
Persico, 2010[10]: N = 135, 3D, 16-24 weeks Measured in the exact median plane. Landmarks not specifically defined.		
Vos, 2012: N = 109, 3D, 15-33 weeks Measured from the nasion to the distal end of the white ossification line. Care taken not to include the frontal bone in the measurement.		

PART III facial markers

CHAPTER 9

Prenasal thickness-to-nasal bone length ratio: a strong and simple second- and third-trimester marker for trisomy 21

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ABSTRACT

Objectives

To study the ratio of prenasal thickness (PT) to nasal bone length (NBL) in normal and trisomy-21 fetuses in the second and third trimesters of pregnancy.

Methods

The PT and NBL were measured retrospectively in 106 normal fetuses (in three-dimensional (3D) volumes) and in 30 fetuses with trisomy 21 (10 on two-dimensional (2D) images and 20 in 3D volumes).

Results

In normal fetuses the mean PT and NBL increased between 15 and 33 weeks' gestation from 2.3 to 6.1 mm ($r = 0.85$, $P < 0.001$) and from 3.3 to 9.6 mm ($r = 0.87$, $P < 0.001$), respectively. The PT :NBL ratio was stable throughout gestation, with a mean of 0.61 (95% CI, 0.59–0.63; $r = -0.04$, $P = 0.7$). The 5th and 95th percentiles were 0.48 and 0.80, respectively. In trisomy-21 fetuses the mean PT and NBL increased between 14 and 34 weeks from 3.0 to 9.2 mm ($r = 0.86$, $P < 0.001$) and from 1.9 to 7.8 mm($r = 0.85$, $P < 0.001$), respectively. The PT :NBL ratio was significantly higher than in normal fetuses ($P < 0.001$) but also stable throughout gestation, with a mean of 1.50 (95% CI, 1.20–1.80; $r = -0.35$, $P = 0.07$). Twenty-three (77%) of the 30 fetuses with trisomy 21 had a PT above the 95th percentile and 20 (67%) had an NBL below the 5th percentile. All the trisomy-21 fetuses had a PT :NBL ratio above the 95th percentile. When the 95th percentile of the PT :NBL ratio was used as a cut-off value the detection and false positive rates for trisomy 21 were 100 (95% CI, 89–100)% and 5 (95% CI, 2–11)%, respectively. The positive likelihood ratio was 21.2.

Conclusions

The PT :NBL ratio is stable in the second and third trimesters of pregnancy in both normal and trisomy-21 fetuses, but all trisomy-21 fetuses in this series had a PT :NBL ratio above the 95th percentile. The ratio is therefore a strong marker for trisomy 21.

INTRODUCTION

The word 'syndrome' comes from the Greek 'syn' (together) and 'dramein' (to run) andmeans 'run together'. A syndrome is suspected when a combination of anomalies or dysmorphic features occur together in the same patient. The more characteristic features are recognized the higher the chance of a syndromal association. Prenatal identification of a syndrome is important, as it may change the management of pregnancy and perinatal care.
A variety of anomalies and dysmorphic traits are known to be associated with trisomy 21[1,2]. Major structural anomalies like heart defects account for only 27% of affected fetuses[3]. In contrast more subtle deviations of the phenotype are present in the majority of affected individuals[3–5]. Currently there is overwhelming evidence that the observations reported by J.L.H. Down in 1866 such as a flat profile, a small nose and redundant skin are useful ultrasound markers[2].
Nasal bone length (NBL) was introduced in 1995 by Guis *et al.*[6] as a possible marker for trisomy 21, while prenasal thickness (PT) was proposed in 2005 by Maymon *et al.*[7]. Both markers are visualized in the same profile view and even share a landmark, the nasion. Because in trisomy 21 NBL tends to be smaller while PT tends to be larger than in normal fetuses,we speculated that their ratio may be a sensitive and specific indicator for trisomy 21.
Recently we showed that three-dimensional (3D) ultrasound enhances the accuracy of facial measurements by enabling definition of the exact midline by multiplanar correction of the volumes[8].
In this study the PT :NBL ratio was evaluated in 3D volumes of second- and third-trimester normal fetuses and subsequently compared with the PT :NBL ratio of trisomy-21 fetuses.

METHODS

We retrospectively measured PT and NBL in two groups of patients. The first group comprised 219 fetuses with stored volumes collected cross-sectionally from nonsmoking, healthy, low-risk Caucasian women with a singleton pregnancy. Only non-anomalous fetuses from uncomplicated pregnancies were included. Volumes were acquired from fetuses facing the transducer, starting as close as possible to the exact median profile view during periods of quiescence. An attempt was made to collect at least two such volumes per fetus. For each fetus, the volume with the best median view was selected. At first, all images were corrected by multiplanar mode to the exact median view and scored from 1–5 in terms of quality for contrast and clarity (quality score; 1 being bad and 5 excellent). Only images of above-average quality (score 4 or 5) were included. Secondly PT and NBL were scored from 1–3 in terms of visualization of landmarks (measurability score; 1 being bad and 3 excellent). Fetuses with score 1 for PT or NBL were excluded. The second group comprised trisomy-21 fetuses confirmed by karyotyping. In prenatal databases of the Academic Medical Centre, Amsterdam, University Medical Centre, Utrecht and the St Antonius Hospital, Nieuwegein, 39 cases of second- and third-trimester trisomy-21 fetuses were found, 19 with two-dimensional (2D) images and 20 with 3D volumes. Only images of satisfactory quality and with landmark visualization were included.
Transabdominal ultrasonography had been carried out by experienced sonographers using a General Electric Voluson 730 Expert or E8 ultrasound system equipped with a RAB 2-5L or RAB 4-8L abdominal transducer (GE Medical Systems, Zipf, Austria). Images and volumes were stored and examined either offline on 4D View software version 7.0 (GE Medical Systems) or on stored

images in the GE ultrasound system. The nasal bone was measured from the nasion – defined as the most anterior point of the junction between the frontal and nasal bones – to the distal end of the white ossification line (Figure 1). Care was taken not to include the frontal bone in the measurement as the frontal bone extends posteriorly of the nasal bone[9].
PT was measured as the shortest distance between the nasion (same landmark as used for measuring the NBL) and the frontal skin (Figure 1). Calipers were placed on the outermost borders of the skin or bone, and the mean of three measurements was used for analysis. Multiples of the median (MoM) values were calculated using our own regression equation, but absolute values are reported except where indicated.

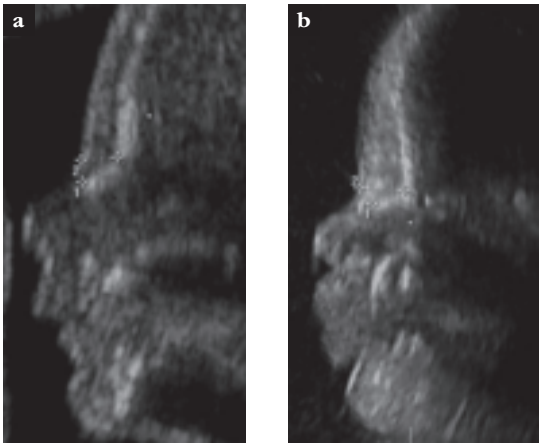

Figure 1 Ultrasound images of a normal fetus (a) and a fetus with trisomy 21 (b) showing nasal bone length (caliper 1) and prenasal thickness (caliper 2) measurements.

Statistical analysis
Data were analyzed using the statistical software SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA) and Excel for Windows 2000. Correlations were calculated by Pearson's correlation test after excluding outliers beyond three SDs from the mean. The statistical significance of the difference of the means of two groups was tested with the unpaired Student's t-test, and $P < 0.05$ was considered statistically significant.

RESULTS

One hundred and eleven of the 219 volumes had an aboveaverage quality score. Five volumes were excluded because of a measurability score of 1 for PT or NBL. Median maternal age and median gestational age at measurement for the groups are given in Table 1. The median birth weight of the babies was 3450 (range, 1590–4885) g, with 91% of the babies having a birth weight between the 5th and 95th percentiles.
The mean PT and NBL increased between 15 and 33 weeks' gestation from 2.3 to 6.1 mm ($r = 0.85$, $P < 0.001$) and from 3.3 to 9.6 mm ($r = 0.87$, $P < 0.001$), respectively (Table 1; Figures 2 and 3). There was a highly significant positive correlation between PT and NBL ($r = 0.83$,

$P < 0.001$) and their MoM values ($r = 0.50$, $P < 0.001$) (Table 1). The PT :NBL ratio was stable throughout gestation, with a mean of 0.61 (95% CI, 0.59–0.63 (range, 0.36–0.85); SD 0.096; $r = -0.04$, $P = 0.7$) (Table 1). The 5th and 95th percentiles were 0.48 and 0.80, respectively (Figure 4). Nine of the 39 fetuses with trisomy 21 were excluded because of unsatisfactory quality or landmark visualization (all 2D images). Of the remaining 30, 10 were imaged in 2D and 20 on 3D volumes. The PT, NBL and PT :NBL ratio with the corresponding MoM values for each trisomy-21 fetus are presented in Table 2. The mean PT and NBL increased between 14 and 34 weeks from 3.0 to 9.2 mm ($r = 0.86$, $P < 0.001$) and from 1.9 to 7.8 mm ($r = 0.85$, P < 0.001), respectively. Twentythree of the 30 (77%) trisomy-21 fetuses had a PT above the 95th percentile and 20 (67%) had an NBL below the 5th percentile (Figures 2 and 3). In trisomy-21 fetuses there was a highly significant positive correlation between PT and NBL ($r = 0.81$, $P < 0.001$) whereas the positive correlation between the MoM values did not reach significance (r = 0.35, P = 0.06) (Table 1). The PT-MoM values did not differ significantly between fetuses with a normal or small (< 5th percentile) NBL (1.51 and 1.42, respectively; $P = 0.47$), whereas the NBL-MoMs between fetuses with a normal or large (> 95th percentile) PT were significantly different (0.72 and 0.48, respectively; $P = 0.003$). In trisomy-21 fetuses the PT :NBL ratio did not change significantly during gestation, with a mean of 1.50 (95% CI, 1.20–1.80 (range, 0.80–5.22); $r = -0.35$, $P = 0.07$) (Figure 4). The PT :NBL ratio was significantly higher in trisomy-21 fetuses ($P < 0.001$). When the 95th percentile was used as cut-off value the detection rate, false-positive rate and positive likelihood ratio were 100 (95% CI, 89–100)%, 5 (95% CI, 2–11)% and 21.2, respectively. Fifteen trisomy-21 fetuses had both an abnormal PT and NBL, eight had an abnormal PT but normal NBL, five had a normal PT but an abnormal NBL and two fetuses had both PT and NBL within the normal range. However all the trisomy-21 fetuses had a PT :NBL ratio above the 95th percentile (Figure 4 and Table 1).

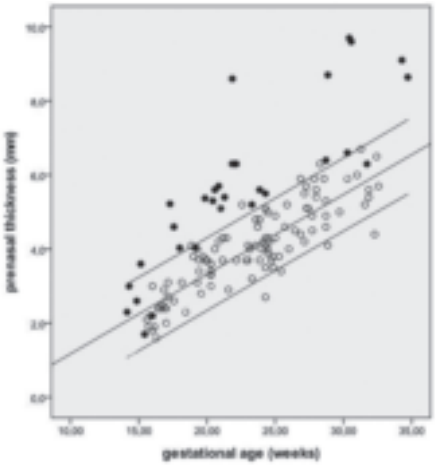

Figure 2 Scatterplot of prenasal thickness (PT) against gestational age (GA) for 30 trisomy-21 fetuses (●) plotted on reference curves (mean, 5th and 95th percentiles) derived from normal fetuses (°) (PT = (0.21 × GA) – 0.873; r = 0.85, P < 0.001).

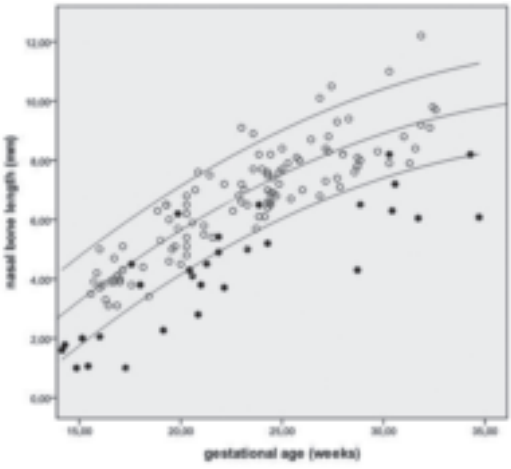

Figure 3 Scatterplot of nasal bone length (NBL) against gestational age (GA) for 30 trisomy-21 fetuses (●) plotted on reference curves (mean, 5th and 95th percentiles) derived from normal fetuses (°) (NBL = –6.927 + (0.830 × GA) – (0.01 × GA2); r = 0.87, P < 0.001).

Table 1 Characteristics of the study groups

Parameter	*Normal fetuses (n = 106)*	*Trisomy-21 fetuses (n = 30)*
Maternal age (years, median (range))	30 (21–40)	37 (23–46)
GA (weeks, median (range))	23 + 6 (15 + 4 to 32 + 4)	21 + 1 (14 + 1 to 34 + 5)
PT		
Range of mean (mm)	2.3–6.1*	3.0–9.2†
Correlation with GA	$r = 0.85$, $P < 0.001$	$r = 0.86$, $P < 0.001$
PT > 95th percentile (%)	5	77
NBL		
Range of mean (mm)	3.3–9.6*	1.9–7.8†
Correlation with GA	$r = 0.87$, $P < 0.001$	$r = 0.85$, $P < 0.001$
NBL < 5th percentile (%)	5	67
Correlations		
PT with NBL	$r = 0.83$, $P < 0.001$	$r = 0.81$, $P < 0.001$
PT-MoM with NBL-MoM	$r = 0.50$, $P < 0.001$	$r = 0.35$, $P = 0.057$
PT :NBL ratio		
Mean (range)	0.61 (0.36–0.85)	1.50 (0.80–5.22)
Correlation with GA	$r = -0.04$, $P = 0.7$	$r = -0.35$, $P = 0.07$
PT :NBL ratio > 95th percentile (%)	5	100

*Between 15 and 33 weeks' gestation. †Between 14 and 34 weeks' gestation. GA, gestational age; MoM, multiples of the median; NBL, nasal bone length; PT, prenasal thickness. Correlations calculated by Pearson's correlation test.

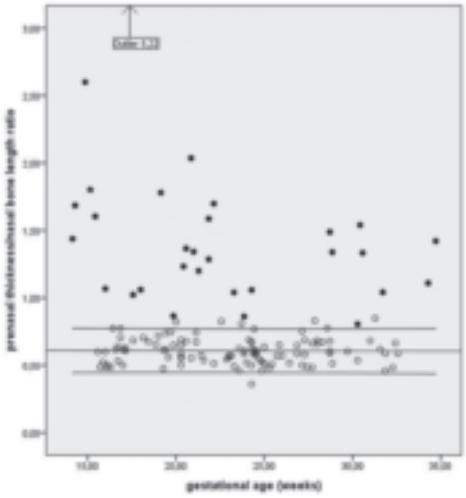

Figure 4 Scatterplot of prenasal thickness : nasal bone length ratio for 30 trisomy-21 fetuses (●) plotted on reference curves derived from normal fetuses (°). Mean, 5th and 95th percentile are 0.61, 0.48 and 0.80, respectively.

DISCUSSION

In both normal and trisomy-21 fetuses the PT :NBL ratio measured on 3D volumes was stable throughout the second and third trimesters, and significantly increased in trisomy-21 fetuses. When the 95th percentile was used as a cut-off value the detection rate, false positive rate and positive likelihood ratio were 100 (95% CI, 89–100)%, 5 (95% CI, 2–11)% and 21.2, respectively. The PT :NBL ratio therefore qualifies as a strong second- and third-trimester marker for trisomy 21. Another important observation is that in normal fetuses PT is always about 2/3 (0.6) of NBL, a stable relationship that enables easy recognition of normality.

In 1995 Guis *et al.*[6] published a normal range for NBL between 14 and 35 weeks' gestation, and absent nasal bone or hypoplasia of the nasal bone became a widely accepted marker for trisomy 21[10–13]. Reference ranges based on a large sample size[14] and on 3D ultrasound have been published[9,15]. In this study screening with NBL achieved a detection rate of 67% for a 5% false-positive rate. Two prospective midtrimester 2D studies, using the 5th percentile as cutoff value, reported detection rates of 59 and 41%, respectively[16,17]. It is noteworthy that in our study no cases with absent nasal bone were found. Also Bunduki *et al.*[16] and Maymon *et al.*[18] found no absent nasal bones in 22 cases between 16 and 24 weeks and in 25 cases between 15 and 33 weeks, respectively. Cusick *et al.*[19] found only one case of absent nasal bone out of 11 cases studied between 16 and 21 weeks. In other reports absence of nasal bone during the second trimester ranges from 23 to 56%[13,20].

The rigorous selection on image quality, the use of 3D ultrasound and especially the more advanced gestational age are the probable explanation for no cases of absent nasal bone, which would result in a grossly abnormal PT :NBL ratio, being found in our study.

Maymon *et al.*[7] introduced the concept of PT measurement and used PT- and NBL-MoM as a way of enhancing NBL screening performance between 14 and 27 weeks' gestation. In normal fetuses the PT :NBL ratio was stable at 0.57 and the PT :NBL-MoM in 21 trisomy-21 fetuses was 1.51. Tables of likelihood ratios based on PT-MoMs were published in 2009[21]. Recently 3D ultrasound-based reference ranges for PT have been constructed[9,22]. Combining second-trimester PT measurement with serum and other markers yields a detection rate comparable with that of first-trimester screening[23].

Our study confirms the diagnostic power of PT measurement. 77% of the 30 trisomy-21 fetuses had a PT above the 95th percentile, which is similar to the 73% reported in a prospective 3D study by Persico *et al.*[22]. In a meta-analytic study Miguelez *et al.*[23] reported a detection rate of 60% at a 5% false-positive rate.

We found stable PT :NBL ratios in normal and trisomy-21 fetuses, but the ratio was significantly higher in the latter. As already mentioned, when 0.8 (the 95th percentile) was used as a cut-off value the sensitivity, specificity and positive likelihood ratio were 100%, 95% and 21.2, respectively. When 1.0 (NBL = PT) was used as the cut-off value the sensitivity and specificity were 90 and 100%, respectively. Maymon *et al.*[7] found a positive likelihood ratio of 13 for a cut-off value of 0.80 for the PT :NBL-MoM. We used absolute values to make recognition of normality simple and the ratio easily applicable in routine settings. Although the results need to be validated

Table 2 Prenasal thickness (PT), nasal bone length (NBL) and PT :NBL ratio with their multiples of the median (MoM) values in 30 fetuses with trisomy 21

GA (weeks)	*PT (mm)*	*PT MoM*	*NBL (mm)*	*NBL MoM*	*PT :NBL ratio*	*PT :NBL ratio MoM*
14 + 1	2.3	1.10	1.6	0.57	1.44	2.36
14 + 2	3.0	1.41	1.8	0.62	1.69	2.76
14 + 6	2.6	1.16	1.0	0.31	2.60	4.26
15 + 1	3.6	1.56	2.0	0.60	1.80	2.95
15 + 3	1.7	0.72	1.1	0.30	1.60	2.63
16 + 0	2.2	0.88	2.1	0.54	1.07	1.75
17 + 2	5.2	1.89	1.0	0.23	5.22	8.56
17 + 4	4.6	1.63	4.5	0.98	1.02	1.68
18 + 0	4.0	1.39	3.8	0.80	1.06	1.74
19 + 1	4.0	1.28	2.3	0.43	1.78	2.92
19 + 6	5.4	1.63	6.2	1.10	0.87	1.42
20 + 3	5.3	1.55	4.3	0.73	1.23	2.02
20 + 4	5.6	1.62	4.1	0.69	1.37	2.24
20 + 6	5.7	1.63	2.8	0.46	2.04	3.34
21 + 0	5.1	1.44	3.8	0.62	1.34	2.20
21 + 2	5.4	1.50	4.5	0.72	1.20	1.97
21 + 6	8.6	2.31	5.4	0.84	1.59	2.60
21 + 6	6.3	1.69	4.9	0.76	1.29	2.11
22 + 1	6.3	1.67	3.7	0.57	1.70	2.78
23 + 2	5.2	1.29	5.0	0.72	1.04	1.70
23 + 6	5.6	1.35	6.5	0.90	0.86	1.41
24 + 2	5.4	1.28	5.2	0.71	1.04	1.70
28 + 5	6.4	1.24	4.3	0.50	1.49	2.44
28 + 6	8.7	1.68	6.5	0.75	1.34	2.19
30 + 2	6.6	1.20	8.2	0.91	0.80	1.32
30 + 3	9.7	1.76	6.3	0.69	1.54	2.52
30 + 4	9.6	1.73	7.2	0.79	1.33	2.19
31 + 5	6.1	1.04	5.3	0.56	1.14	1.87
34 + 2	9.1	1.54	8.2	0.87	1.11	1.82
34 + 5	8.6	1.35	6.1	0.62	1.42	2.33

GA, gestational age.

by a large prospective study, the PT :NBL ratio appears to be an excellent second- and third-trimester screening test.

In this study 10 trisomy-21 fetuses were measured with 2D ultrasound although our reference ranges were based on 3D ultrasound. It is known that NBL measurements obtained by 2D ultrasound tend to be larger than those obtained by 3D ultrasound[9,15] and that this modality derived difference happens less for PT[15,22]. Therefore, the PT :NBL ratios of the trisomy-21 fetuses would probably have been even higher had 3D ultrasound been used in all cases.

The ratio shows a better screening performance than does NBL or PT alone. However for risk calculations the sequential use of the two markers (with two likelihood ratios) may yield better results than combining the two measurements into one ratio (with one likelihood ratio)[7].

However for sequential use it is important that the markers are independent.
In trisomy 21, interdependency of the two markers is supported by the theory that accumulation of hyaluronic acid (related to chromosome 21 gene-related overexpression of collagen type VI) in the dermis is responsible for excessive hydration of the extracellular matrix. This causes increased skin thickness and may at the same time influence intramembranous ossification of the nasal bone[24–26]. Another theory, suggesting that delayed migration of the neural crest cells alters the membranous ossification of the nasal bones, supports independency of the two markers[27].
Persico *et al*.[22]. found no significant difference in delta PT between trisomy-21 fetuses with and without a nasal bone. Similarly, in this study PT-MoMs were not different between the trisomy-21 fetuses with a normal or small NBL. Also, the non-significant correlation between PTMoM and NBL-MoM of trisomy-21 fetuses indicates independency of the two markers. However the finding of significantly different NBL-MoMs in fetuses with a normal or increased PT contradicts this assumption. Therefore more data are needed to clarify the relationship between the two markers.
In conclusion, the PT :NBL ratio is stable in the second and third trimesters in normal and trisomy-21 fetuses. In normal fetuses PT is consistently about 2/3 of the NBL. All trisomy-21 fetuses in this series had a PT :NBL ratio above the 95th centile. The stability and high sensitivity make this ratio a powerful screening tool for trisomy 21.

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PART IV effect on mothers

CHAPTER 10

Three-dimensional ultrasound and maternal bonding, a third trimester study and a review

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ABSTRACT

Objective

To compare the effect of third trimester three-dimensional and four-dimensional (3D/4D) versus twodimensional (2D) ultrasound (US) of the fetal face on maternal bonding. Studies quantifying the psychological effect of 3D/4D US on mothers, pregnant of a fetus with no detectable abnormalities, were reviewed.

Methods

One hundred sixty Caucasian women attended a third trimester 3D/4D or 2D US examination. Women filled out the Maternal Antenatal Attachment Scale (MAAS) 1 to 2 weeks before (MAAS1) and 1 to 2 weeks after (MAAS2) the US examination. Visibility, recognition and attractiveness were assessed.

Results

Within both US groups, the MAAS2 scores were significantly higher than the MAAS1 scores ($p < 0.0001$). No differences in MAAS scores between the US groups emerged. Visibility and recognition were significantly positively related with the increase in MAAS scores ($p = 0.003$ and $p = 0.042$) in the 3D/4D group.

Of 13 psychological studies, eight studies evaluated bonding and found no difference between 3D/4D and 2D US. The effect of 3D/4D US on satisfaction or perception showed conflicting results, and on anxiety/stress, reduction was the same as after 2D US.

Conclusions

Bonding increases after either a 3D/4D or 2D US. The effect of 3D/4D US on bonding is stronger at better degrees of visibility and recognition.

INTRODUCTION

Prenatal maternal bonding must be old as mankind but is first mentioned in modern literature by Deutsch in 1945.[1] Bonding during pregnancy seems a good predictor of the mother–newborn relationship and is regarded as a necessary element for the process of motherly care.[2–4] Ultrasound (US) is a unique way to catch a glimpse of the fetus, and three-dimensional and four-dimensional (3D/4D) US may convey a much more realistic impression of the US image because of the real-life like images.[5–11] Positive consequences of two-dimensional (2D) US at 12 and 20 weeks on maternal–fetal bonding are well established especially before quickening.[12–17] Studies of 3D/4D US and maternal bonding in the second trimester are published,[18–21] but the effect of 3D/4D US in the third trimester, in spite of its increasing use, has not been studied extensively.[10,11,22–24] Because the fetus in the third trimester looks more like a newborn baby, the impact of especially 3D/4D US images on the mother may be great.

The aim of this study is to compare the effect of 3D/4D versus 2D US of the fetal face in the third trimester on maternal bonding. In addition, the ultrasonographer rated visibility, and the mother, the recognition and attractiveness of the US images. A review of studies quantifying the psychological effect of 3D and/or 4D US on women, pregnant with a fetus with no detectable abnormalities, is presented.

METHODS

The study was approved by the local ethics committee of the St. Antonius Hospital Nieuwegein, and all women gave written consent. Women were recruited from midwifery practices at the time of the dating scan or routine second trimester anomaly scan. Only women without a previous experience of 3D/4D US were asked to participate. All women lived in the urbanized area of western Netherlands and received antenatal care by midwives (low risk). Women of group 1 were invited to undergo an additional 3D/4D, followed by women of group 2 who were invited to undergo an additional 2D US examination. There was a time difference of about 1 year between the last inclusions in both groups. The additional examination was not routinely scheduled and performed only for the purposes of the study. All examinations, randomly assigned between 28 and 36 weeks of gestation, were carried out by specifically instructed experienced ultrasonographers certified in performing anomaly scans: a Voluson 730 Expert or a Voluson Pro ultrasound unit (GE Medical Systems, Kretz Ultrasound, Zipf, Austria). All women were healthy, low-risk, Caucasian women with an uncomplicated singleton pregnancy.

Socio-economic and obstetric characteristics were noted prior to the US investigation. In both groups, a basic US examination was performed including assessment of the amniotic fluid volume, placental location, fetal position, biometry and an anatomical survey. Approximately 5 min was spent looking at the face when it could be best visualized during the examination. Three-dimensional volumes were collected starting from the mid-sagittal, coronal and axial planes, with display of the multiplanar mode. Finally, the render mode was activated, and moving surface rendered images of the face were shown to the mother. In group 2, an equal time was spent showing images of the face, aiming at obtaining clear mid-sagittal, coronal and axial views of the face. In both groups, the maximum examination time was 30 min. All ultrasonographers were instructed to create a friendly and reassuring atmosphere with positive and friendly verbal

feedback. Special attention was paid to explain the specific age-related appearances of the fetuses and effects of artefacts.

The Maternal Antenatal Attachment Scale (MAAS) developed by Condon was used to explore maternal–fetal bonding.[25] The MAAS questionnaire has been translated into Dutch and validated.[26] The nineteen 5-point scale items of the MAAS questionnaire explores two aspects: quality of attachment and time spent in attachment mode. Ten items assess the quality of attachment (closeness/distance, positive/negative feelings toward the fetus) (Q items) and eight items assess the time spent in attachmentmode (amount of time spent thinking of or feeling the fetus) (T items). One item (feeling whether the baby is dependent on the mother for its well-being) is not included in either aspect and is only included in the global score. In both groups, women were asked to complete MAAS questionnaires twice at home; the first time (MAAS1) at one to two weeks before the US examination and the second time 1 to 2 weeks thereafter (MAAS2). The two MAAS questionnaires were handed at the time of invitation by the ultrasonographer. The weeks in which the questionnaire had to be completed and returned by prepaidmail were written on the questionnaires.

In both groups, at the end of the examination, the ultrasonographer asked the women to complete a short questionnaire, addressing recognizability and attractiveness of the fetal face according to a graded score from1 to 4. Recognition was scored as follows: 1, not recognizable; 2, recognizable with difficulty; 3, recognizable; 4, easily recognizable. Attractiveness was scored as follows: 1, not beautiful; 2, neutral; 3, beautiful; 4, breathtakingly beautiful. At the same time, the ultrasonographer completed a questionnaire addressing the visibility of the face. Visibility was scored as follows: 1, low visibility: very disturbing artefacts or face not visible; 2, moderate visibility: less than half of the face is clearly visible or blurred vision of half the face; 3, good visualization: half of the face is clearly visible or blurred vision of the entire face; 4, excellent visualization: entire face is clearly visible.

Both groups were asked to fill in a form after pregnancy, with some general questions about the outcome of pregnancy and the baby's health, and returned it with prepaid mail. The first group was also asked whether they would like to have another 3D/4D US in a next pregnancy.

Statistical analyses

Data were analysed using the statistical software SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA) and Microsoft Excel 2010 for Windows.

Sample size calculations are based on the assumption that the effect on maternal bonding is stronger after a 3D/4D US than after a 2D US. On the basis of the result of a previous study,[19] it is expected that 3D/4D US leads to a 2.7-point higher score of maternal bonding as compared with 2D US. With an alpha of 0.05 and a power of 80% using a one-sided Mann–Whitney test, 67 patients need to be included in each group. In this study, 80 women were invited to participate in each group.

Group characteristics were compared using the chi-square test or unpaired Student's t-test. Correlations of MAAS1 with gestational age, MAAS1 with MAAS2 and assessment score for US with an increase in MAAS score were determined by Pearson's correlation test. For all other statistical calculations, multiple linear regression analysis was used with adjustment for confounding when necessary. $p < 0.05$ was considered statistically significant (two-sided tests).

Table 1 Sample characteristics (socio-demographic, obstetric), variables that may influence quality of scan and gestational age at time of completing the questionnaires

	Group 1 3D/4D N=66	*Group 2 2D N=67*	*p*
A: Socio-demographic characteristics			
Maternal age (years)	31 (4.2; 23–39)	32 (3.3; 24–39)	NS
Smoking	1 (1.5%)	1 (1.5%)	NS
Religion	13 (19.7%)	12 (17.9%)	NS
Education mother			$p < 0.05$*
Preparatory or secondary VE/GE 3	8 (57.6%)	5 (7.5%)	
Higher VE or UE	28 (42.4%)	62 (92.5%)	
Living with partner	65 (98.5%)	67 (100%)	NS
B: Obstetric characteristics			
Pregnancy was considered as an option	62 (94.0%)	65 (97.0%)	NS
(History of) assisted conception	6 (9.1%)	5 (7.5%)	NS
Primigravidity	22 (33.3%)	44 (65.7%)	$p < 0.05$*
Knowing sex of fetus (MAAS1/MAAS2)	42/46 (63.6%/69.7%)	43/45 (64.2%/67.2%)	NS
First trimester screening	18 (27.3%)	21 (31.3%)	NS
Second trimester anomaly scan	66 (100%)	67 (100%)	NS
C: Variables possibly influencing quality of scan			
GA at US	31 4/7 (2 3/7; 28–35 4/7)	32 1/7 (2 5/7; 27 4/7–36 5/7)	NS
BMI	23.2 (3.5; 17.9–34.3)	24.0 (2.6; 18.6–30.1)	NS
Amniotic fluid (subjective assessment)			
Normal	59 (89.3%)	62 (92.5%)	NS
Less than normal but no oligohydramnios	4 (6.1%)	2 (3.0%)	
More than normal but no polyhydramnios	3 (4.6%)	3 (4.5%)	
Location of placenta			NS
Posterior	29 (44.0%)	30 (44.8%)	
Anterior	27 (40.9%)	31 (46.3%)	
Fundus	5 (7.6%)	4 (6.0%)	
Lateral	5 (7.6%)	2 (3.0%)	
Position of fetus			NS
Cephalic	56 (84.9%)	58 (86.6%)	
Breech	9 (13.6%)	8 (11.9%)	
Transverse	1 (1.5%)	1 (1.5%)	
D: Gestational age			
GA at MAAS1	30 (2 3/7; 26 1/7–34 1/7)	31 6/7 (2 5/7; 25 4/7–36 3/7)	NS
GA at MAAS2	33 (2 3/7; 29 2/7–37)	33 5/7 (2 5/7; 29 1/7–38 3/7)	NS

Data are presented as mean (with standard deviation and range) or absolute value (with percentage). VE, vocational education; GE, general education; UE, university education; EUG, extra uterine gravidity; GA, gestational age in weeks; NS, not significantly different; US, ultrasound; 2D, two dimensional; 3D, three dimensional; 4D, four dimensional; *, difference is significant; p-values are calculated with unpaired Student's *t*-test [for maternal age, body mass index (BMI) and gestational ages] or chi-square test (for all other characteristics).

RESULTS

In each group, four of the 80 invited women declined or cancelled the appointment. In group 1, 10 women did not return one or both questionnaires, resulting in 66 MAAS pairs we could analyse. In group 2, one woman was excluded by the investigator (as she had a 3D US investigation previously). Eight women did not return one or both questionnaires, resulting in 67 MAAS pairs we could analyse. The socio-demographic and obstetric characteristics of the study groups are presented in Table 1A and B. Significant differences were found in education and gravidity: women in the 2D group had a higher education level and were more often in their first pregnancy. No significant differences emerged from variables that may influence the quality of the scan or the gestational ages at the time of completing the questionnaires (Table 1C and D).
The MAAS2 scores (global, Q and T) were, within both US groups, significantly higher than the MAAS1 scores ($p < 0.0001$ in all cases). The MAAS1 and MAAS2 (sub)scores were strongly correlated (range of *Rs* 0.753–0.833; $p < 0.0001$ for all relationships). When adjusted for confounding (parity and education), there was no difference in MAAS1 or MAAS2 (sub)scores or the increase in MAAS (sub)scores between the 3D/4D and 2D groups (Table 2).
The results of the questionnaires completed after the scan concerning visibility, recognition and attractiveness of the face are presented in Table 2. Although the scores for visibility, recognition and attractiveness were higher in the 3D/4D group, this did not reach statistical significance. Relationships betweenUS assessment scores and increase inMAAS scoreswere calculated; only in the 3D/4Dgroupwas visibility and recognition of the fetal face significantly positively correlated with the increase in MAAS score ($p = 0.003$ and $p = 0.042$, respectively).
In group 1, one woman reported the 3D/4D US image of the face as 'not beautiful', despite of her high scores on visibility and recognition (4 and 3). Two women in group 2 reported the 2D US image of the face as 'not beautiful', but the reported scores on visibility and recognition were also low (2 and 2; 2 and 1, respectively).
In group 1, the post-partum questionnaire was returned by 58 women (88%). Fifty-four women (93%) indicated that they would like to have another 3D US in their next pregnancy, and four (7%) did not. The latter four scored the attractiveness of 3D US low (mean: 1.5), although visibility and recognition were scored high (mean: 3.7 for both). Nevertheless, even in these four women, there was a clear increase in MAAS scores after the scan (mean: 4.8).

Review

A literature search yielded 13 studies quantifying the psychological effect of 3D and/or 4D US. These are summarized in Table 3. Many studies had a small sample size (less than 50 women)[5,9,10,19,20] or did not use a control 2D group.[5,8,21,27] No study focused specifically on the third trimester.
Four studies used validated questionnaires to evaluate bonding.[18–21] None of these four studies were conducted during the third trimester. No additional effect of 3D and/or 4D on bonding was described. Four studies evaluated 'feeling of closeness to the fetus' or 'relation towards the fetus' that we considered as a measure of bonding.[8–11] Three of these studies included the third trimester, and no additional effect of 3D and/or 4D on bonding was described.[8,10,11] Only one study found that mothers after 3D US at 28 weeks felt closer to the baby than after 2D US at 18 weeks.[10]
Studies on the effect of 3D/4D US on maternal satisfaction showed contrasting results. In second trimester studies, Rustico *et al*. found no change, whereas Antonelli *et al*. found more satisfaction

Table 2 MAAS (sub)scores and assessment score for ultrasound (US)

	Group 1 3D/4D N=66	*Group 2 2D N= 67*	*Difference between groups}*
MAAS1			
Global	77.0 (5.6)	75.8 (6.5)	NS
Quality	45.6 (3.0)	45.3 (2.7)	NS
Time	27.1 (3.7)	26.4 (4.3)	NS
MAAS2			
Global	80.5 (5.0)	78.7 (6.4)	NS
Quality	47.3 (2.2)	46.2 (2.5)	NS
Time	28.6 (3.7)	28.2 (4.3)	NS
Difference MAAS1–MAAS2			
Global	3.5* (3.3)	3.0* (3.7)	NS
Quality	1.7* (2.0)	0.9* (1.7)	NS
Time	1.5* (2.6)	1.8* (2.6)	NS
Assessment score			
Visibility	2.8 (1.1)	2.7 (0.8)	NS
Recognition	3.3 (0.7)	3.0 (0.9)	NS
Attractiveness	3.1 (0.5)	2.9 (0.7)	NS

The nineteen 5-point scale items of the Maternal Antenatal Attachment Scale (MAAS) questionnaire (maximum global score is 95) explores two aspects: 10 items assess the quality of attachment (maximum quality score is 50) and eight items assess the time spent in attachment mode (maximum time score is 40). Visibility, recognition and attractiveness were assessed according to a graded score from 1 to 4. Data are presented as mean (standard deviation). NS, not significantly different; 2D, two dimensional; 3D, three dimensional; 4D, four dimensional; }, multiple linear regression analysis was used adjusted for education mother and primigravidity; *, the MAAS2 scores were, within both US groups, significantly higher than the MAAS1 scores (Student's *t*-test, $p < 0.0001$ in all cases).

after 3D/4D US.[18,9] Similarly in late second/early third trimester studies, Lapaire *et al*. found that dimensionality did not affect satisfaction, whereas Edwards *et al*. found more satisfaction after 3D US.[10,11] Romero *et al*. found no relation between objective assessment of 3D/4D images and maternal satisfaction at any gestational age.[27]

3D/4D US has been reported to reduce stress and anxiety[5,9]; however, the reduction is the same after 2D US.[9,31] A positive effect of 3D/4D US on perception and recognition was found for all trimesters in most studies.[5–11] However, Rustico *et al*. and Sedgmen *et al*. found no additional effect of second trimester 3D/4D on maternal perception.[18,20]

DISCUSSION

The terms bonding and attachment are both used in literature. We use bonding as this is the parents' tie towards the fetus, whereas attachment refers to a bilateral relationship developing post-partum.[21] However, we will use attachment when referring to questionnaires/studies that originally use the term attachment.

This study shows that both 3D/4D and 2D US increase maternal–fetal bonding in the third trimester. In both US groups, the global, Q and T scores increase significantly after the scan. Neither the MAAS1 (sub)scores nor the MAAS2 (sub)scores nor the increases in MAAS (sub)scores were significantly different between the two US groups. In our study, the global, Q and T scores

Table 3 Overview of psychological studies quantifying the effect of 3D and/or 4D ultrasound on the mother

Author (year)	*Objective*	*Method of data collection/questionnaire*	*Moment of assessment*	*Number of analysable cases*	*GA at US*	*Major findings*
Maier *et al.* (1997)	Evaluate influence of 3D on high risk women	Standardized questionnaire	Immediately after 3D	*N* = 20	24–32	75% express better perception, reduced anxiety and more motivation to endure difficulties
Scharf *et al.* (2001)	Assess psychological effects of 3D on mothers	Questionnaire assessing (1) attitude towards and (2) understanding of image	Immediately after 2D and 3D	*N* = 433	7–41	(1) 85% were enthusiastic about 3D, (2) 38% needed explanation and 5% were not able to understand image
Ji *et al.* (2005)	Compare effect of 2D to 3D on maternal bonding	Retrospective; telephone survey analysing (1) extends of prenatal picture sharing, (2) ability to form mental picture of baby and (3) mother's comments about US image	Post-partum	*N* = 50, had 2D *N* = 50, had 2D + 3D	12–37	Mothers who had 3D (1) showed pictures to a greater number of people, (2) 3D appears to more positively influence the perception of mothers and (3) 3D experience was more exclamatory
Rustico *et al.* (2005)	Assess whether the addition of 4D to 2D facilitates maternal recognition and causes emotional impact	Questionnaire listing (1) recognition of structures and movements, and parts and movements mothers wished to see, (2) satisfaction with US and (3) assessing MFA by MAAS questionnaire[25]	Immediately after a booked US	*N* = 52, had 2D of which 21 completed MAAS *N* = 48, had 2D + 4D of which 25 completed MAAS	18–25	Addition of 4D does not significantly change (1) perception, (2) satisfaction nor (3)emotional attachment
Righetti *et al.* (2005)	Investigate the role of 4D on maternal attachment	Assessing MFA by MAAS questionnaire[25]	Immediately before and 2 weeks after second trim US	N= 22 had 2D N= 22 had 4D	19–23	Significant higher scores for MFA after 2D and 4D. No significant differences are shown between 2D and 4D
Sedgmen *et al.* (2006)	Explore impact of timing and US type on maternal attachment, maternal perception and health behaviour	(1) Assessing MFA by MAAS,[25] (2) assessing perception by 'Child as an individual person' questionnaire (factor from Child-Schema questionnaire)[28] and (3 questions concerning health related behaviour (number of cigarettes or drinks and dietary supplements)	Immediately before and 1–3 weeks after routine US	*N* = 24 had US in first trim *N* = 44 had US in second trim *N* = 30 had 2D/*N* = 38 had 3D	12–14 18–22	(1) Higher MFA after both 2D and 3D; greatest change with those receiving US at first trimester, (2) US had no effect on maternal perception and (3) significant reduction in alcohol consumption after both 2D and 3D
Leung *et al.* (2006)	Test hypothesis that 2D with 3/4D reduces anxiety to a greater extent than 2D alone in high risk women	Assessing anxiety by STAI[29]	After counselling (about 12 weeks), immediately after US at 18 weeks and at 28 weeks	*N* = 62 had 2D *N* = 62 had 2D + 3D/4D	18	3D/4D does not cause a significant reduction in maternal anxiety in high risk pregnancies compared with 2D alone

Pretorius *et al.* (2006)	Determine whether there is a change in bonding and attitude towards the fetus after 3D/4D	(1) Assessing MFA by Cranley,30 (2) indication of excitement about US on line instrument, (3) questionnaire assessing feelings about fetus: positive feelings/ appiness/anxiety/freedom of fear/hope	Immediately before and after 3D/4D	*N* = 89	18–28	(1) Significantly higher scores for MFA after 3D/4D, (2) excitement about US was already at the maximum before US, (3) significant positive increase for all feelings
Herrero *et al.* (2006)	Explore women's perception and attitudes towards 3D/4D	Questionnaire concerning (1) tranquillity, emotion closeness to baby and (2) precision of image, quality of image, easiness of interpretation	Immediately after 2D + 3/4D	*N* = 1000	Any GA	Feeling described after 4D: 86% tranquillity, 75% emotion, 45% closeness to baby, 41% more precise image; 99% found 4D US of excellent/ good quality and easier to interpret than 2D
Antonelli *et al.* (2006)	Evaluate emotional impact of 3D during third trimester and compare understanding and satisfaction after 2D and 3D	(1) Questionnaire evaluating stress after 2D and 3D, (2) assessing anxiety by STA I[29] before and after 3D, (3) questionnaire evaluating understanding and satisfaction after 2D and 3D and (4) post-partum questionnaire evaluating understanding and satisfaction	Before and after 2D at 20 weeks Before and after 3D at 28 weeks	*N* = 40	20,28	(1) No difference in stress level after 2D or 3D (2) Anxiety was significantly lower after than before 3D (3) After 3D, mothers were significantly more reassured, felt closer to the baby and understood images better (4) Understanding/satisfaction were higher after 3D
Romero *et al.* (2006)	Compare maternal and physicians attitude towards 3/4D	Questionnaire concerning quality and satisfaction	Immediately after 3/4 D	*N* = 1000	Any GA	There is no agreement between objective assessment of 3/4D images and maternal satisfaction
Lapaire *et al.* (2007)	Assess impact of 3D versus 2D on maternal bonding	(1) Questions for 2D and 3D separately rating recognition, relationship towards fetus, partners opinion, closeness toward partner and satisfaction (2) Dichotomous questions concerning preference 2D or 3D	Immediately after US	*N* = 30, had2D followed by 3D *N* = 30, had3D followed by 2D	23–34	(1) Recognition was significantly better fter 3D. Dimensionality did not affect maternal bonding, paternal opinion or satisfaction. Recognition was significantly associated with examiner-reported quality of scan for 3D but not for 2D, (2) 88% preferred 3D
Edwards *et al.* (2010)	Compare maternal reaction viewing a 3D image of the fetal face to 2D	Questions for 2D and 3D separately (1) rating emotions (Excitement/Relief/Amazement/ Satisfaction) and (2) rating responses to statements regarding Clear/ Excited/Close/ Amazed/Frightened/Real/ Resemble parents/Would not take 3D image again	Immediately after US	112 all had 2D + 3D	24–36	(1) 3D elicits significantly stronger reactions regarding excitement/ amazement/satisfaction not for relief, (2) 3D was significantly better in statements regarding clear/excited/ amazed/real/ resemble parent, not for relief, feeling of 'closeness' or becoming 'frightened'. 99% would take a 3D image again

GA, gestational age in weeks; US, ultrasound investigation; MFA, maternal–fetal attachment; trim, trimester; 2D, ultrasonography with real-time two-dimensional ultrasound; 3D, ultrasonography with static three-dimensional ultrasound; 4D, ultrasonography with real-time three-dimensional ultrasound.

before the scan of both groups were comparable with the 75.5/76.8, 45.2/46.0 and 26.4/29.0 as described by Condon and Van Bussel, respectively, for the third trimester.[26,32]

As soon as 3D/4D US was introduced, it was noticed that the response of women to 3D US seems stronger than to 2D US, and several studies have tried to explore the psychological reaction (Table 3). Maier *et al*. described that the vivid 3D images have a positive effect on the perception of the fetus, reduces anxiety and motivates to endure pregnancy-related difficulties.[5] Scharf *et al*. recorded enthusiasm in 85% of the mothers.[6] Ji *et al*. showed that women who had had 3D US describe their experience more exclamatory, showed their pictures to a greater number of people and have a more positive perception of the baby than women who had 2D US.[7]

Subsequently, it was suggested that these maternal responses to 3D and/or 4D US may positively affect maternal–fetal bonding,[7,33,34] and studies using measures of bonding were published. Similar to our study, two other studies including the third trimester (performed with static 3D) report no difference between US groups rating the statement 'I felt closer to the baby'[11] and the question 'How would you assess your relationship to the baby at this moment'[10] after the scan. In keeping with our results, an equal increase in bonding has been reported in women receiving 2D or 3D and/or 4D US in the first and second trimesters.[10,11,18–20] Neither did analysis of MAAS subscores show a significant difference between women receiving second trimester 2D or 4D US.[18,19] Only one study describes that women felt closer to the baby after a 3D US at 28 weeks than a 2D US at 18 weeks.[9] However, only 40 women were included, and adjustment for gestational age was not applied. Although most studies were preliminary and had small sample sizes, these data suggest that no clear additional effect of 3D and/or 4D on maternal bonding is demonstrable.

Although in our study visibility, recognition and attractiveness were scored higher in the 3D/4D group, the difference was not statistically significant. Interestingly, visibility and recognition were positively related to the increase in bonding in the 3D/4D group, suggesting that with a clearer 3D/4D visual encounter with the fetus bonding is better facilitated. Therefore, it may be that with further technical improvement and increasing experience of the ultrasonographers, the effect of 3D/4D on maternal bonding will further increase in the future.

In our study, only one woman in the 3D/4D group and two women in the 2D group scored the US image as 'not beautiful'. In the 3D/4D group, the vast majority (93%) of the women indicated that they would like to have another 3D US in a next pregnancy, including all cases where the ultrasonographer scored the visibility of the face as moderate or low because of disturbing artefacts (score 1 or 2). Remarkably, the women who would decline another 3D US in a next pregnancy showed a high increase in maternal bonding. These women had lower scores for attractiveness but high scores for visibility and recognition. This might indicate that the reason for declining another 3D US is very personal and cannot be explained by disturbing artefacts or unrecognizable images. Maier *et al*. described that some women found that the realistic 3D images deprived them of their own mental perception of the baby.[5] Two other studies at 18, and 24 to 36 weeks also found high numbers (88% and 99% respectively) of women who would like to have a 3D/4D US in a future pregnancy.[11,31] This indicates that a high number of women appreciate 3D/4D US in the second and especially in the third trimester. Ultrasonographers should be aware that a minority of women may not appreciate 3D /4D images. Edwards *et al*. described in a study performed between 24 and 36 weeks that seven of 106 women agree or strongly agree that 3D images of the fetal face are frightening. However, this was also the case for 11 of 106 women viewing 2D images.[11]

The general positive attitude of women towards both 2D and 3D/4D US gives reassurance towards possible negative effects. However, similar to the unrequested disclosure of fetal sex, the ultrasonographer should always be aware of the impact in demonstrating unrequested 3D/4D images.

A limitation of the study is the chronological gap between the groups. This may have introduced a bias, such as possible changes in demographics. This may partly be responsible for the difference in gravidity and education found between the groups. It is suggested that first-time pregnant women have higher scores and women with a higher education have lower scores for maternal–neonatal attachment.[35] Prenatally, the relation is described as weak or not significant,[19,36–39] which is underlined by the same MAAS1 scores found in both groups. In order to limit as much as possible the influence of external factors on the outcome of the study, great care was taken to prevent changes in the medical staff and in their attitude towards women in the study. Statistical correction was applied to minimize the effect of possible confounding. The present study does not indicate for how long the effect on maternal bonding persists, nor if this has an effect on other important issues such as lifestyle, improvement in women with disturbed bonding or on post-partum attachment. In conclusion, most women appreciate 3D/4D US in the third trimester. Both 2D and 3D/4D US equally increase maternal bonding. The effect of 3D/4DUS on maternal bonding is stronger at better degrees of visibility and recognition of the fetal face.

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WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Two-dimensional ultrasound has positive consequences on maternal–fetal bonding.
- It is not established that three-dimensional ultrasound has stronger impact on maternal–fetal bonding than two-dimensional ultrasound.

WHAT DOES THIS STUDY ADD?

- The effect of three-dimensional ultrasound on maternal–fetal bonding is stronger at better degrees of visibility and recognition.

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CHAPTER 11

Summary, general discussion and future perspectives

11.1 SUMMARY

Chapter 1 provides a summary of various known aspects of ultrasound of the fetal face.
A brief overview of the embryology of the human face is given since knowledge of normal development is a prerequisite for the understanding of facial anomalies.
The history of prenatal ultrasound, especially related to ultrasound of the fetal face, is presented.
The development from static A-mode (one dimensional) ultrasound, through real- time B-mode (two-dimensional (2D)) ultrasound to four-dimensional (4D) ultrasound is described, underlining the importance of the development of three-dimensional (3D) ultrasound for the recent special interest in the fetal face.
Facial anomalies are frequently associated with other anomalies or are part of syndromes and sequences. This is discussed and an overview of the literature concerning associated anomalies of the two most common facial anomalies, facial clefts and micro/retrognathia, is given.
A classification for facial anomalies is proposed.
A description of how the face is currently studied is given, taking into account the differences between the use of ultrasound as a screening or a diagnostic tool.
Finally, the importance for the parents of the prenatal demonstration of a facial anomaly is briefly touched upon.

In **chapter 2** an overview of the current literature concerning objective analysis of different elements of the fetal face is presented i.e: forehead/skull/fontanelles, eyes, ears, nose, mouth, maxilla and mandible accompanied by figures and tables presenting the relationship of the measurement with gestational age.

The aims and outlines of this thesis are presented in **chapter 3.**
Aims:

- to explore the additional value of 3D multiplanar ultrasound in the evaluation of the fetal profile,
- to define and test reproducible measurement tools to quantify the fetal profile,
- to investigate the contribution of 3D multiplanar ultrasound in the evaluation of facial markers for trisomy 21, singularly and combined as the nasal bone length/ prenasal thickness ratio,
- to investigate the effect of ultrasound demonstration of the fetal face on maternal-fetal bonding and whether the effects differ after 2D or 3D/4D ultrasound images of the fetal face.

Outlines:

- Part 1 (Chapter 4): additional value of three-dimensional multiplanar ultrasound in the evaluation of the fetal profile
- Part 2 (Chapter 5 t/m 7): objective tools to quantify the fetal profile
- Part 3 (chapters 8 and 9): facial markers for trisomy 21
- Part 4 (Chapter 10): effect of mothers on ultrasound images of the fetal face

In **chapter 4** the additional value of 3D multiplanar ultrasound in the examination of the fetal profile was evaluated in 84 fetuses at 22 to 29 weeks' gestation.
In 81 (96.4%) cases we succeeded in obtaining a profile volume, 70% of the volumes being obtained within 10 minutes. It was possible to define by multiplanar mode the exact midsagittal plane in less than 1 minute.
The mean rotation necessary to obtain the exact midsagittal plane with 3D multiplanar mode was significantly larger around the y-axis (11.9◦) than around the z-axis (4.3◦) of the fetus.
Of six measurements, related to the fetal nose and jaws, the success rate and the intraobserver reproducibility between the 2D and the 3D multiplanar ultrasound were compared. For between 5 and 12% of the six measurements under investigation it was not possible to obtain values with 2D ultrasound. However, 3D ultrasound made these measurements possible in at least one volume. Especially mandible related measurements seemed to benefit from 3D multiplanar ultrasound. The intraobserver reproducibility was higher with 3D multiplanar ultrasound than with 2D ultrasound, this difference being statistically significant for five of the six measurements.
We conclude that depicting the exact midsagittal profile view with 3D multiplanar ultrasound is feasible and does not take much extra time. 3D multiplanar ultrasound improves the accuracy of depicting the midsagittal profile view, which enables correct measurement of anatomical details and improves intraobserver reproducibility.

In **chapter 5 and 6** objective measures for evaluation of the fetal profile were sought for.
The maxilla-nasion-mandible angle and the fetal profile line were newly introduced. Of both tools normative date were collected between 16 and 36 weeks' gestation. The feasibility and reproducibility were assessed and the diagnostic ability was retrospectively tested in a group of pathological cases.

The maxilla-nasion-mandible (MNM) angle, retrieved from orthodontic literature, is introduced in **chapter 5**. The MNM angle quantifies the antero-posterior relationship of the maxilla and mandible. The MNM angle is defined as the angle between the lines maxilla–nasion and mandible–nasion in the exact median plane. The nasion is defined as the most anterior point at the intersection of the frontal and nasal bones. Jaw landmarks are defined as the middle points of the anterior borders of the maxilla and mandible. The feasibility and reproducibility of measurement of the MNM angle is good: intra- and interobserver ICC (intraclass correlation coefficient) was 0.92 and 0.81, respectively and the difference between paired measurements performed by one or two observers was less than 2.5° and 3.6°, respectively in 95% of the cases.
The MNM angle was measured in normal fetuses (241 fetuses cross-sectionally and in 11 fetuses longitudinally).The mean MNM angle was 13.5° (95% CI, 13.28–13.78°, range, 8.96–19.58°, 5th and 95th centiles were 10.39° and 16.91°, respectively) and did not change significantly during pregnancy ($r = -0.08$, $P = 0.25$).
The MNM angle was then tested in 18 pathological cases with facial malformations or syndromes with specific facial features. The MNM angle was above the 95th centile in all six cases of retrognathia and all three cases with maxillary alveolar ridge interruption. The MNM angle was below the 5th centile in Apert syndrome, Thanatophoric dysplasia and in two of the three Down syndrome cases. The MNM angle was normal (> 5th and < 95th percentile) in single cases with CHARGE association, Trisomy 18, Trisomy 21 (all without evidence of retrognathia or cleft alveolus) and 1 case with Velo-Cardio-Facial syndrome and cleft lip and palatum molle but intact alveolar ridge.

The MNM angle quantifies the convexity of the profile. When the MNM angle is small, the profile is flat. This can be the result of maxillary hypoplasia or forward displacement of the mandible; the latter is however rare finding in prenatal life. When the MNM angle is abnormally large, the fetal profile is exaggeratedly convex. The mandible is then moved backward or the maxilla forwards, as shown by retrognathia and facial cleft cases.
We conclude that the MNM angle is a promising tool to establish the convexity of the fetal profile by enabling an objective assessment of the anteroposterior relationship of the jaws. This method has the potential of assisting in the prenatal recognition and classification of abnormal profile findings.

The second measurement, presented in **chapter 6,** is an easily applicable line, which we named the fetal profile (FP) line and proposed as a potential new reference to identify and quantify forehead and mandible anomalies. The FP line was defined as the line that passes through the middle point of the anterior border of the mandible and the nasion. When the FP line passed the frontal bone anteriorly its position was called 'negative'. When the FP line passed lengthwise through the frontal bone, this was called 'zero'. When the FP line passed the frontal bone posteriorly, its position was called 'positive' and the largest distance (F distance) from the FP line to the outer border of the frontal bone could be measured. The feasibility and reproducibility of measurement of the FP line is good. The ICC for the F distance was 0.96 for both intraobserver and interobserver variability.
The FP line was tested in normal fetuses (237 fetuses cross-sectionally and in 11 fetuses longitudinally). The FP line position was never negative in these normal fetuses. We showed that before 27 weeks' gestation the forehead of almost all fetuses is straight and the FP line is aligned with the lower part of the frontal bone for at least 5 mm (position 'zero'). After 27 weeks the forehead changes to a curved shape with a positive FP line position in up to 25% of the cases with a maximum F distance of 3.6 mm.
Subsequently, the FP line was tested retrospectively on stored three-dimensional volumes of 24 fetuses that were suspected to have a facial anomaly or syndrome with specific facial features. The FP line correctly identified 13 cases with retrognathia, 5 cases with frontal bossing and 3 cases with a sloping forehead.
We conclude that the FP line might serve as a reference line and may be useful in the detection of second trimester profile anomalies such as sloping foreheads, retrognathia and frontal bossing with the possibility of quantifying the latter.

In **chapter 7** the MNM angle was used to retrospectively study premaxillary position in fetuses with different types and different degrees of severity of facial clefts. The FP line was used to exclude retrognathia as a possible confounder of an enlarged MNM angle. The mean MNM angle was normal in all 9 cases with cleft lip and intact alveolar ridge (15.2°; range, 12.5°-16.9°). In 24 cases with unilateral complete cleft lip with or without cleft palate the mean MNM angle was 20.0° (range, 13.3-26.2°), above the 95th percentile in 79% (n = 19) and normal in 21% (n = 5). In 14 bilateral complete cleft lip and palate cases the mean MNM angle was 26.5° (range, 19.2°-33.7°) and above the 95th percentile in all cases. In 1 case with a Tessier 4 cleft the MNM angle was above the 95th percentile (25.2°). We found no difference in MNM angle between the isolated cases and cases with other anomalies.

We suggested the existence of forces that push and/or pull the premaxilla forward and the absence of premaxillary protrusion may indicate pathophysiology. However, if protrusion occurs, the amount of protrusion is determined by many different factors and these are discussed.
We conclude that when there is a cleft of the alveolar ridge, the premaxilla tends to protrude. The degree of protrusion varies greatly especially in the bilateral complete cleft lip and palate cases.

In **Chapter 8** the imaging and measurability of three facial markers, nasal bone length (NBL), prenasal thickness (PT) and the frontomaxillary facial (FMF) angle of 219 healthy fetuses were evaluated retrospectively with 3D multiplanar ultrasound.
The quality of images and measurability of the markers were assessed with 5-point and 3-point scoring systems, respectively. A high-quality score was assigned to 111 images. Among these, a high measurability score was significantly more often achieved for NBL (98.2%) and PT (97.3%) than for the FMF angle (26.1%) ($P < 0.001$). The intraobserver 95% limits of agreement were −1.03 to 0.86 mm, −0.61 to 0.76 mm and −8.18 to 5.29°, for NBL, PT and FMF angle, respectively. The respective interobserver 95% limits of agreement were −1.20 to 1.30 mm, −0.52 to 0.69 mm and −6.22 to 8.50°.
Differences in definition or measurement techniques on individual markers in the most relevant published literature were reviewed. We re-defined the measurement technique for NBL. In the new technique care was taken not to add part of the frontal bone to the measurement of the NBL, as this would erroneously increase the measurement. We found that when measured on 3D volumes, NBL and PT are reproducible markers and easy to measure, whereas the FMF angle is far more challenging. We presented novel reference ranges for NBL and PT. Both NBL and PT show growth with gestation, with less pronounced growth for the NBL after 28 weeks. NBL showed a systematically smaller length than those in other on 2D ultrasound based publications.
We conclude that good visualisation leading to high-quality measurements was achieved significantly more often for NBL and PT than for the FMF angle. Following measurement in the exact mid-sagittal plane and with care taken to exclude the frontal bone, our reference range for the NBL showed a systematically smaller length.

Chapter 9 investigates the PT/NBL ratio as a marker for trisomy 21. The ratio was studied retrospectively on 3D volumes in both normal and trisomy 21 fetuses.
The PT/NBL ratio, measured in106 normal fetuses (in 3D volumes) was stable, with a mean of 0.61 (95% CI, 0.59–0.63; $r = -0.04$, $P = 0.7$). The 5th and 95th percentiles were 0.48 and 0.80, respectively. The PT/NBL ratio, measured in 30 fetuses with trisomy 21 (10 on 2D images and 20 in 3D volumes), was significantly higher than in normal fetuses ($P < 0.001$) but also stable throughout gestation, with a mean of 1.50 (95% CI, 1.20–1.80; $r = -0.35$, $P = 0.07$). When the 95th percentile was used as a cut-off value the detection rate, false positive rate and positive likelihood ratio were 100 (95% CI, 89–100)%, 5 (95% CI, 2–11)% and 21.2, respectively. An important observation was that in normal fetuses PT is always about 2/3 (0.6) of NBL. This stable relationship enables easy recognition of normality.
We conclude that the PT/NBL ratio qualifies as an extremely strong second- and third trimester marker for trisomy 21.

Chapter 10 compares the effect on mothers of third trimester 3D/4D with third trimester 2D ultrasound of the fetal face on mothers, with special focus on maternal-fetal bonding. One hundred sixty low risk Caucasian women attended a third trimester 3D/4D or 2D ultrasound

examination. Women filled out the Maternal Antenatal Attachment Scale (MAAS) 1-2 weeks before and 1-2 weeks after the ultrasound examination. The nineteen 5-point scale items of the MAAS questionnaire explore two aspects: quality of attachment and time spent in attachment mode. The ultrasonographer scored the visibility of the face, based on the proportion and quality of the visible part of the face according to a graded score from 1-4. All women in both groups assessed recognisability and attractiveness of the fetal face according to a graded score from 1-4. The 3D/4D group was asked (through a questionnaire post-partum) whether they would like to have another 3D/4D ultrasound examination in a next pregnancy. Of 66 women of the 3D/4D group and 67 of the 2D group we had complete sets of analysable data.
We found that both 3D/4D as 2D ultrasound significantly increased bonding (3D/4D: 3.5, 1.7, 1.5 and 2D: 3.0, 0.9, 1.8, for increase in global, quality and time score respectively, $P < 0.0001$ for all cases). The increase was not significantly different between both ultrasound groups. However the effect of 3D/4D ultrasound on bonding was stronger at better degrees of visibility and recognition of the fetal face ($p = 0.003$ and $p = 0.042$).
Although the scores for visibility, recognition and attractiveness were higher in the 3D/4D group this did not reach statistical significance (3D/4D: 2.8, 3.3, 3.1 and 2D 2.7, 3.0, 2.9 for visibility, recognition and attractiveness respectively). Only one woman reported the 3D/4D imaging of the face as 'not beautiful', despite high scores on visibility and recognition and two women reported the 2D imaging of the face as 'not beautiful', but the reported scores on visibility and recognition were also low. Four women indicated that they would not want to have another 3D ultrasound in their next pregnancy. These 4 women had low scores for attractiveness of the 3D/4D imaging, although visibility and recognition were scored high. Nevertheless, even for these women, there was an increase in MAAS scores after the scan.
We conclude that women have a general positive attitude towards both 2D and 3D/4D ultrasound of the fetal face. In the few cases that 3D/4D imaging is not considered a positive experience by the mother this does not seem to adversely affect the bonding. Bonding increases after either a 3D/4D or 2D ultrasound. The effect of 3D/4D ultrasound on bonding is stronger at better degrees of visibility and recognition.

Finally, a review is presented of studies quantifying the psychological effect of 3D/4D ultrasound on mothers, pregnant with a fetus with no detectable abnormalities. Of thirteen psychological studies, eight studies evaluated bonding and found no difference between 3D/4D and 2D ultrasound. The effect of 3D/4D ultrasound on satisfaction or perception showed conflicting results and on anxiety/stress reduction was the same as after 2D ultrasound.

Summary of the most important findings
3D multiplanar ultrasound examination of the fetal profile:

- 3D multiplanar mode is essential for defining the exact midsagittal profile view.
- Alignment is easier around the z-axis than y-axis of the fetus.
- The use of 3D multiplanar mode improves intraobserver reproducibility.
- Especially mandible related measurements benefit from 3D multiplanar ultrasound.

The MNM angle

- is a promising tool to establish the convexity of the fetal profile, by enabling an objective assessment of the antero-posterior relationship of the jaw.
- is stable during the second and third trimester of pregnancy with a mean of 13.5°.

The FP line

- is an easy to use reference line to identify forehead and mandible anomalies, especially in the second trimester.
- is the first objective tool to identify sloping foreheads and to quantify bossing foreheads.
- In up to 25% of the fetuses the forehead changes after 27 weeks from a straight to a mildly curved appearance.

In fetuses with (a) cleft(s) of the alveolar ridge

- the premaxilla tends to protrude.
- the protrusion of the premaxilla is influenced by many different factors.

Facial measurements in screening for Down syndrome:

- There are several definitions used in literature for the landmarks of NBL, PT and FMF angle measurements. Care has to be taken not to include the frontal bone in the NBL measurement.
- When using 3D volumes NBL and PT are reproducible, easy to measure markers, whereas the FMF angle is a far more challenging marker.
- A reference range for the NBL based 3D multiplanar ultrasound without including the frontal bone shows smaller measurements than in other on 2D ultrasound based publications.
- In normal fetuses PT is always about 2/3 of NBL.
- The PT/NBL ratio qualifies as an extremely strong second- and third trimester marker for trisomy 21.

Maternal bonding:

- Both 3D/4D and 2D ultrasound of the fetal face significantly increase maternal-fetal bonding in the third trimester of pregnancy.
- The effect of 3D/4D ultrasound on bonding is stronger at better degrees of visibility and recognition of the fetal face.
- In the few cases where 3D/4D imaging is not considered by the mothers to be a positive experience there is no measurable adverse effect on maternal-fetal bonding.

11.2 GENERAL DISCUSSION

The reason for choosing the fetal face as subject for this thesis is that a lot of information can be obtained from its ultrasound examination. Not only clear anomalies like clefts and anopthalmia, with clinical relevance themselves, can be visualised in the face, but also subtle dysmorphic traits or markers that can serve as clues to diagnose syndromes. In addition, ultrasound visualisation of the fetal face has a major emotional impact on parents and is probably the most frequently viewed part of the fetus.
The study focuses on the second and third trimester, as this is the period where the fetal face is mostly examined. However, the knowledge gained so far can be extended to first trimester research.

The aim of prenatal ultrasound is to diagnose fetal anomalies and fetal diseases, with as the most attractive scenario to be able to offer timely information with treatment options and solve the problem. Although diagnostic possibilities have enormously increased, treatment possibilities are still limited to a few conditions. In spite of continuous technological advances clinicians are still confronted with conditions for which diagnosis and treatment remain a great challenge.

Another meaningful element of prenatal ultrasound is to enhance the psychological wellbeing of the mothers and their families. One example of this is to be able to exclude the occurrence of hereditary diseases in carrier couples. However, when anomalies are found through prenatal ultrasound, parents can be informed regarding the diagnosis, prognosis, life expectancy and risks for new pregnancies. Providing clear information and guidance in fatal cases are also obligations we must meet. Eventually, the fact of being able to view the child prenatally can, where necessary, be of help in the bereavement and mourning process.

The additional value of three-dimensional multiplanar ultrasound in the evaluation of the fetal profile
Both multiplanar and surface rendering of the fetal face improve understanding of the complex anatomy of the face; multiplanar mode by enhancing spatial awareness and rendering mode by facilitating a lifelike three-dimensional view of the face. We choose multiplanar mode to study the fetal profile as with this mode the exact midsagittal plane is easier to identify. Furthermore, at the beginning of this research project it was not possible to perform measurements on three-dimensional surface rendered images.
When examining the fetal profile subjectively, the true midsagittal plane is usually assumed to be present. The multiplanar imaging mode of 3D ultrasound provides the ultrasonographer with a unique tool: the possibility to visualise contemporarily the three orthogonal planes. Any deviation from a true sagittal, coronal or axial plane is easily recognised and can be corrected to the true mid sagittal plane. Evaluation of the fetal profile in an incorrect midsagittal plane will probably lead to diagnostic inaccuracies. Deviation from this plane changes the appearance of the profile. For example, in a view deviating from the midsagittal plane the most protruding part of the chin will not be visualized creating the impression of retrognathia. That is why isolated retrognathia is easily missed in a routine setting as this is a not an unusual appearance for ultrasonographers and thereby not noticed.

This is in line with our finding that especially mandible-related measurements (like facial height measurements and the maxilla-nasion-mandible angle) seem to benefit from 3D ultrasound. In fact especially for mandible related measurements 3D ultrasound allows identification of landmarks that are difficult to visualise with 2D ultrasound and improves their reproducibility.
The lack of landmarks localised posteriorly in the fetal head visible with 2D ultrasound is underlined by our finding that, when displaying the orthogonal planes of a volume obtained starting from a supposedly good profile view, the deviation around the y-axis was significantly larger than around the z-axis of the fetus. Midline structures in the centre or in the back of the head like hard palate, corpus callosum or cerebellar vermis (ideally with the fastigium (Tepper 09)) are necessary to define the correct midsagittal plane. However the palate and the corpus callosum have a certain width, which also makes them visible in planes deviating from the exact midsagittal plane and the cerebellar vermis is not easy to visualise from a frontal view. Maybe the vomer, although located rather anteriorly, has the potential to be helpful to identify the exact midsagittal plane (Persico 10).
Previous studies on an ultrasound mimicking phantom in a water bath had demonstrated that 3D ultrasound measurements of distance and volume are sufficiently accurate to be used clinically (Riccabona 96). We demonstrated that 3D technique improves intraobserver reproducibility, implying that 3D multiplanar ultrasound improves accuracy. However the clinical relevance of this finding needs further investigations by larger studies.
Identification of the exact midsagittal plane with 3D ultrasound takes extra time and requires some skills. We succeeded in 96.4% of the cases in obtaining a profile volume, which is comparable to rates obtained with 2D ultrasound (Turner 93, Viñals 07). Thereafter it was possible to define by multiplanar mode the exact midsagittal plane in less than 1 min. To push the '3D button', instead of the 'freeze button', and adjust the planes on the multiplanar view ultimately requires little time but guarantees that the true profile view is examined. However, in this study an experienced sonographer performed the examinations with low risk patients without clinical or parental pressure to achieve a diagnosis.
We have to accept that three-dimensional ultrasound is promising and is here to stay. When we want to offer our patients the most advanced high quality prenatal examinations we have to accept the 'burden' and master the technique of three-dimensional ultrasound.

Objective tools to quantify the fetal profile

The universally used word to describe the science of measuring the human body is 'anthropometry', which is derived from the Greeks words 'antropos' and 'metron' meaning 'human' and 'measure'. Ultrasound measurements match this definition. However, traditionally, with anthropometry the measurements are taken directly, physically, from the surface of the human body. 'Biometry' (a branch of biology that studies biological phenomena and observations by means of statistical analysis) is used in prenatal ultrasound.
The Greek were the first to measure the human face (Vegter 00). With knowledge of ideal proportions, artists attempted to create the perfect paradigm of beauty (Farkas 81). The intention to translate proportions of the face into objective values was different during certain phases of history and is intimately related to sociological, psychological, religious, technical and political developments. The purpose of prenatal face measurements is to be able to correctly diagnose facial malformations before birth so that medical decisions can be taken and parents can be informed properly. The reassurance on the absence of malformations is just as important.

The study of the fetal face has benefitted from advances in prenatal ultrasound like improved image quality and the introduction of three-dimensional ultrasound. These upgrades have renewed interest in the fetal face and offered the potential to refine diagnosis of fetal face anomalies (Lee 95, Pretorius 95, Merz 97, Dyson 00, Cmait 01, Lee 02, Rotten 04, Merz 05, Picone 08).
Facial anomalies and dysmorphic traits can be subtle and easily escape attention. Subjective judgement of unusual facial features is valuable, but beside experience in ultrasound also knowledge of prenatal facial growth and facial anomalies is needed to recognise and categorise facial anomalies. Subjective evaluation can be misleading. For example; the depressed nasal bridge and the epicanthic folds in trisomy 21 newborns give the impression of hypertelorisme, while in fact the eyes are significantly nearer than the norm (Goodman 77). Specific objective measurements can supplement the subjective visual impression. Objective measurements have become desirable not only to identify minor deviation from the norm and facilitate early detection but also to quantitatively record anomalies. This will ultimately stimulate research by providing researchers with a tool to communicate and compare findings.

The onset of deviating growth in various conditions is not determined yet. Care has to be taken to rule out an anomaly when the process of altered growth is not established yet. Some phenotypic traits emerge while others will fade away with increasing age (Pooh 99, Allanson 85, 90, 93, 96). Some dysmorphic features may be more recognisable during certain stages of development and it would even be possible that for some syndromes prenatal observation may enhance syndrome recognition. Study of the natural prenatal growth may shed light on the natural history of some diseases and lead to better understanding of the underlying pathophysiological mechanisms.

The development of prenatal ultrasonographic nomograms cannot be a simple imitation of existing postnatal nomograms. Postnatal nomograms are usually developed either by direct measurements of the face (anthropometry), by X-ray (cephalometry) or photogrammetry (Farkas 94, Broadbent 31, Allanson 77), although three-dimensional imaging is also available (Zonneveld 94). Prenatal ultrasonography is a different technology with its own advantages and limitations.

We introduced two tools that may be of help when evaluating the fetal profile: the maxilla-nasion-mandible angle and the fetal-profile line. We chose bony landmarks as reference for these measurements as these are easier to identify when the face is not surrounded by amniotic fluid and to exclude (sub)cutaneous tissue as a confounding factor.

Maxilla-Nasion-Mandible angle
We introduced the maxilla-nasion-mandible (MNM) angle. The MNM angle quantifies the convexity of the profile by measuring the anteroposterior relationship of the jaws. When the MNM angle is small, the profile is flat. This can be the result of maxillary hypoplasia or forward displacement of the mandible; the latter is however rare finding in prenatal life. When the MNM angle is abnormally large, the fetal profile is exaggeratedly convex. The mandible is then moved backward or the maxilla forward, as shown by retrognathia and facial cleft cases. Convexity has not previously been mentioned as a possible variable to assess the profile. It has to be kept in mind that the forehead (not part of the viscerocranium) is not involved in the MNM angle, but will influence the subjective evaluation of the profile.
We found that in normal fetuses the MNM angle is stable during gestation with a mean of 13.5°. This makes the usage of this tool easy, because tables and charts are not necessary. This prenatal

angle is much larger than the postnatal ANB angle (the postnatal counterpart of the MNM angle) found in adulthood (approximately 3º) (Hamdan 01) and illustrates the subjective roundness of the fetal and neonatal profile compared to adults.

Fetal Profile line
We introduced the Fetal profile (FP) line as an easily applicable reference line for identifying profile anomalies especially forehead and mandible anomalies. Quantification of the forehead is hardly done prenatally.
Especially before 27 weeks' gestation the FP line will be an easy and helpful way to evaluate the profile as the line is in position 'zero' in almost all cases and no further measurements are necessary. After 27 weeks the application of the line will be more complicated as a positive FP line is also normal in up to 25% of the normal cases. However a negative FP line seems always pathological.
It is for the first time described that after 27 weeks the forehead changes to a mildly curved shape with a positive FP line position in up to 25% of the cases. This means that this curved shape of the frontal bone may influence IFA, FMF angle or other measurements using the forehead as a reference point when applied in the third trimester (Rotten 02, Sonek 07, Palit 08).
The FP line is the first objective tool for possible assessment of a sloping forehead. A negative FP line may indicate a sloping forehead as an early symptom of disproportional growth of the skull compared with the face, resulting in microcephaly. This may be a valuable tool in the early diagnosis of microcephaly, a very serious disorder difficult to diagnose early in pregnancy.
We speculate that in early severe growth restriction the opposite effect may occur: the face growth may lag behind compared to the skull growth (brain sparing), resulting in a positive FP line. Case nr 22, a child with severe growth restriction illustrates this possibility.
Interesting is the publication of the relation between open spina bifida and changes in the FMF angle, initiated by displacement of the forehead relative to the position of the anterior end of the maxilla in the first trimester (Lachman 10, Acuna 11). Open spina bifida may influence the position of the FP line. However studies are needed to evaluate these last two speculations.

Some landmarks and measurements are influenced by the position of the head (e.g. the vertex, head height). For these measurements a standard position of the head is required to achieve sufficient reproducibility. Also for subjective evaluation a standard position of the head may be useful. We noticed for example, that in fetuses with a sloping forehead, the ultrasonographer has the tendency to rotate the profile and put the forehead in an upright position, giving the chin (by the rotation) a retrognathic appearance. Postnatal the Frankfurter horizontal (synonyms: orbitomeatal plane, auriculo-infraorbital plane, eye-ear plane), a standard craniometrical reference plane, is widely used and well known by many healthcare professionals working with images of the head (Farkas 94). When the head is in a standard orientation based on the Frankfurter horizontal, the line connecting the lower part of the orbit and porion is horizontal. This reference line is difficult to use in prenatal ultrasound, with 2D ultrasound even almost impossible. Measuring the head prenatally is extra complicated; it is impossible to use a head-holder, the position of the head is unpredictable and hardly steerable by the investigator. Moreover parts of the face may be obscured by the placenta, or shadows from limbs.
A reference line to put the profile in a standard position may be of value in prenatal diagnosis. The FP line may serve as a reference line when evaluating the face.

In the end the subjective visual impression and specific objective measurements of the face should be integrated with additional factors such as associated anomalies, growth, information obtained from invasive procedures and family history into an overall impression and when possible a diagnosis. Ultimately this will assist the physician to provide the parents with adequate counseling regarding prognosis, treatment options, preventative care, pathogenesis and recurrence risk.

Maxillary protrusion in fetuses with a facial cleft

In fetuses with facial clefts we were able to study with the MNM angle the position of the premaxilla and found that the premaxilla has the tendency to protrude. In many cases with a subjective normal profile, the MNM angle was increased. This illustrates the additional value of a quantitative evaluation; the protrusion was subtle and subjectively hardly recognisable.

We discussed that this protrusion is the result of normal events, like the initial forward growth potential of the jaw. We could not confirm that in cases with other anomalies the protrusion was less than in isolated cases. However, facial clefts can be part of numerous syndromes, each with a very heterogenic pathophysiology and even the expression can vary greatly within a particular syndrome. Therefore large studies are needed to establish the behavior of the premaxilla in relation to specific syndromes with a facial cleft.

The factors that may affect the position of the premaxilla were discussed, completeness and size of the clefts, the misbalance of the forward force of the tongue and the restraining effect of the lips, muscle strength and tone of the tongue or muscular orbicularis oris and primary growth potency. However the groups were too small to draw firm conclusions.

Measuring the MNM angle will probably not increase the detection rate of facial clefts but may be of value in equivocal cases. However, we believe that this finding contributes to our understanding of the pathological events that affect the face and this will ultimately improve diagnostic capacity.

The study also illustrated the value of combining the MNM angle and the FP line. In the study the normal FP line excluded retrognathia, also a potential cause of increase in MNM angle.

We suggest that when measuring the MNM angle, the two line option should be used. When the first ray of the MNM angle is positioned on the frontal border of the mandible and through the nasion, this line represents the FP line. The relationship between the forehead and the mandible can be assessed, almost at a glance, before the MNM angle is measured.

As the face is a complex three-dimensionally curved structure, measuring elements of the face is complicated. Changes in position of one landmark will influence other measurements. In addition in dysmorphic faces disproportional growth will often be present in several areas and several directions. When a face is for example a bit narrow and a bit long, the overall subjective impression will be that of an oblong facial shape, while the separate measurements still can be within the normal range. It will therefore be likely that when several measurements are combined the diagnostic power increases.

Escobar (Escobar 88, 90, 93) was the first who tried to combine prenatally several craniofacial measurements into an index, based on the cephalometric work of Garn (Garn 85). However the ultrasound machine then used is outdated and some landmarks are puzzling like the gonion identified in a profile view, while the gonion is located at the lateral side of the face (the gonion is an anthropometric landmark located at the most inferior, posterior, and lateral point on the external angle of the mandible). Roelfsema repeated the work with 3D ultrasound (Roelfsema 07, 07). Escobar found abnormal indexes for 3 fetuses with Fetal Alcohol Syndrome/Effects, 1 fetus with Crouzon syndrome and 1 with Thanatophoric dysplasia (Escobar 93) and Roelfsema

found abnormal indexes in syndromal fetuses with facial clefts (Roelfsema 07). The results are interesting however calculating the index is rather time consuming, therefore not suitable for everyday practice. Recently Tsai presented a new automatic algorithm that measures automatically and precisely 5 craniofacial measurements form three-dimensional volumes of the fetal head. They intend to include more facial parameters, such as the MNM angle (Tsai 12). Such automatic image analysis techniques have the potential to become a clinically useful tool for delineating and distinguishing syndromes.

Facial markers for trisomy 21

Markers are slight deviations from the normal anatomy without being an anomaly itself. They are not diagnostic but add risk to the likelihood of fetal pathology, usually a chromosomal trisomy. Detection of (a) marker(s) causes a lot of stress and uncertainty for the parents. A detailed exam to rule out associated anomalies is an essential next step. To be sure whether a given measurement differs and therefore can be labelled as a marker needs a high degree of precision. Therefore we must thoroughly study the markers to be able to counsel as accurately as possible and reduce anxiety whenever possible.

A lot of attention is focused on the first trimester screening. Although legal rules differ between countries, termination of a pregnancy is usually an option in the first trimester and considered a less traumatic experience than terminations later in pregnancy (Korenromp 05 & 07).

However as first trimester screening is not accepted by all parents, we can be confronted with anomalies, which may part of a genetic or chromosomal anomaly, later in pregnancy. Moreover, there will always be pregnant women who book late for prenatal care. Also in these cases detecting or excluding a genetic or chromosomal aberration is important as it may change prenatal and perinatal care. Moreover, we experience that once an abnormality is discovered, parents are often less reluctant to further investigation; first trimester screening may initially be rejected, but when fetal abnormalities are found, the situation changes. In this anxious and uncertain situation further investigation is usually valued by the parents.

We evaluated the influence of 3D ultrasound on nasal bone length (NBL), prenasal thickness (PT) and frontomaxilla-facial (FMF) angle measurements. Our most important finding was that especially the NBL measurements are influenced by dimensionality: 3D derived measurements are systematically shorter than 2D derived measurements. Therefore the appropriate normal range to the used technique should be employed.

We also pointed out the need to define correct landmarks for NBL as several definitions are used. We signalled that the frontal bone continues behind the nasal bone. Therefore we suggest to use the most anterior point in the junction of nasal bone and frontal bone (nasion) as landmark for the measurement. Only then the frontal bone is not included in the measurement. This makes the measurement comparable with measurements of hypoplastic nasal bones of trisomy 21 fetuses, as in these latter due to the nasal bone–frontal bone disjunction the frontal bone is also excluded from the measurement.

We evaluated the possibility to retrieve NBL, PT and FMF angle measurements from 3D volumes and found that NBL and PT are easily measured using 3D ultrasound whereas FMF angle measurement is more challenging. Probable FMF angle measurements experience more problems with acoustic shadows. The MNM angle may be a good alternative during the second half of pregnancy.

The PT/NBL ratio was proposed as a marker for trisomy 21. The tendency for the PT to increase and for the NBL to decrease in trisomy 21 was combined into a powerful ratio. The PT/NBL ratio

is not only stable during the 2nd and 3rd trimester (0.63), and thereby easy to use, but indeed turned out to be a very strong (likelihood ratio of 21.2) and promising marker of trisomy 21.

Effect on mothers

the terms *bonding* and *attachment* are both used in literature. We used *bonding* as this is the parents' tie towards the fetus while *attachment* refers to a bilateral relationship developing between parents and the child after birth (Pretorius 06). We maintain the term *attachmen*t when referring to questionnaires/studies that originally use this term.

The earliest tie formed by the child with the caregivers has a tremendous impact on the child that continues throughout his entire live. Attachment is a biological need which is extremely important and essential for the mental health of a person (Bowlby 51, Ainsworth 79, Schore 01). The postnatal attachment theory was initially described by child psychiatrist Bowlby and expanded by the developmental psychologist Ainsworth (Bolwby 82, Ainsworth 79, Bretherton 92). Bowlby described attachment as a "deep and enduring emotional bond that connects one person to another" and devoted extensive research to the concept of attachment.

For a mother the relationship with her child develops already before the child is born. The development from prenatal bonding to the, for the child so important, postnatal attachment is a continuous psychological process. Although probably as old as mankind, prenatal bonding is first mentioned by Deutsch in 1945 (Deutsch 45). The first prenatal questionnaire on this issue was developed by Cranley (Cranley 81). We chose the Maternal Antenal Attachment Scale (MAAS) developed by Condon not only because other researches have already used the MAAS questionnaire (making comparison and the application of a power analysis possible), but also because the MAAS questionnaire differentiates the attitude towards the fetus from the attitude towards the state of pregnancy (Condon 93). Condon describes that the core experience of bonding is 'love'. He mentioned five subjective 'needs' which derive from the core experience 'love' i.e. the desire 'to know', 'to be with', 'to avoid separation from', 'to protect' and 'to identify and to gratify the needs of' the loved object. The desire of parents to see their baby with ultrasound (desire 'to know') can be seen as an expression of 'love' or bonding.

Positive consequences of two-dimensional (2D) ultrasound at 12 and 20 weeks on maternal-fetal bonding are well established especially before quickening (Campbell 82, Villeneuve 88, Lerum 89, Lumley 90, Dykes 01, Adhusen 08). As 3D/4D ultrasound gives a more realistic presentation of the fetus, it was speculated the effect of 3D/4D ultrasound on maternal-fetal bonding may be greater. In our study, like other studies (Ji 05, Herrero 06, Lapaire 07, Edwards 10, Righetti 05, Sedgmen 06, Rustico 05), the increase in bonding was not significantly greater, after a 3D/4D ultrasound, than after a 2D ultrasound. However a positive relation between recognisability and attractiveness of the image with increase in bonding was demonstrated, implying that with technical advances the effect of 3D/4D ultrasound may further increase.

3D/4D ultrasound is increasingly used for medical indications or on parental request (Carlson 00, Maarse 10, Lee 07). It is reassuring to know that bonding increases when the 3D/4D images are shown. Even when the images were assessed by the mother as not recognisable/not beautiful or the mothers indicated that they did not want a 3D/4D ultrasound in a next pregnancy, an increase in bonding was demonstrated. However, the ultrasonographer should always be aware of the impact of showing unrequested 3D/4D images. Explaining artifacts and gestational age related appearances of the face are part of the ultrasonographer's task.

Ultrasonographers are responsible for the well-being of the parents watching the ultrasound images. Therefore ultrasonographers should be aware of potential harmful or beneficial psychological effects caused by 3D/4D ultrasound images, especially when the parents are psychologically or socially vulnerable.

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11.3 FUTURE PERSPECTIVES

When during a prenatal ultrasound investigation multiple anomalies or markers are observed the likelihood of a syndrome increases. However correct syndrome diagnosis, especially syndrome to syndrome discrimination is still a challenge prenatally. As the face contains lots of information, improvement of our ability to 'read' the face could significantly improve our diagnostic capacity.

Reviewing what has already been measured from the face, it was striking that most studies are only retrospective in nature, did not include pathological cases and sometimes included small numbers. In order to be able to make a step forward and to decide which measurements are most sensitive and accurate, larger prospective studies are needed.
We also found in many reports the definition of landmarks to be vague. For nuchal translucency measurement various technical aspects are standardised (insonation angle, gain, magnification) and the position of the caliper is exactly defined. In order to improve reproducibility and accuracy of facial measurement technical aspects and the location of the calipers has also to be exactly defined.

As many anomalies and syndromes are rare, joining forces, by collecting cases from several centres would provide the opportunity to study all kinds of rare syndromes and anomalies adequately. The development of three-dimensional ultrasound with the possibility to store and share volumes in, for instance, a web based registry would be an option.

With improvements of ultrasound techniques, we will be able not only to detect clear anomalies of the face but also to recognise dysmorphic features. Volumes of faces, suspected to be syndromal, could be submitted by telemedicine, to a postnatal dysmorphologist expert in certain rare syndromes and strengthen the branch of fetal dysmorphologists.

Increasing numbers of semi-automatic and automatic ultrasound measurement systems have been developed, like for nuchal translucency thickness measurements[1,2]. Recently these systems have been extended to the fetal heart[3,4] and to some craniofacial measurements[5]. It is also likely that automatically guided systems may assist in capturing the exact mid-sagittal plane of the profile.

In syndromic faces the deviation in growth is usually not limited to one isolated component deviating in a single direction. Probably, a combination of several deviations gives the face the appearance typical for a particular syndrome. Therefore automatic systems that can measure and combine several dimensions will be of value in the evaluation of the face.

Three-dimensional ultrasound gives us the opportunity to evaluate our technique, for example the effect of a certain angle of insonation on the image quality, and improve our two-dimensional awareness and performance.

It may be of value to compare the prenatal measurements with postnatal normal values, in order to understand pathophysiological events. However, one should be aware of the differences between prenatal and postnatal appearance. Teething, chewing, swallowing, speaking and

muscle activity influences the postnatal facial growth and the effect of the fluid on the soft tissue surrounding the prenatal face is unknown.

Four-dimensional ultrasound facilitates the possibility to study facial movements and expression. This offers the opportunity to study the relation between facial movements and fetal neurological development and well-being of the fetus.

In this thesis second and third trimester Caucasian fetuses were evaluated. Further studies are needed to extrapolate the finding to the first trimester and non-Caucasian fetuses.

The psychological effect of ultrasound images on the mother is generally positive. We found a relation between recognisability/ attractiveness of the third trimester 3D/4D images and increase in maternal-fetal bonding. Therefore it is likely that the effect will be stronger with technical improvements, like the recently introduced HD*live* technique[6] generating realistic images of the human fetus.
Mothers included in this study were psychologically healthy with uncomplicated pregnancies and normal maternal-fetal bonding. Little is known yet about the effect on mothers with psychological or emotional problems or sub-optimal bonding. One may speculate that to be able to realistically view the baby may have a positive effect on maternal lifestyle and health behavior and enhance the change from prenatal bonding to postnatal attachment. The relationship between 3D/4D ultrasound and postnatal attachment or the emotional health of the child is also scarcely studied.

When an anomaly is diagnosed, informing and counseling parents is extremely important. In order to do this well extensive research and collaboration is still needed to improve our diagnostic capacity and to improve counseling tools.

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6. www.gehealthcare.com/volusonHDLive

CHAPTER 12

Nederlandse samenvatting (Summary in Dutch)

Hoofdstuk 1 vat verschillende reeds bekende aspecten van het foetale gezicht samen. Om het ontstaan van gezichtsafwijkingen te kunnen begrijpen volgt een introductie van relevante embryologische aspecten.
De volgende paragraaf schetst de geschiedenis van de echografie, met aandacht voor de echografie van het foetale gezicht. De schets beschrijft de ontwikkeling vanuit de statische A-mode (één-dimensionale) echografie via real-time B-mode (twee-dimensionale (2D)) echografie tot vier-dimensionale (4D) echografie. Speciaal aandacht wordt gegeven aan de ontwikkeling van de drie-dimensionale (3D) echografie in het kader van de hernieuwde belangstelling voor het foetale gezicht.
Gezichtsafwijkingen zijn vaak geassocieerd met andere afwijkingen of onderdeel van een syndroom. Een overzicht van de literatuur presenteert de frequentie van geassocieerde afwijkingen bij de twee meest voorkomende gezichtsafwijkingen, te weten lip/kaak/gehemelte spleten en micro/retrognatie.
Een apart paragraaf geeft een mogelijke classificatie van gezichtsafwijkingen.
Het daaropvolgende volgende deel beschrijft het echografisch onderzoek van het gezicht, waarbij onderscheid wordt gemaakt tussen het gebruik van echografie als een screenings- of als diagnostisch instrument.
Hoofdstuk 1 eindigt met de psychologische impact van het prenataal diagnosticeren van een gezichtsafwijking op ouders.

Hoofdstuk 2 geeft een overzicht van de huidige literatuur over studies van objectieve echoscopische analyses per anatomische onderdelen van het foetale gezicht. Achtereenvolgens komen in dit hoofdstuk aan de orde: voorhoofd/schedel/fontanellen, ogen, oren, neus, mond, bovenkaak en onderkaak. De beschrijvingen worden gecompleteerd met figuren en tabellen die de relatie met de zwangerschapsduur weergeven.

Hoofdstuk 3 presenteert de doelstellingen en hoofdlijnen van dit proefschrift.
De doelstellingen van dit proefschrift zijn:

- het verkennen van de toegevoegde waarde van 3D multiplanar echografie voor de evaluatie van het foetale profiel
- het ontwikkelen en testen van reproduceerbare meetinstrumenten ten behoeve van de beoordeling van het foetale profiel
- het onderzoeken van de bijdrage van 3D multiplanar echografie voor de evaluatie van gezichtsmarkers voor trisomie 21, enkelvoudig en gecombineerd als 'prenal thickness/nasal bone length' verhouding.
- het verkennen van het effect van 2D of 3D/4D echo afbeelding van het foetale gezicht op de moeder-foetus binding en de daarmee samenhangende mening van de moeders

De hoofdlijnen van dit proefschrift zijn:

- deel 1 (hoofdstuk 4): de toegevoegde waarde van multiplanar 3D echografie bij de beoordeling van het foetale profiel
- deel 2 (hoofdstuk 5 t/m 7): objectieve maatstaven voor de beoordeling van het foetale profiel
- deel 3 (hoofdstuk 8 en 9): faciale kenmerken van foetussen met trisomie 21
- deel 4 (hoofdstuk 10): reacties van moeders op echobeelden van het foetale gezicht

Hoofdstuk 4 evalueert de toegevoegde waarde van 3D multiplanar echografie bij het onderzoek van het foetale profiel in 84 foetus tussen 22 en 29 weken zwangerschapsduur.
In 81 (96.4%) gevallen slaagden we erin een profielvolume op te slaan; 70% van de volumen werden al verkregen binnen 10 minuten tijd. Vervolgens was het meestal mogelijk om met behulp van de multiplanar mode het exact midsagittale profiel vlak af te beelden in minder dan 1 minuut tijd.
De gemiddelde rotatie die nodig was om het exacte midsagittale profiel te verkrijgen met 3D multiplanar mode was significant groter rond de y-as (11.9º) dan rond de z-as (4.3º) van de foetus.
Van zes metingen met betrekking tot de foetale neus of kaken zijn het succespercentage en de intraobserver reproduceerbaarheid tussen 2D en 3D multiplanar echo vergeleken. Van 5-12% van de onderzochte zes metingen was het niet mogelijk om waarden te verkrijgen met 2D echografie, terwijl met 3D multiplanar echo deze metingen wel mogelijk was in tenminste één volume.
Vooral mandibula gerelateerde metingen leken te profiteren van 3D multiplanar echografie.
De intraobserver reproduceerbaarheid bleek met 3D multiplanar echografie beter dan met 2D echografie. Dit verschil was statistisch significant voor vijf van de zes metingen.
Wij concluderen dat het afbeelden van het exacte midsagittale profiel met 3D multiplanar echografie goed uitvoerbaar is en niet veel extra tijd in beslag neemt. 3D multiplanar echografie verhoogt de nauwkeurigheid waarmee het exact midsagittale profiel wordt afgebeeld, waardoor anatomische details correcter gemeten kunnen worden en de intraobserver reproduceerbaarheid verbetert.

Hoofdstuk 5 en 6 introduceren de maxilla-nasion-mandible hoek en de foetale profiel lijn als nieuwe objectieve maatstaven voor de evaluatie van het foetale profiel. Van beide tools werden normaal waarden verzameld tussen 16 en 36 weken zwangerschapsduur. De haalbaarheid en reproduceerbaarheid werden beoordeeld en de diagnostische mogelijkheden werden retrospectief getest in een groep van pathologische casussen.

Hoofdstuk 5 De maxilla-nasion-mandibula (MNM) hoek is afkomstig uit orthodontische literatuur. De MNM hoek meet de voor-achterwaartse positie van de kaken. De MNM hoek is de hoek tussen de lijnen maxilla-nasion en mandibula-nasion. Het nasion is het voorste punt op het snijpunt van de frontale en nasale botten. De meetpunten van de kaken liggen centraal aan de voorzijde van de maxilla en mandibula. Het meten van de MNM hoek is haalbaar en reproduceerbaar; de intra- en inter ICC (intraclass correlation coefficient) was respectievelijk 0.92 en 0.81 en het verschil tussen gepaarde metingen met een of twee waarnemers was minder dan respectievelijk 2.5º en 3.6º in 95% van de gevallen. De MNM hoek werd gemeten bij normale foetussen (241 foetussen cross-sectioneel en in 11 foetussen longitudinaal). De gemiddelde MNM hoek was 13.5º (95% BI: 13.28-13.78º, range: 8.96-19.58º, 5e en 95e percentiel: 10.39 en 16.91º) en veranderde niet significant tijdens de zwangerschap ($r = -0.08$, $P = 0.25$). De MNM hoek werd vervolgens getest in 18 pathologische casussen met gezichtsafwijkingen of syndromen met specifieke gelaatstrekken. De MNM hoek lag boven het 95e percentiel in alle zes gevallen met retrognathia en in alle drie gevallen met een spleet in de bovenkaak. De MNM hoek lag beneden het 5e percentiel in Apert syndroom, thanatophore dysplasie en in twee van de drie gevallen met trisomie 21. De MNM hoek was normaal (> 5e en < 95e percentiel) in een casus met CHARGE associatie, een casus met trisomie 18, een casus met trisomie 21 (allemaal zonder aanwijzingen voor retrognathia of gespleten bovenkaak) en een casus met Velo-Cardio-Facial syndroom (met gespleten lip en gespleten palatum molle maar intacte bovenkaak).

De MNM hoek kwantificeert de convexiteit van het profiel. Wanneer de MNM hoek klein is, is het profiel plat. Dit kan het gevolg zijn van de maxillaire hypoplasie of voorwaartse verplaatsing van de mandibula, dit laatste zal echter niet of nauwelijks prenataal voorkomen. Wanneer de MNM hoek abnormaal groot is, is het foetale profiel bovenmatig convex. De mandibula is dan naar achteren verplaatst of de maxilla is naar voren verplaatst, zoals geïllustreerd door de retrognathia casussen of casussen met een gespleten bovenkaak.
Wij concluderen dat de MNM hoek een veelbelovend tool lijkt om de convexiteit van het foetale profiel vast te stellen, via een objectieve beoordeling van de voor-achterwaartse positie van de kaken. Deze methode heeft de potentie om de prenatale herkenning en classificatie van abnormale bevindingen in het foetale profiel te ondersteunen.

De tweede meting, gepresenteerd in **hoofdstuk 6**, is een eenvoudig toe te passen lijn, die we de foetale profiel (FP) lijn hebben genoemd. De FP lijn is geïntroduceerd als een potentiële nieuwe referentie lijn voor het identificeren en kwantificeren van voorhoofd- en mandibula afwijkingen. De FP lijn is gedefinieerd als de lijn die centraal door de voorzijde van de mandibula en het nasion loopt. Wanneer de FP lijn voor het frontale bot langs loopt is de FP lijn positie als 'negative' geclassificeerd. Wanneer de FP lijn longitudinaal door het onderste deel van frontale bot loopt is de positie als 'zero' geclassificeerd. Wanneer de FP lijn het frontale bot achterlangs passeert, is de positie als 'positive' geclassificeerd en de grootste afstand (F afstand) van de FP lijn naar de buitenste rand van de frontale bot gemeten. De toepassing van de FP lijn is haalbaar en reproduceerbaar gebleken. De ICC voor de F afstand bedroeg 0.96 voor zowel intraobserver als interobserver variabiliteit.
De FP lijn is getest in normale foetus (237 foetussen cross-sectioneel en 11 foetussen longitudinaal). De FP lijn positie was bij deze normale foetussen in geen enkel geval 'negative'. We toonden aan dat voor een zwangerschapsduur van 27 weken het voorhoofd van bijna alle foetus recht is en de FP lijn uitgelijnd is met het onderste deel van de frontale bot over een lengte van ten minstens 5 mm (positie 'zero'). Tot maximaal 25% van de gevallen ontwikkelt het voorhoofd na 27 weken een rondere vorm met een 'positive' FP lijn positie en een maximum F afstand van 3.6 mm.
Vervolgens werd de FP lijn retrospectief getest in opgeslagen 3D volumen van 24 foetussen met een verdenking op een gezichtsafwijking of een syndroom met specifieke gelaatstrekken.
De FP lijn identificeerde correct 13 casussen met retrognatie, 5 casussen met 'frontal bossing' en 3 casussen met een 'sloping forehead'.
Wij concluderen dat de FP lijn zou kunnen dienen als referentielijn om vooral in het tweede trimester profiel anomalieën zoals een 'sloping forehead', retrognatie en 'frontal bossing' te identificeren, met de mogelijkheid om 'frontal bossing' te kwantificeren.

Hoofdstuk 7 laat zien hoe de MNM hoek wordt toegepast om retrospectief de positie van de premaxilla in foetussen met verschillende soorten en verschillende gradaties van ernst van lip/kaak/gehemelte spleten te onderzoeken. De FP lijn werd gebruikt om retrognathia als mogelijke mede oorzaak (confounder) van een vergrootte MNM hoek uit te sluiten.
De gemiddelde MNM hoek was normaal (> 5^{e} en < 95^{e} percentiel) in 9 casussen met een gespleten lip maar intacte bovenkaak (15.2^{o}, range: 12.5 – 16.9^{o}). In 24 casussen met een eenzijdige gespleten lip en bovenkaak met of zonder gespleten gehemelte was de gemiddelde MNM hoek 20.0^{o} (range: 13.3 – 26.2^{o}), boven het 95^{e} percentiel bij 79% (n = 19) en normaal in 21% (n = 5) van de casussen. In 14 casussen met een bilaterale gespleten lip, bovenkaak en gehemelte was de

gemiddelde MNM hoek 26.5^{o} (range: 19.2 – 33.7^{o}) en steeds boven de 95^{e} percentiel. In één geval met een Tessier 4 spleet was de MNM hoek boven het 95^{e} percentiel (25.2^{o}).
Wij vonden geen verschil in MNM hoek tussen de geïsoleerde casussen en casussen met andere afwijkingen.
Wij veronderstellen dat er normaal gesproken krachten zijn die de premaxilla naar voren duwen/trekken en dat de afwezigheid van naar voren verplaatsing van de premaxilla dus op pathologie kan duiden. Indien er naar voren verplaatsing van de premaxilla optreedt, wordt de mate van verplaatsing bepaald door verschillende krachten, die worden besproken.
Wij concluderen dat wanneer er een spleet in de bovenkaak aanwezig is, de premaxilla de neiging heeft zich naar voren te verplaatsen. De mate van verplaatsing varieert sterk vooral in de casussen met een bilaterale kaakspleet.

Hoofdstuk 8 richt zich op de beeldvorming en meetbaarheid van drie gezichts-markers, neusbeen lengte (NBL), 'prenasal thickness' (PT) en de 'frontomaxillary facial' (FMF) hoek, bij in totaal 219 normale foetussen in een retrospectief onderzoek met behulp van 3D multiplanar echografie. Beoordeling van de kwaliteit van de beelden en meetbaarheid van de markers vond plaats respectievelijk met 5-punts en 3-punts scoringssystemen. Honderdelf echobeelden kregen een hoge kwaliteit score. Hiervan werd een hoge meetbaarheid score significant vaker toegekend aan NBL (98.2%) en PT (97.3%) dan aan de FMF hoek (26.1%) ($p < 0.001$). De intra-observer 95% limits of agreement waren –1.03 en 0.86 mm, –0.61 en 0.76 mm en –8.18 en 5.29^{o}, voor respectievelijk NBL, PT en FMF hoek. De interobserver 95% limits of agreement waren –1.20 en 1.30 mm, –0.52 en 0.69 mm en –6.22 en 8.50^{o} voor respectievelijk NBL, PT en FMF hoek.
Een literatuuroverzicht evalueert aansluitend verschillen in definitie van meettechnieken van de individuele markers. We herdefinieerden de meettechniek voor NBL. In onze nieuwe techniek wordt het onderste deel van het voorhoofdsbot niet in de meting betrokken, zodat de meting niet te groot uitvalt.
In 3D volumen bleken NBL en PT reproduceerbare en relatief eenvoudig te meten markers, terwijl de FMF hoek meting een veel grotere uitdaging vormde. Wij presenteerden nieuwe referentiewaarden voor NBL en PT. Zowel NBL als PT namen toe in de zwangerschap, met minder uitgesproken toename na 28 weken voor NBL. Onze NBL vertoonde een systematisch kleinere afmeting dan NBL metingen in andere, op 2D echografie gebaseerde, publicaties.
Wij concluderen dat een goede visualisatie, die leidt tot kwalitatief hoogwaardige metingen, significant vaker mogelijk is voor de NBL en de PT dan voor de FMF hoek. Na meting in het exact midsagittale vlak en met uitsluiting van het frontale bot, zijn onze referentiewaarden systematisch kleiner dan de referentiewaarden in eerdere op 2D echografie gebaseerde publicaties.

Hoofdstuk 9 onderzoekt de PT/NBL ratio als een marker voor foetussen met trisomie 21.
De verhouding werd retrospectief onderzocht in 3D volumen van zowel normale als trisomie 21 foetussen.
De PT/NBL ratio, gemeten van 106 normale foetussen (in 3D volumen) was stabiel, met een gemiddelde van 0.61 (95% BI: 0.59-0.63, $r = –0.04$, $P = 0.7$). De 5^{e} en 95^{e} percentiel waren respectievelijk 0.48 en 0.80. De PT/NBL ratio, gemeten in 30 foetussen met trisomie 21 (10 op 2D beelden en 20 in 3D volumen), was significant hoger dan in normale foetussen ($P < 0.001$), maar ook stabiel, met een gemiddelde van 1.50 (95% BI: 1.20-1.8; $r = –0.35$, $P = 0.07$). Als de 95^{e} percentiel werd gebruikt als een cut-off waarde was het detectie percentage, de vals-positieve en positieve likelihood ratio respectievelijk 100 (95% BI: 89 tot 100)%, 5 (95% BI: 2-11)% en 21.2. Een

belangrijke waarneming is dat in normale foetussen de PT altijd ongeveer 2/3 (0.6) van de NBL bedraagt. Deze vaste verhouding maakt het eenvoudig een normale ratio te herkennen.
Wij concluderen dat de PT/NBL ratio zich kwalificeert als een zeer sterke tweede en derde trimester marker voor foetussen met trisomie 21.

Hoofdstuk 10 vergelijkt het effect van derde trimester 3D/4D met derde trimester 2D echografie van het foetale gezicht op de moeder, met speciale aandacht voor de moeder-foetus binding. Honderdzestig laag risico Caucasische vrouwen namen deel. Alle vrouwen vulden de Maternal Antenatal Attachment Scale (MAAS) 1-2 weken vóór en 1-2 weken na het echo-onderzoek in. De negentien (5-punten schaal) items van de MAAS vragenlijst onderzoeken twee aspecten: de kwaliteit van de binding en de tijd doorgebracht met positieve gedachten/gedragingen ten opzichte van de foetus. De echoscopist scoorde objectief, volgens een cijfer score van 1-4, de zichtbaarheid van het gezicht, op basis van de grootte van het deel dat zichtbaar was en de kwaliteit van het zichtbare deel van het gezicht. Alle vrouwen in beide groepen evalueerden subjectief de herkenbaarheid en de aantrekkelijkheid van het foetale gezicht volgens een cijfer score van 1-4. De 3D/4D groep werd gevraagd (door middel van een vragenlijst post-partum) of ze in een eventueel volgende zwangerschap weer 3D/4D echo onderzoek zouden willen ondergaan. Van 66 vrouwen uit de 3D/4D groep en 67 uit de 2D-groep waren de gegevens compleet en analyseerbaar.
We vonden dat zowel 3D/4D als 2D echografie de binding significant verhoogd (3D/4D: 3.5, 1.7, 1.5 en 2D: 3.0, 0.9, 1.8 voor toename van de respectievelijk totale score, kwaliteit score en tijd score, $P < 0.0001$ voor alle gevallen). De (sub)scores en de toename in (sub) scores waren niet significant verschillend tussen beide groepen. Alleen in de 3D/4D groep was het effect op de moeder-foetus binding significant sterker naarmate de zichtbaarheid en herkenbaarheid van het foetale gezicht beter was ($P = 0.003$ en $P = 0.042$).
Hoewel de scores voor de zichtbaarheid, herkenning en aantrekkelijkheid hoger waren in de 3D/4D groep was dit verschil niet statistisch significant (3D/4D: 2.8, 3.3, 3.1 en 2D 2.7, 3.0, 2.9 voor respectievelijk de zichtbaarheid, herkenbaarheid en aantrekkelijkheid). Slechts één vrouw vond de 3D/4D afbeelding van het foetale gezicht 'niet mooi', ondanks hoge scores voor zichtbaarheid en herkenbaarheid. Twee vrouwen vonden de 2D afbeeldingen van het foetale gezicht 'niet mooi', maar de gerapporteerde scores op zichtbaarheid en herkenning waren in deze gevallen ook laag. Vier vrouwen gaven aan niet meer een 3D/4D te willen in een eventueel volgende zwangerschap. Deze 4 vrouwen hadden lage scores voor de aantrekkelijkheid van de 3D/4D afbeeldingen, hoewel de zichtbaarheid en herkenbaarheid hoog scoorden. Maar zelfs voor deze vrouwen was er een stijging van de MAAS scores na de scan.
Wij concluderen dat vrouwen over het algemeen een positieve houding ten aanzien van zowel 2D als 3D/4D echografie van het foetale gezicht hebben. In de enkele gevallen dat de 3D/4D afbeeldingen door de moeder niet als een positieve ervaring wordt beschouwd lijkt dit geen negatieve invloed op de binding te hebben. De moeder-foetus binding neemt toe na zowel een 2D als een 3D/4D echo. Het effect van een 3D/4D echo op de binding is sterker naarmate met 3D/4D echografie het foetale gezicht betere zichtbaarheid en herkenbaar is.

Tenslotte presenteren we een overzicht van studies naar het psychologische effect van 3D/4D echografie op moeders, zwanger van een foetus zonder detecteerbare afwijkingen. Van dertien psychologische studies, evalueerden acht studies de moeder-foetus binding en vonden geen verschil tussen 3D/4D en 2D echografie. Het effect van 3D/4D echografie op tevredenheid of perceptie toonde tegenstrijdige resultaten en angst/stress vermindering was hetzelfde als na 2D echografie.

Samenvatting van de belangrijkste bevindingen

3D multiplanar echografie van het foetale profiel:

- De 3D multiplanar modus is essentieel voor het bepalen van het exacte midsagittale profiel vlak.
- Alignement van het foetale profiel is gemakkelijker rond de z-as dan de y-as van de foetus.
- Het gebruik van de 3D multiplanar modus verbetert de intraobserver reproduceerbaarheid.
- Vooral mandibula gerelateerde metingen hebben voordeel van 3D multiplanar echografie.

De MNM hoek

- is een veelbelovend instrument om door middel van objectivering van de voor achterwaartse positie van de kaken, de convexiteit van de foetale profiel vast te stellen,
- is stabiel tijdens het tweede en derde trimester van de zwangerschap met een gemiddelde van 13.5°.

De FP lijn

- is een relatief eenvoudig toe te passen referentielijn, die vooral in het tweede trimester gebruikt kan worden om voorhoofd en mandibula afwijkingen te detecteren.
- is het eerste tool om een 'sloping forehead' te identificeren en 'frontal bossing' te objectiveren.
- In maximaal 25% van de foetussen verandert het voorhoofd na 27 weken van een rechte vorm in een wat rondere vorm.

In foetussen met een spleet in de bovenkaak

- neigt de premaxilla zich naar voren te verplaatsen.
- is de mate van verplaatsing van de premaxilla beïnvloed door veel verschillende factoren.

Faciale metingen in screening op het trisomie 21:

- Er zijn verschillende definities in de literatuur voor de meetpunten van NBL, PT en de FMF hoek. Zorg moet worden gedragen dat de NBL meting niet het frontale bot omvatten.
- Bij het gebruik van 3D volumen zijn NBL en PT reproduceerbare en relatief eenvoudig te meten markers, terwijl meting van de FMF hoek een veel grotere uitdaging vormt.
- Op 3D multiplanar echografie gebaseerde normaal waarden van NBL, zonder inbegrip van het frontale bot, tonen systematische kleinere afmetingen dan in andere op 2D echografie gebaseerde publicaties.
- In normale foetussen is PT altijd ongeveer 2/3 van de NBL.
- De PT / NBL ratio kwalificeert zich als een zeer sterke tweede en derde trimester marker voor trisomie 21.

Moeder-foetus binding in het derde trimester van de zwangerschap:

- Zowel 3D/4D als 2D echografie van het foetale gezicht geven een significant versterking van de moeder-foetus binding.
- Het effect van 3D/4D echografie op de moeder-foetus binding is sterker naarmate de zichtbaarheid en herkenning van het foetale gezicht beter is.
- In de weinige gevallen waarin door de moeders de 3D/4D afbeelding van het foetale gezicht niet wordt beschouwd als een positieve ervaring is er geen meetbaar nadelig effect op de moeder-foetus binding.

APPENDIX

Abstracts

Dankwoord (acknowledgement)

List of publications

Curriculum vitae

Reference line for recognizing retrognathia is not applicable to 3D corrected profile images

Oral Poster at the 20th World congress on Ultrasound in Obstetrics and Gynecology
10-14 October 2010, Prague, Czech Republic.

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Objective

Before the advent of 3D ultrasound a line was proposed as tool to recognize retrognathia in daily ultrasound practice. The line, drawn in the profile view, has as landmarks the distal part of the nasal bone and the anterior border of the maxilla and in normal profiles is supposed to touch the anterior border of the mandible, but not in case of retrognathia where it remains at a distance from the mandible. In this study the line was tested in 3D corrected profile images of normal second and third trimester fetuses.

Methods

3D volumes of the fetal profile were acquired by Voluson 730 Expert (GE Healthcare) in 100 Caucasian women. The proposed reference line was drawn on by multiplanar mode corrected exact median profile images. The distance between the reference line and the mandible was measured by the 'distance between two lines' option.

Results

Median gestational age was 24 5/7 week (range 15 4/7-36 4/7 weeks). In only 1 case the reference line touched the frontal border of the mandible. In the other 99 cases the median distance between mandible and reference line was 3.3 mm (SD: 1.3 mm, range: 0.8-6.5 mm).

Conclusion

The proposed reference line is not suitable for the exclusion of retrognathia in 3D corrected profile images.

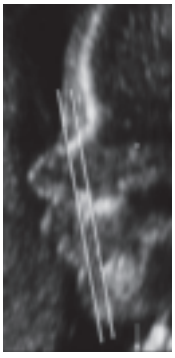

Figure 1 In this normal fetus the reference line remains at 4.0 mm distance from the mandible.

How flat is the profile, measured with the MNM angle, in second and third trimester trisomy 21 fetuses?

Oral Poster at the 20th World congress on Ultrasound in Obstetrics and Gynecology
10-14 October 2010, Prague, Czech Republic.

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Objective
The MNM angle, defined as the angle between the lines maxilla-nasion and mandible-nasion in the exact median plane, enables objective evaluation of the anteroposterior relationship of the jaws. Fetuses with trisomy 21 are known to have a flat profile caused by underdevelopment of the maxilla. This study evaluates the MNM angle in second and third trimester trisomy 21 fetuses.

Methods
Databases were searched for digitally stored 3D volumes and images of the fetal profile in second and third trimester trisomy 21 fetuses. The MNM angle was measured in good median 2D images and in by multiplanar mode corrected images from 3D volumes. Measurements in the trisomy 21 fetuses were compared with the reference range derived from 3D volumes of 241 euploid fetuses in an earlier study. Volumes and images were acquired by Voluson 730 Expert and Voluson E8 (GE Healthcare).

Results
In the 241 euploid fetuses (median gestational age: 24 + 5 weeks, range:15 + 4 – 35 + 4 weeks) the mean MNM angle was 13.53° (95% Ci: 13.28°–13.78°, range: 8.96°–19.58°). The MNM angle was measured in 19 trisomy 21 fetuses (15 on 3D volumes, 4 on 2D images) at a median of 21 + 6 weeks (range: 14 – 34 + 5 weeks). In trisomy 21 fetuses the mean MNM angle was 10.74° (95% Ci: 9,38 – 12,10, range: 6.19° – 14.99°) and, similarly to euploid fetuses, did not change with gestational age (r = 0.22, P = 0,36). The MNM angle was significantly smaller in trisomy 21 fetuses (P = 0.001) and was below the mean or 5th percentile in 84.2% and 36.8% of the cases, respectively.

Conclusions
The MNM angle is significantly smaller in second and third trimester trisomy 21 fetuses and in 37% of the cases is below the 5th percentile. Measurement of the MNM angle may be used for counselling together with other markers, when trisomy 21 is suspected.

Assessment of facial height and facial width in the second and third trimester of pregnancy, preliminary results

Oral Communication OC20.04 at the 22th World congress on Ultrasound in Obstetrics and Gynecology 9-12 September 2012, Copenhagen, Denmark.

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Objectives

To study facial height (FH) and width (FW) within one 3D volume as objective measurements for facial shape, by assessing feasibility, inter- and intraobserver reproducibility and establishing normal values. The results were compared with pathological cases.

Methods

Volumes taken slightly off the exact midsagittal plan of the profile were used. After multiplanar correction FH was measured from the nasion (most anterior point in the midline at the intersection of frontal and nasal bone) to the gnathion (lowest point in the midline of the mandible). FW was measured, on the clearest side, just below the orbits in the axial plane with the 'distance-between-two- lines' option from midsagittal to the most lateral point on the cheekbone and doubling it. 192 healthy Caucasian fetuses, 11 with trisomy 21, 3 with bilateral facial clefts and 1 with Apert syndrome (32 weeks) were included.

Results

The intraclass correlation coefficient for inter- and intraobserver variability was > 0.98 for both FH and FW. FH and FW increased significantly from 1.48 to 5.08 cm (FH = −16.1 + 3.8 x logGA, r^2 = 0.93) and from 2.20 to 6.42 cm (FW = −17.2 + 4.2 x logGA, r^2 = 0.85) respectively.
The measurements of the cases with trisomy 21 and bilateral clefts were within the normal range, apart from two trisomy 21 cases with a FH exceeding the 95th percentile, one trisomy 21 case with a FW below the 5th percentile and two cleft cases with a FH below the 5th percentile. The case with Apert syndrome had a FH near the 95th and a FW above the 95th percentile.

Conclusion

The feasibility and inter- and intraobserver reproducibility of FH and FW measurements within one volume are good. FH and FW increase logarithmic with gestational age. FH and FW can quantify the facial shape and may assist in distinguishing between normal and abnormal facial shapes.

3/4D ultrasound and maternal-fetal bonding: second versus third trimester

Poster at the 22th World congress on Ultrasound in Obstetrics and Gynecology
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Objective
To compare the effect of 2nd versus 3rd trimester 3/4 dimensional ultrasound (3/4D US) on maternal-fetal bonding.

Methods
173 healthy Caucasian women completed the Maternal Antenatal Attachment Scale 1-2 weeks before (MAAS1) and 1-2 weeks after (MAAS2) a 2nd or 3rd trimester 3D/4D US examination. A subset of the total score (Total) explores quality (Q) and another part the time (T) spent in attachment mode, i.e. being positively aware of the fetus. Visibility (V) was scored by the ultrasonographer and recognition (R) and attractiveness (A) of the 3/4 D images were assessed by the mother according to a graded score from 1-4. A Voluson 730 Expert was used in both groups. Socio-demographic, obstetric and ultrasound characteristics were noted. T- or Chi-square-tests were used for statistics.

Results
107 2nd trimester (T2) and 66 3rd trimester (T3) women participated. Socio-demographic (age, education, smoking, living with partner), obstetric (planned pregnancy, assisted conception, primigravidity, first trimester screening) and ultrasound characteristics (BMI, amniotic fluid, placenta location) were not different between the groups (P > 0.05 for all). T2 had lower Total, T and Q MAAS1 scores than T3 (74.0 vs. 77.0 (P = 0.002); 24.9 vs. 27.1 (P < 0.001); 44.9 vs. 45.6 (n.s.). The MAAS 2 scores were not significantly different (79.2, 27.4, 47.2 vs. 80.5, 28.6, 47.3, respectively). Increases in Total, T and Q scores were greater in T2 than in T3 (5.2 vs. 3.5 (P = 0.010); 2.5 vs. 1.5 (P = 0.017); 2.3 vs. 1.7 (n.s.)). The scores on V, R and A were similar in both groups (T2: 2.1, 1.7, 1.9, T3: 2.2, 1.7, 1.9). Only in T3 women, the increases in Total and T scores were significantly correlated with V (P = 0.003; P = 0.044) and R scores (P = 0.006, P = 0.001).

Conclusions
Increase in maternal-fetal bonding following 3/4D US is greater in the 2nd trimester. In the 3rd trimester the effect on maternal-fetal bonding of 3D/4D US is stronger at better degrees of visibility and recognition.

Dankwoord

Eind 2005 schreef ik de maatschap Gynaecologie van het St. Antonius Ziekenhuis Nieuwegein (destijds bestaand uit: Lucie Ribbert, Erik van Beek, Pepino Graziosi, Jessica van der Leij, Jules Schagen van Leeuwen, Sien The en Bas Veersema) een brief met het verzoek om steun voor wetenschappelijk onderzoek t.b.v. een promotie. Mijn verzoek werd uitermate positief beantwoord. Het vertrouwen dat de maatschap steeds in mij toonde, de tijd die mij werd gegund en de tegemoetkomingen die ik mocht ontvangen heb ik nooit als 'vanzelfsprekend' beschouwd en ik ben blij dat dit proefschrift er nu ligt. Ook de maatschapsleden van na de fusie wil ik betrekken in mijn dank: Michael Kars, Wilma Monincx, Adriënne Blankhart, Annet Bouwmeester, Arne van Heusden Joost Lange, Jur Oosterhuis en Elly Vernooij.

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Utrecht, november 2012
Els de Jong-Pleij

List of Publications E.A.P. de Jong-Pleij

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Winner of prize for the best free communication presentation in the category Fetal Anomalies.
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Curriculum vitae

De auteur van dit proefschrift werd geboren in Maastricht als Elisabeth Anna Paulina Pleij. Zij woonde tot haar vierde jaar in Maastricht en groeide daarna verder op in Utrecht. Zij behaalde haar Atheneum-B diploma aan het St. Bonifatius college Utrecht. Haar medicijnen studie volgde ze aan de Universiteit van Utrecht. Het laatste jaar coschappen werden gelopen in het Catharina Ziekenhuis in Eindhoven, waar zij ook haar eerste baan vond als arts-onderzoeker en zich specialiseerde in de verloskundige en gynaecologische echoscopie. In 1992 verhuisde ze terug naar Utrecht en ging werken in het St. Antonius Ziekenhuis in Nieuwegein, waar zij de afdeling echoscopie opstartte, die uitgegroeid is tot een op volle toeren draaiend 10 koppige afdeling, satelliet van het Universitair Medisch centrum Utrecht. In 1991 trouwde ze met haar grote liefde Cees de Jong. Samen hebben ze 2 kinderen Julia (1992) en Jelle (1994).

'…en 't is tesaam zo weinig wat de dokters weten.'

Regel uit het gedicht 'Ik noem uw kleine naam nog',
een rouwgedicht naar aanleiding van een perinatale sterfte.
Circa midden 20e eeuw
Auteur onbekend

'... and it's all together, so little that doctors know.'

Line from the poem 'I still call your tiny name',
a mourning poem following a perinatal mortality.
Approximately mid-20th century
Author unknown