Ultrasound Obstet Gynecol 2010; **35**: 377–384
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/uog.7639

Editorial

Fetal micrognathia: almost always an ominous finding

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WHY AN EDITORIAL ON MICROGNATHIA?

The fetal mandible is a common site for defects induced by a large number of genetic conditions and adverse environmental factors. Its complex development, described briefly below, requires several elements from different embryonic components to interact and fuse, both among themselves and with the cranial neural crest cells; this multistep process is highly susceptible to a series of molecular and genetic insults. These elements explain why an abnormal form of mandibular development, i.e. micrognathia, is a characteristic feature of a long list of chromosomal and non-chromosomal conditions, a good number of which are detectable in the fetus.

A search for the word 'micrognathia' with no time limits in the OMIM website[1], retrieved 363 hits. The conditions that can be associated with micrognathia and for which prenatal diagnosis is deemed feasible are reported in Tables 1–4[2].

NORMAL DEVELOPMENT

Concurrent with the nasal capsule becoming a crucial cartilaginous structure of the developing embryonic skeleton, the Meckel's cartilages begin to provide support to the mandibular arch, which derives from the first branchial arch during the 7^{th} and 8^{th} gestational weeks, when the primary mandibular joint is formed. This structure is functional until the 16^{th} week of pregnancy, when the secondary temporomandibular joint develops. The body of the mandible forms as a rectangular membranous bone lateral to the Meckel's cartilage, with the condyles developing posteriorly to and separately from the mandibular bone at 8–12 weeks; they eventually fuse with the latter at 13 weeks. The harmonic development of different anatomical entities, such as the Meckel's cartilage, the inferior alveolar nerves, the mandibular body and the condylar and coronoid processes, as well as the overall growth of the mandible, depend upon several factors[3]: interactions between the oral epithelium and underlying mesenchyme, prenatal activity of the masticatory muscles, growth of the tongue, the inferior alveolar nerve and its branches, and development and migration of the teeth. An important role in this developmental process is also played by the cranial neural crest cells, a cell population that originates in the dorsal neural tube and migrates into the branchial arches[4]. In particular, signaling interactions between the ectoderm of the branchial arches and the postmigratory neural crest cells are critical for subsequent organogenesis of mandibular process derivatives such as teeth, Meckel's cartilage and mandibular bone.

ABNORMAL DEVELOPMENT

The normal development of the mandible can be disrupted by genetic factors (chromosomal and non-chromosomal syndromes) or environmental ones. For example, environmental factors are involved in the severe micrognathia characteristically present in neuromuscular conditions such as FADS (fetal akinesia deformation sequence): in this case, it is the fixed contracture of the temporomandibular joint that prevents opening of the mouth and, consequently, normal development of the mandible. In extreme cases, the same mechanism may also cause

Table 1 Syndromic conditions primarily involving the mandible

Syndromic condition	*Other features potentially detectable* in utero	*Inheritance*	*Prenatal diagnosis reported*
Acrofacial dysostosis	*Preaxial limb deficiencies*, CHD, CNS anomalies	AD	Yes
Treacher–Collins (Franceschetti) type			
Rodriguez type	*Preaxial limb deficiencies*, CHD	AR	Yes
Nager type	Microcephaly, *preauricular tags*, CHD, *preaxial limb defects: radial aplasia, syndactyly, missing toes*	Sporadic	Yes
Miller (Genee–Wiedemann) type or POADS (postaxial)	*Syndactyly, thumb hypoplasia, postaxial limb defects:* absence of fifth digit	AR	—
Branchio-oculofacial S.	Microcephaly, *ear anomalies*, hypertelorism, *microphthalmia*, renal anomalies, *polydactyly, vermian agenesis*	AD	Yes
Cerebrocostomandibular S.	*Microcephaly*, CHD, *small thorax, abnormal ribs*, renal ectopia, polyhydramnios	AD-AR	Yes
Mandibuloacral dysplasia	Joint contractures, wide cranial sutures	AR	—
Orofaciodigital I S.	*Facial asymmetry, bifid tongue, polycystic kidney, syndactyly, CNS anomalies*	X-linked dominant	Yes
Orofaciodigital II S. (Mohr)	*Hypertelorism, polydactyly, porencephaly*	AR	Yes
Oromandibular-limb hypogenesis spectrum	Acral hypoplasia, syndactyly	Sporadic	—
Otopalatodigital S., Type II	Hypertelorism, omphalocele	X-linked dominant	—
Robin sequence	(Glossoptosis, cleft palate)		Yes

Most common signs in the fetus are in italics. AD, autosomal dominant; AR, autosomal recessive; CHD, congenital heart defects; CNS, central nervous system; POADS, postaxial acrofacial dysostosis; S., syndrome.

Table 2 Skeletal and neuromuscular diseases frequently associated with micrognathia

Disease	*Other features potentially detectable* in utero	*Inheritance*	*Prenatal diagnosis reported*
Achondrogenesis, Types IA and IB	Severe *micromelia*, short ribs	AR	Yes
Amyoplasia congenita disruptive sequence*	Diffuse *joint contractures, gastroschisis*, polyhydramnios	Sporadic	Yes
Atelosteogenesis, Type I	Frontal bossing, *midface hypoplasia, small thorax*, 11 ribs, *rhizomelia*, talipes, *encephalocele*, polyhydramnios	Sporadic	Yes
Campomelic dysplasia	Large anterior fontanel, hypertelorism, CHD, *small thorax*, sex reversal in males, hydronephrosis, *bowing of tibiae and less so of femora*	AD	Yes
Cerebro-oculofacioskeletal (COFS) S.	Microcephaly, *microphthalmia*, CHD anomalies, *flexion contractures*	AR	Yes
Chondrodysplasia punctata, X-linked dominant type*	Microcephaly, rhizomelia	X-linked dominant	Yes
Diastrophic dysplasia*	*Hitchhiker thumbs*, scoliosis, short limbs	AR	Yes
Langer mesomelic dysplasia	*Mesomelia*	AR	Yes
Multiple pterygium S.	*Pterygia* of neck, axillae, antecubital region, popliteal region	AR	Yes
Neu–Laxova S.	*Microcephaly, exophthalmos, CNS anomalies, joint contractures, syndactyly, subcutaneous edema*	AR	Yes
Pena–Shokeir phenotype (FADS)	*Diffuse joint contractures, cystic hygroma*, microstomia	AR	Yes

Most common signs in the fetus are in italics. *Micrognathia occasionally. AD, autosomal dominant; AR, autosomal recessive; CHD, congenital heart defects; FADS, fetal akinesia deformation sequence; S., syndrome.

microstomia, due to paralysis of the mouth orbicular muscles.

Definitions

Agnathia

Agnathia is the most severe form of mandibular maldevelopment. Also known as otocephaly, this is an exceedingly rare anomaly in which there is complete derangement of facial development, with agenesis or severe hypoplasia of the mandible, juxtaposition of the temporal bones and abnormal position of the ears, which are horizontal and may also be fused. The postulated pathogenetic mechanism is a complete arrest of mandibular development, which would induce the other abnormalities[5].

Table 3 Chrosomomal syndromes frequently associated with micrognathia

Chromosomal syndrome	*Other features potentially detectable* in utero	*Inheritance*	*Prenatal diagnosis reported*
Cat-eye S.	*Preauricular tags, TAPVR*, renal agenesis	AD inv dup (22)(q11)	Yes
Deletion 3p S.	Microcephaly, malformed ears, polydactyly of the hands	Del 3p	—
Deletion 4p S. (Wolf–Hirshhorn)	Hypertelorism, *preauricular tags, CHD*, polydactyly, talipes, *CNS anomalies*	Isolated, 4p16.3	Yes
Deletion 5p S. (Cri du cat)	Microcephaly, hypertelorism, CHD	5p15.2	Yes
Deletion 9p S.	Trigonocephaly, abnormal ears, hypertelorism, CHD	AD, isolated	—
Deletion 11q S.	Trigonocephaly, microcephaly, joint contractures		—
Deletion 13q S.	Microcephaly, CHD, small/absent thumbs	Isolated	—
Deletion 22q11.2 S.	*Conotruncal CHD, thymus aplasia*	AD	Yes
Monosomy X (Turner) S.	*Left-sided CHD, cystic hygroma*	Sporadic	Yes
Pallister–Killian S.	*Thin upper lip, CDH, CHD*, CNS anomalies, *rhizomelia*	Sporadic	Yes
Triploidy S.	*IUGR, hypotonia, hypertelorism, syndactyly, CHD, CNS anomalies*	Sporadic, 69,XYY	Yes
Trisomy 8 mosaic S.	Hypertelorism, joint contractures	Sporadic	Yes
Trisomy 9 mosaic S.	Joint contractures, CHD	Sporadic	Yes
Trisomy 13 S.*	IUGR, *microcephaly, microphthalmia, cleft lip/palate, CNS anomalies (HPE), CHD, renal anomalies, polydactyly*	Sporadic	Yes
Trisomy 18 S.	*Clenched hands, CHD, omphalocele, renal anomalies, CHD anomalies*	Sporadic	Yes

Most common signs in the fetus are in italics. *Micrognathia occasionally. AD, autosomal dominant; AR, autosomal recessive; CDH, congenital diaphragmatic hernia; CHD, congenital heart defects; CNS, central nervous system; del, deletion, inv dup, inverse duplication; HPE, holoprosencephaly; IUGR, intrauterine growth restriction; S., syndrome; TAPVR, total anomalous pulmonary venous return.

Micrognathia and retrognathia

Both micrognathia and retrognathia involve abnormal, arrested development of the mandible, but the former refers to the size of the mandible whereas the latter refers to its position in relation to the maxilla. In most cases, these two abnormalities are concurrent, as a small mandible is by definition abnormally positioned. However, the opposite is not always true: there are rare situations in which there is retrognathia but not micrognathia.

SONOGRAPHY

Normal fetal mandible

The fetal mandible can be studied by ultrasound from 10 weeks of gestation virtually until term, if the position of the fetal head is favorable. Axial planes in particular are used to assess the mandibular bone (Figure 1a), the alveolar ridge (Figure 1b) and the rami (Figure 1c); the uppermost plane corresponds to the maxilla (Figure 1d). Three-dimensional ultrasound allows precise alignment of orthogonal planes in which accurate measurements can be made and allows creation of rendered casts of the irregularly shaped mandibular bone (Figure 2). Several growth charts of the mandible have been published over the last 10 years, deriving measurements from two-dimensional and three-dimensional images[6–8].

Micrognathia

The prenatal ultrasound diagnosis of micrognathia can be made subjectively or objectively. Subjective diagnosis is carried out by evaluating the midsagittal view of the facial profile and assessing the geometric relationship between the mandible and the rest of the profile (Figure 3). To assist in objective diagnosis, a number of studies have reported the use of indices[9,10], ratios or facial angles[11]. In particular, the two most reported methods are the inferior facial angle (IFA)[11] and the jaw index[9]. The former is measured in a midsagittal view of the fetal profile at the crossing of two lines: one orthogonal to the vertical part of the forehead, drawn at the level of the synostosis of the nasal bones; and a second joining the tip of the mentum and the anterior border of the more protrusive lip. Its normal value is 65° (SD, 8°)[11]. The jaw index is measured on an axial view of the fetal mandible. A line is drawn connecting the bases of the two rami (laterolateral diameter) and the anteroposterior diameter is then measured, drawing a second line from the symphysis mentis to the middle of the laterolateral diameter. This value is normalized to the biparietal diameter to derive a ratio (the jaw index) which is independent of gestational age. In the original articles describing them, both ratios proved effective in diagnosing micrognathia: sensitivity and specificity were 100% and 98.9% for the IFA and 100% and 98.7% for the jaw index[9,11]. In my own recent series of 19 cases, the two methods showed fair correlation (Figure 4). The advantage of the IFA is that it can be also measured retrospectively on a midsagittal view of the fetal profile; however, if the fetal position is

Table 4 Other non-chromosomal syndromic conditions associated with micrognathia

Syndromic condition	*Other features potentially detectable* in utero	*Inheritance*	*Prenatal diagnosis reported*
Aniridia–Wilms tumor association	Nephroblastoma (Wilms)	AD (11p13)	
Baller–Gerold S.	Hypertelorism, microstomia, CHD, renal anomalies, absent radius, absent thumbs	AR	—
Carpenter S.*	Brachycephaly, *partial syndactyly, polydactyly, CHD*	AR	—
de Lange S.	Microcephaly, *CHD, CDH*, renal anomalies, *phocomelia*	AD, isolated	—
Dubowitz S.	Microcephaly, microphthalmia	AR	—
Femoral hypoplasia-unusual facies S.	Focal *femoral hypoplasia, cleft lip/palate*, maxillary hypoplasia	Sporadic	Yes
Fetal aminopterin/methotrexate S.	Microcephaly, mesomelia, talipes	Sporadic	—
Fetal valproate S.*	CHD, joint contractures	Sporadic	—
Fryns S.	*CDH*, microphthalmia, *CHD*, omphalocele, GI anomalies, renal anomalies, *CNS anomalies*	AR	Yes
Hallermann–Streiff S.	Microcephaly, microstomia, wide cranial sutures	Sporadic	—
Hydrolethalus S.	Microphthalmia, *CHD*, CDH, *preaxial polydactyly*	AR	Yes
Lenz–Majeweski hyperostosis S.*	Hypertelorism, macrocephaly, syndactyly	Sporadic	—
Marden–Walker S.	Microcephaly, wide cranial sutures, dextrocardia, kidney anomalies, joint contractures, CNS anomalies	AR	—
Marshall–Smith S.	Cataract, hypertelorism, flat nasal bridge	AD	—
Meckel–Gruber S.	*Encephalocele, CNS anomalies, polycystic kidneys, polydactyly*	AR	Yes
Melnick–Needles S.	Large fontanel, omphalocele, bowed mesomelic bones, clubfeet	X-linked dominant	—
Miller–Dieker S.	*Microcephaly*, CHD, duodenal atresia, omphalocele, renal anomalies, *lissencephaly*	AD	Yes
Moebius sequence	Microphthalmia, limb deformities	AD isolated	—
Noonan S.*	*Cystic hygroma*, enlarged NT, CHD, abnormal ductus venosus	Sporadic	Yes
Oculo-auriculovertebral spectrum (Goldenhar)	*Hemifacial microsomia* (microtia, microphthalmia), *preauricular tags*, hemivertebrae	Sporadic	Yes
Opitz G/BBB S.	CHD, renal anomalies, CNS anomalies	AD	—
Pallister–Hall S.	IUGR, microphthalmia, microtia, CHD, micropenis, hemivertebrae, polydactyly	AD	—
Peters' plus S.	IUGR, rhizomelia, CHD	AR	Yes
Radial aplasia-thrombocytopenia (TAR) S.*	*Bilateral radial aplasia*, hypoplasia of ulnae	AR	Yes
Restrictive dermopathy	*Hypertelorism, joint contractures*, rocker-bottom feet, polyhydramnios	AR	Yes
Retinoic acid embryopathy	Microtia, CHD, CNS anomalies	Sporadic	—
Roberts-SC phocomelia	IUGR, *cleft lip/palate,* hypertelorism, *hypomelia*	AR	Yes
Rubinstein–Taybi S.*	Microcephaly, *beaked nose, abducted and large thumbs/toes,* CNS anomalies	Sporadic	Yes
Seckel S.	*Microcephaly, arachnoid cysts, beaked nose*, talipes	AR	Yes
Smith–Lemli–Opitz S.	Microcephaly, syndactyly, genital and renal anomalies, CHD, talipes	AR	Yes
Toriello–Carey S.	*Agenesis of corpus callosum, CHD*	AR	Yes
Yunis–Varon S.	IUGR, microcephaly, large fontanels, agenesis of thumbs/toes, absence/hypoplasia of clavicle(s)	AR	—
Zellweger S.	CNS anomalies, large fontanels, *joint contractures, hepatomegaly*	AR	—

Most common signs in the fetus are in italics. *Micrognathia occasionally. AD, autosomal dominant; AR, autosomal recessive; CDH, congenital diaphragmatic hernia; CHD, congenital heart defects; CNS, central nervous system; GI, gastrointestinal; IUGR, intrauterine growth restriction; NT, nuchal translucency; S., syndrome.

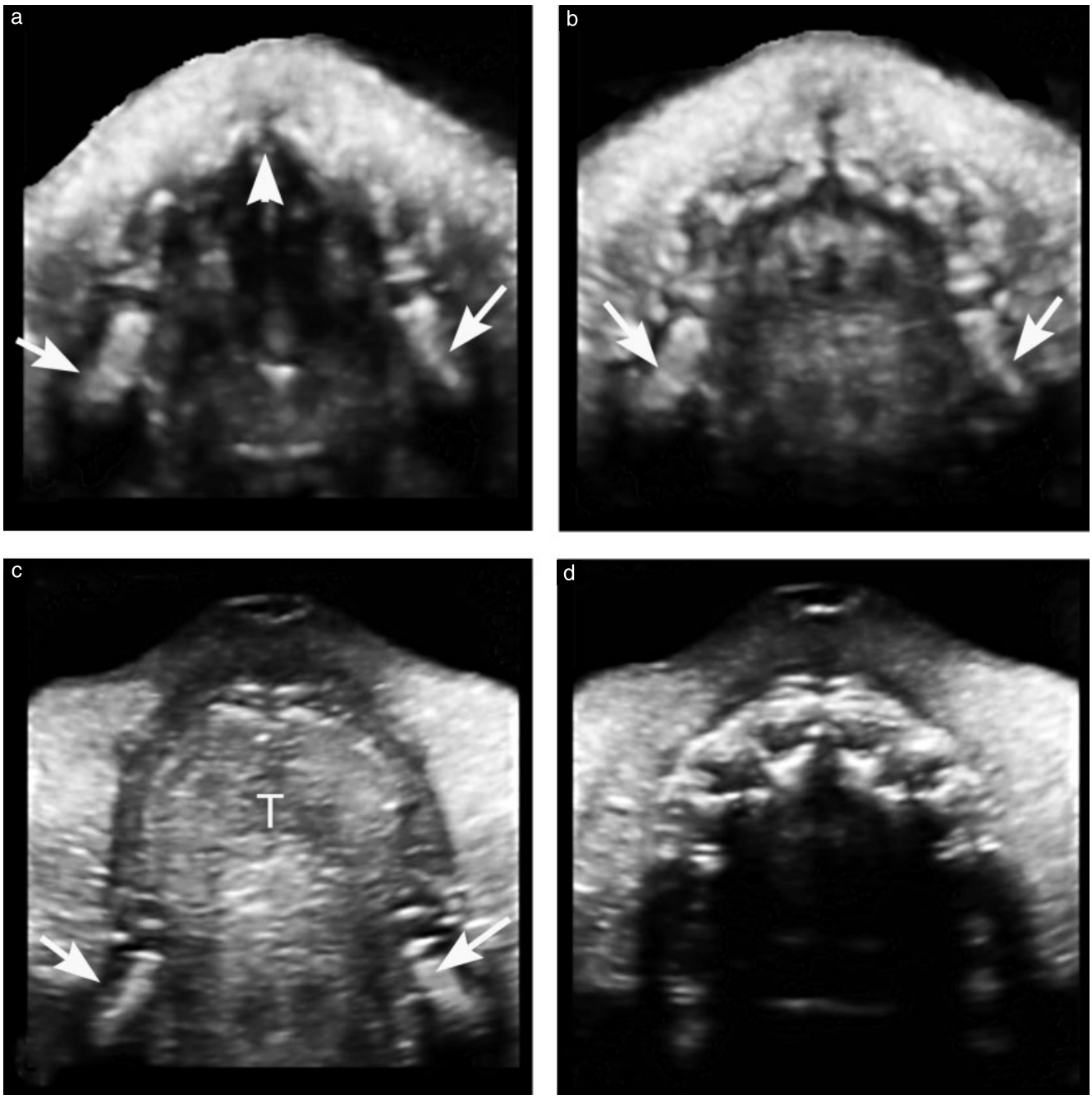

Figure 1 Volume contrast imaging of a normal fetal mandible at 28 weeks of gestation: axial views at different levels. (a) The lowermost plane is used to assess the acutely angled mandibular bone; the symphysis is evident (arrowhead) as are the rami (arrows); (b) a plane just cranial to that of the mandibular bone shows the alveolar ridge, with the rami (arrows); (c) a higher plane at the level of the tongue (T) demonstrates the rami (arrows); (d) the uppermost plane shows the maxillary alveolar ridge.

not favorable, the IFA cannot be measured. In contrast, the jaw index can be measured even if the fetal profile is not readily visible, because it requires only an axial view of the mandible. However, occasionally, shadowing from one side may reduce visualization of the whole mandibular bone, making measurement less precise.

SYNDROMIC CONDITIONS ASSOCIATED WITH MICROGNATHIA IN THE FETUS

There are many syndromes associated with micrognathia. As evident from Tables 1–4, diseases that are associated with impaired mandibular development can be classified into four groups: primary mandibular disorders (Table 1), skeletal and neuromuscular diseases (Table 2), chromosomal aberrations (Table 3), and a variety of other non-chromosomal syndromic conditions (Table 4). The first group of diseases includes the Robin anomalad[12], the various forms of acrofacial dysostosis (Treacher–Collins or Franceschetti, Rodriguez, Nager, Miller or Genee–Wiedemann) and orofaciodigital syndromes. Among skeletal dysplasias, due to the fixed contracture of the temporomandibular joint there can be

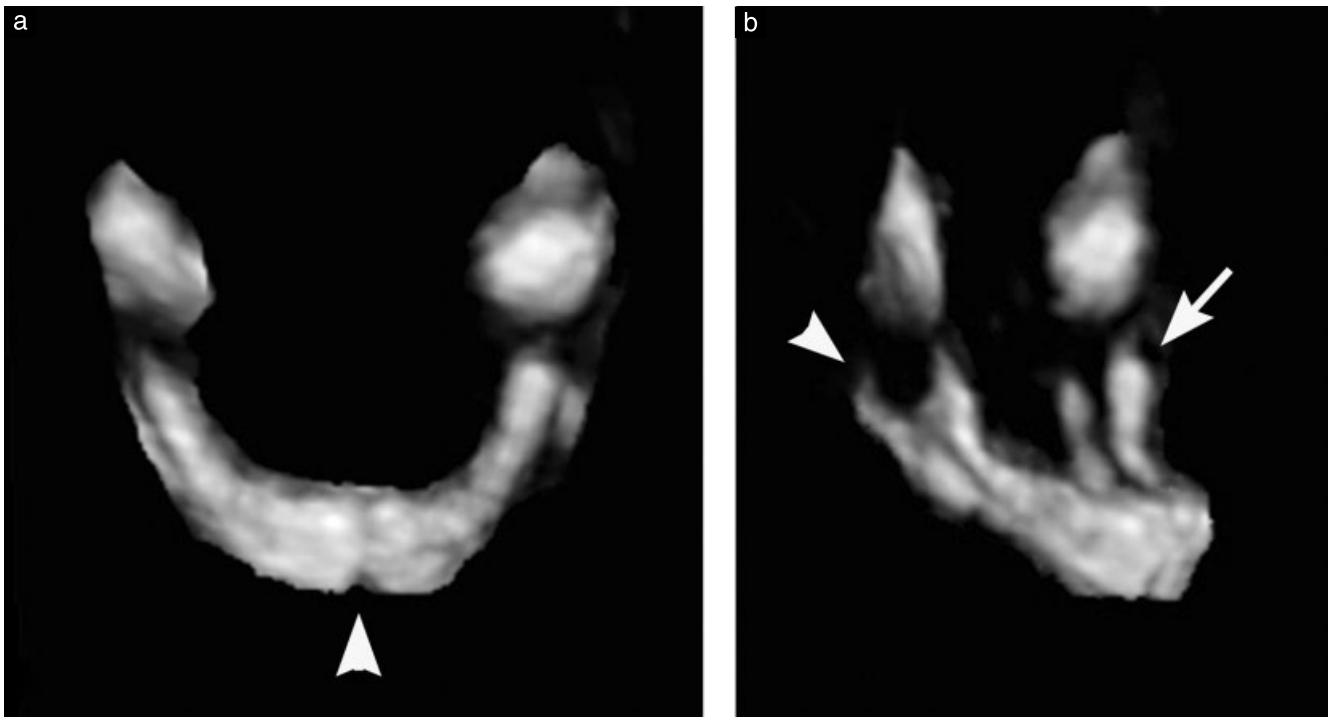

Figure 2 Three-dimensional rendering (maximum mode) of the normal fetal mandible at 20 weeks of gestation. (a) Frontal view, with symphysis indicated by the arrowhead; (b) lateral oblique view, with coronoid (arrow) and condylar (arrowhead) processes clearly visible bilaterally.

a variable degree of mandibular hypoplasia present in achondrogenesis and campomelic dysplasia, occasionally in diastrophic dysplasia, and in the entire group of neuromuscular conditions. However, the group of diseases that accounts for most cases of micrognathia in the fetus is chromosomal aberrations. In fact, micrognathia has been reported at autopsy in 80% of cases of trisomy 18 and triploidy[2],[13] and, conversely, an abnormal karyotype has been found in 66% of fetuses with micrognathia[14]. My group's figures differ somewhat from those reported by Nicolaides *et al.*[14] in 1993, possibly due to the time elapsed since then and the higher prenatal detection rates of the various non-chromosomal conditions associated with micrognathia. Combining the historic series we published roughly 10 years ago[9] with cases diagnosed over the last 10 years in our Fetal Medicine Unit gives a total of 50 cases of micrognathia. Twenty-two (44%) of these were associated with chromosomal aberrations, including 17 cases of trisomy 18, two cases of trisomy 13 and one case each of del4p (cri du chat), del 5p (Wolf–Hirshhorn) and trisomy 16p. Of note, the association with an abnormal karyotype was 82% in the historic series of 11 cases (9/11) and 31% in the more recent series (12/39), wherein there was a prevalence of neuromuscular diseases (FADS and related disorders) and non-chromosomal syndromes (e.g. acrofacial dysostosis, orofaciodigital syndrome) in addition to the classic Robin sequence. Also of note, as for other conditions, with the increased uptake of nuchal translucency (NT) screening for aneuploidies, the most severe cases of micrognathia tend to be diagnosed at the time of the NT scan (Figure 5).

MAKING A PROGNOSIS

The most important steps to take when micrognathia is detected in the fetus are: 1) to check whether there are associated anomalies that may point to a non-chromosomal syndrome; 2) to determine the karyotype in order to exclude primarily trisomy 18 but also the other abnormal arrangements that may be associated with micrognathia (Table 2); 3) to consider Robin sequence as a likely diagnosis only if the finding is isolated, and especially if glossoptosis is also found[15]. This is a condition that, if managed appropriately after birth, is associated with normal life expectancy and good quality of life. However, prior to considering micrognathia as an isolated finding and, consequently, to making a diagnosis of isolated Robin sequence, it should be borne in mind that $>80\%$ of individuals with Pierre–Robin sequence will ultimately be diagnosed with a syndrome[16]. It is needless to underscore that this figure may be expected to be even higher in the fetus, as not all syndromic signs are amenable to prenatal ultrasound diagnosis.

A final issue to consider is the risk of recurrence. As evident from Tables 1–4, most conditions associated with micrognathia are inherited as either an autosomal dominant or a recessive trait. This should be taken into account in prenatal counseling and a detailed autopsy or postnatal clinical evaluation is warranted in order to provide the couple with a reliable estimate of the risk of recurrence.

CONCLUSION

In conclusion, there is evidence that the mandible and the maxilla–mandible complex can be studied

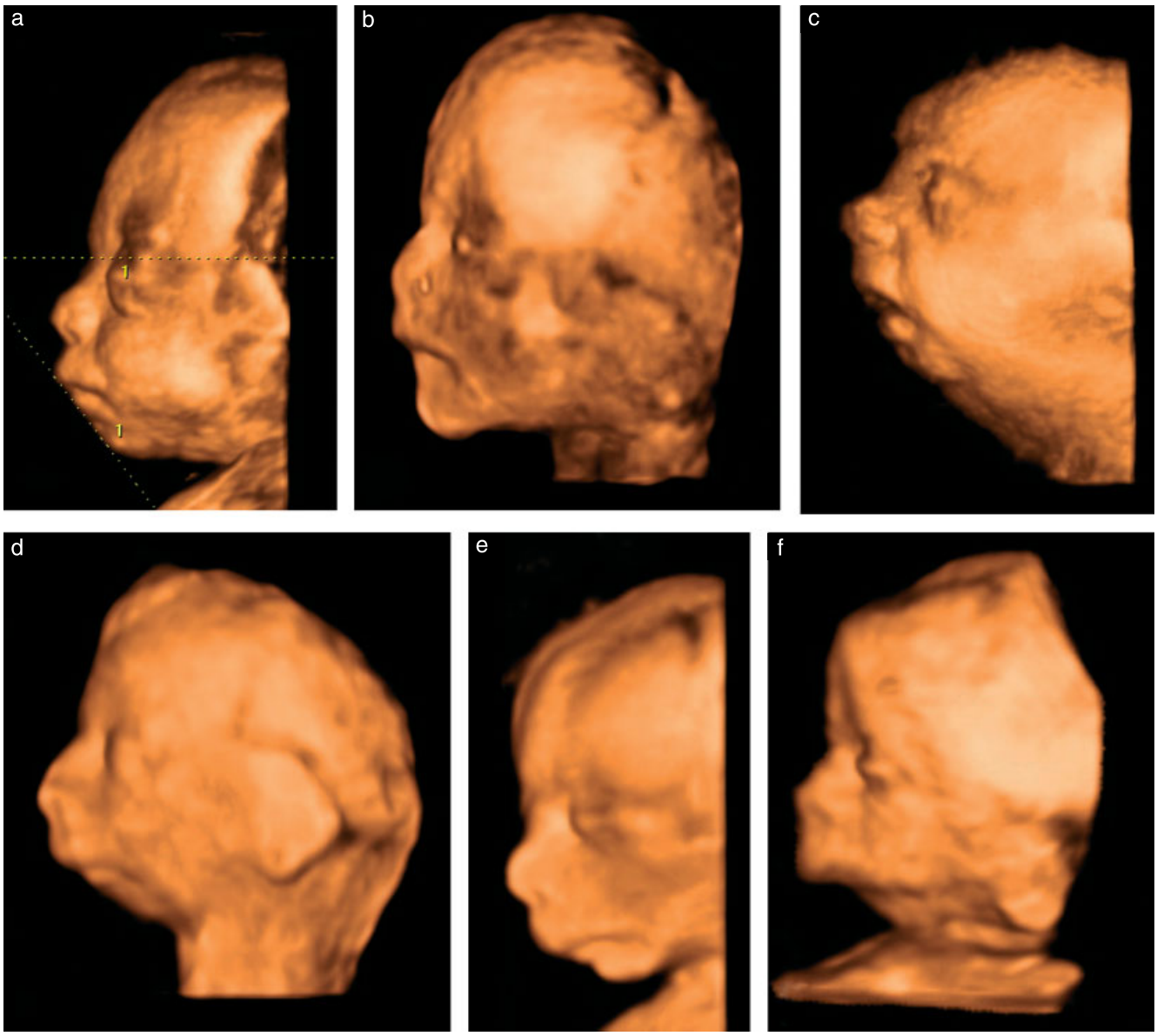

Figure 3 Three-dimensional rendered images of fetuses with syndromic micrognathia. (a) Fetus with multiple anomalies at 23 weeks of gestation; (b) orofaciodigital syndrome at 22 weeks; (c) fetal akinesia deformation sequence (FADS) at 28 weeks; (d) and (e) acrofacial dysostosis in the same patient at 22 and 21 weeks, respectively; (f) another case of acrofacial dysostosis at 19 weeks.

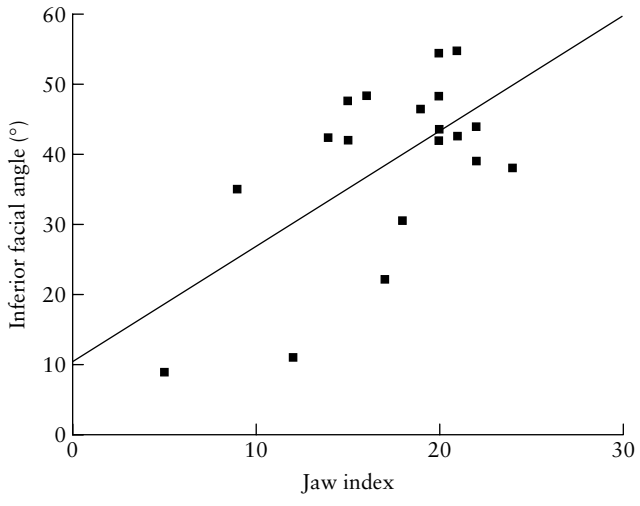

Figure 4 Correlation between inferior facial angle and jaw index in 19 cases of fetal micrognathia.

thoroughly in the fetus, with both two-dimensional and particularly three-dimensional ultrasound. In addition, with the more recent high-resolution ultrasound systems, micrognathia is often detected at the time of the NT scan. The mandible represents a common site for defects associated with genetic conditions, a good number of which can be recognized prenatally (Tables 1–4). However, differential diagnosis can be very challenging, and not all subtle syndromic signs can be detected on prenatal ultrasound. Hence, caution should be adopted when diagnosing an apparently isolated Robin sequence prenatally, because it has been demonstrated that in $>80\%$ of cases a syndromic component will eventually be found, and this will affect the final prognosis.

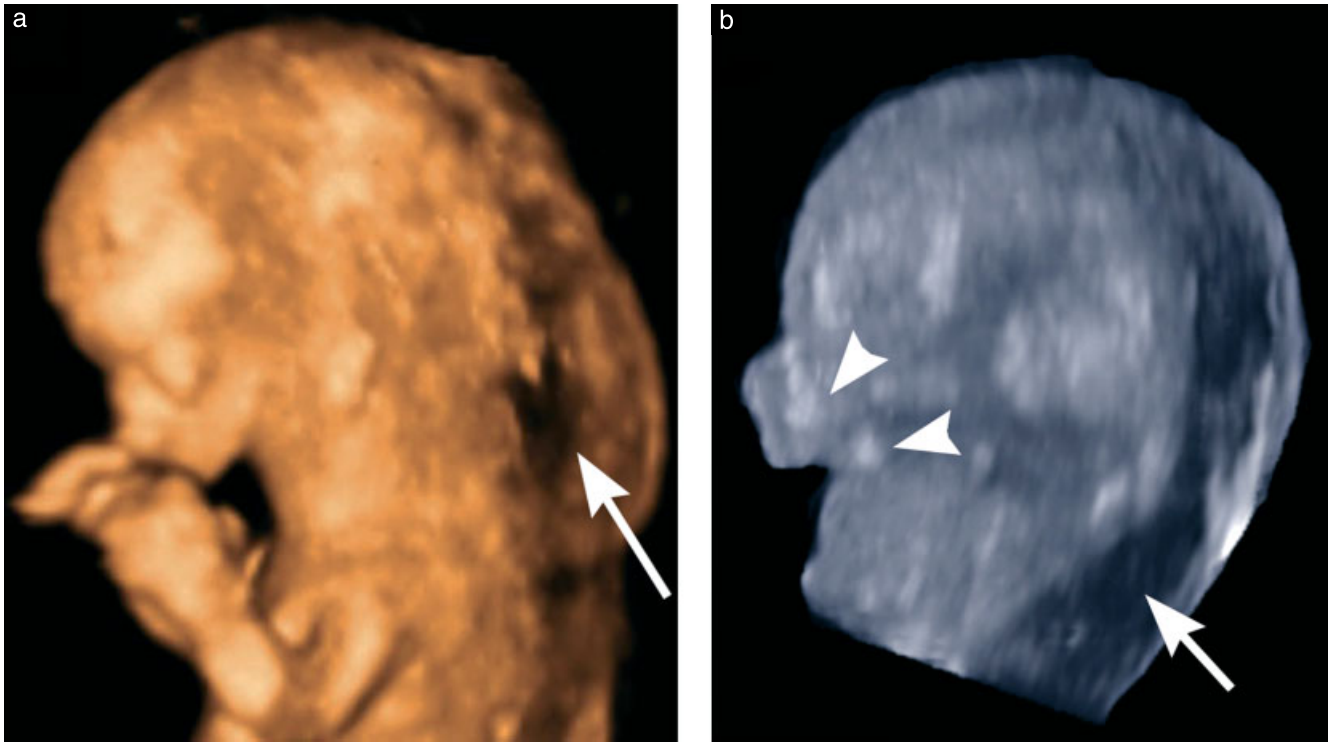

Figure 5 Early diagnosis of micrognathia at the time of nuchal translucency (NT) screening. (a) Three-dimensional surface-rendered image at 13 weeks of gestation. Note the extreme micrognathia and the severely enlarged NT (arrow). (b) Three-dimensional maximum mode rendered image in a case of apparently isolated Robin sequence at 12 weeks of gestation; the two arrowheads indicate the maxilla and the mandible and the arrow indicates the enlarged NT.

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