REVIEW ARTICLE

Can intrauterine surgery improve the quality of life of cleft lip and palate patients?

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It has already been shown that some congenital anomalies are amenable to intrauterine surgical correction, which may be life-saving. However, post-operative premature labour and its extreme invasiveness are considered as major drawbacks for "open" intrauterine surgery, mainly due to the performed hysterotomy. More recently the merger of fetoscopy and advanced video-endoscopic surgery leave to expect a possible application of the feto-endoscopic surgical approaches in the future also by non life-threatening conditions, such as the craniofacial malformations (i.e. cleft lip and palate).

The intrauterine intervention presents the following advantages: (a) scarless wound healing in mid-gestation, (b) interruption of the malformation's cascade of detrimental secondary effects (no occurrence of secondary maxillary growth restrictions), (c) reduction or minimal need of secondary corrections or additional post-natal treatments, and (d) minor morbidity, at least when the endoscopic approach is applied. These advantages would lessen the psychological and financial burden of multiple surgeries and therapies for the young patient with a cleft lip and palate, the patient's family, and the society in general.

Nevertheless, further research is needed to make intrauterine procedures safer, and to achieve such results that would minimize or even eliminate the need of additional post-natal treatments. This way it could be possible to provide a better quality of life to these patients and their families.
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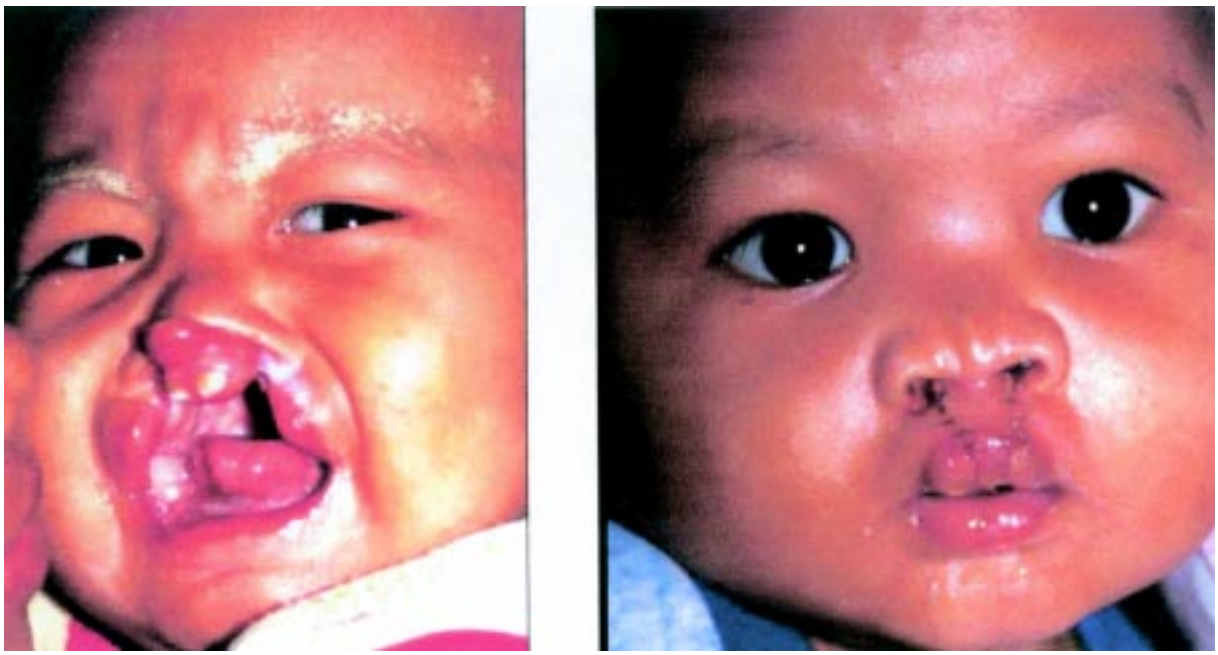
Cleft lip (CL) with or without cleft palate (CP) is one of the most common structural birth defects of the craniofacial area, which appears in humans[1,2]. They usually appear between the 4th and the 6th gestation week when the lip and primary palate develop (CL, cleft alveolus and palate [CAP] or CLP) or in the 9th gestation week, when the secondary palate develops, leading to the creation of clefts of the secondary palate[3-5]. Their etiology is complex, including multiple genetic and environmental factors, since clefts can occur as a result of chromosomal aberrations, or in conjunction with many congenital syndromes that present craniofacial implications[1,2,4-13]. Recent advances in both molecular biology and genetics have begun to identify candidate genes responsible for the rare syndromic or for the more common and complex non-syndromic forms of clefts.

For a patient with CL, CP or CLP, the anomalies can be either mild or severe and can cause complex distortion in the facial structures (Fig. 1). CLP patients often require a prolonged treatment over the first 21 years of life by a multidisciplinary team, including multiple surgeries, speech therapy, psychological support, as well as dental and orthodontic treatments[1,3,4,11,14,15]. The number of operations necessary to achieve satisfactory final results depends on the type and degree of the patient's cleft and associated problems.

All surgical interventions as well as orthodontic treatment have an impact on the craniofacial growth of the young patient and their consequences differ according to the extent of the cleft and the techniques used for its correction. In addition, clefting causes problems with feeding, speech, hearing, as well as emotional problems.

Classification incidence and etiology of cleft lip and palate

Oral clefts can simply be classified as CP alone or cleft lip with or without cleft palate (CL/P). CP may involve soft and hard palates, or just the soft



A. B.

Figure 1. *A newborn infant with a complete bilateral cleft of the lip and palate, as well as forward displacement of the premaxillary segment and medial collapse of the lateral maxillary segments (A). Appearance immediately following repair using the straight line closure technique (Veau III) (B). (Photo courtesy of Dr. Heinrich Schoeneich, Interplast Germany e.V. Munich)*

palate, but hard palate alone it very rarely observed. CL/P can be further divided into CL alone and CLP. Despite the high frequency and serious implications of CLP both their etiology and the precise mechanisms of the their normal development are not yet well known.

More than 400 syndromes have been already associated with CLP[16]. The incidence of CLP in European populations is approximately 1:700 births, varying from 1:500 to 1:2500 births according to race and sex[2,12,17]. The incidence of CL/P is approximately twice that of CP, thus CL/P is most common in males[18], while CP is more common in females[19]. In addition, the left side is affected twice as often as the right[20]. Asians, American Indians, Alaskans, Japanese and have a higher incidence of CLP in comparison to Caucasians, while Negroid races have a lower incidence of oral clefting[7,20-23]. Maternal age can also influence the likelihood of children with clefts[19].

Children of epileptic mothers have a greater risk than the general population for congenital malformations, possibly including CP[18,24]. Anti-epileptic, corticosteroid or prednisolone medication during the first trimester of pregnancy has also been implicated in CP[25-28]. Finally, alcohol consumption and cigarette smoking seems to play also an important role in cleft etiology[29-35].

Laboratory studies have identified numerous genes and molecules with an involvement in non-syndromic cleft development, and although candidate genes have been associated with some cases of orofacial clefting, no single gene mutation responsible for all cleft cases has yet been discovered[36-56].

Craniofacial growth and development in patietns with untreated clefts

Facial growth of patients with CL/P has been studied intensively over the past decades, due to the fact that these patients exhibited different facial growth than the noncleft individuals. However, it is difficult to distinguish intrinsic growth characteristics from iatrogenic effects because nearly all patients with clefts receive some surgical intervention early in life.

The length as well as sagittal maxillary development is often severely affected in patients with repaired CPs. However, most authors have found little effect on this dimension on patients with unrepaired CPs[57-66]. In addition, many authors have observed normal growth or premaxillary protrusion in patients with unrepaired CLP[59,60,63,67-70].

Clinical management of patients with cleft lip and palate

A child with CL, CP, or other craniofacial anomalies may present additional multiple and complex problems. These could include: (a) early feeding and nutritional problems that can lead to deficits in growth and development, (b) middle ear problems, (c) hearing loss, (d) deviations in speech and resonance, (e) dento-facial and orthodontic abnormalities, and (f) possible psychosocial adjustment problems. Although the habilitative process for children with cleft and craniofacial deformities can be a lengthy one, the availability of coordinated, interdisciplinary team care has enabled most affected children to become functioning and contributing members of society.

In 1991, the American Cleft Palate-Craniofacial Association (ACPA) has developed standards for the special needs of children born with CL/P and other craniofacial anomalies[15]. According to the Parameters for Evaluation and Treatment of Patients with Cleft Lip/Palate or Other Craniofacial Anomalies the CPT team is a group of experienced and qualified professionals from medical, surgical, dental, and allied health disciplines working in an interdisciplinary and coordinated system, representing many of the following disciplines. The Cleft Palate Team (CPT): (a) consists of an operating surgeon, orthodontist, speech-language pathologist, and at least one additional specialist from otolaryngology, audiology, pediatrics, genetics, social work, psychology, and general pediatric or prosthetic dentistry, who meet face-to-face at least six (6) times per year to evaluate and develop treatment plans for its patients, (b) evaluates at least 50 patients per year, (c) has at least one surgeon who operates on at least 10 primary CL/Ps per year, (d) coordinates treatment and insures that each patient is evaluated by a primary care physician, and (e) insures that its members attend periodic continuing education programs about CLP[71].

Interdisciplinary team care should begin shortly after birth and continues until the physical growth of an individual has been completed - around 21 years of age. Since skeletal changes continue throughout childhood and soft tissue growth is influenced by the changes, evaluation throughout the maturation process is recommended. Psychosocial adaptation should also continue to be monitored as it may remain a concern until maturity. The professionals on these teams provide care regularly for a reasonable number of patients in a facility with the resources necessary for such care. Each team should provide following care in a multidisciplinary manner: audiologic care, CL/P surgery, cranio- and maxillofacial surgery, dental care, genetic/dysmorphology services, nursing care, otolaryngologic care, pediatric care, psychological and social services, and speech-language services

Due to the large number and the complexity of the various surgical and orthodontic treatment procedures needed for the complete rehabilitation of cleft patients, these two approaches will be discussed in a more comprehensive way in this paper. Although the treatment protocol for the surgical and orthodontic care of CLP patients can differ between each country around the world and within each center, a typical treatment sequence is listed in Table 1.

A. Surgical treatment procedures for patients with cleft lip and palate

Treatment of CLP patients is generally performed in two stages: primary and secondary[72]. ***Primary*** CLP care is usually performed in the first 5 years of life and includes presurgical orthopedics, initial lip repair, initial palate repair, lip-nose revision, and correction of residual velopharyngeal insufficiency. ***Secondary*** CLP care usually begins after age 8 years and includes secondary lip repair, orthodontics and facial orthopedics, and repair of the alveolar and/or maxillary bone defects and correction of any associated facial skeletal disharmonies.

Lip surgery

There are numerous surgical techniques of the original rotation-advancement repair, including modifications and variations, which have been proposed over the years concerning primary lip closure, such as measures to lengthen the columella, increase the size of the lateral advancement flap, and improve nasal symmetry[73]. Many authors believe that primary repair of the unilateral CL and nose needs to be performed in conjunction with muscular reconstruction of the lip[74-83]. Nasal form has frequently been incompletely repaired by most techniques concerning primary lip closure. Therefore, numerous modifications of the primary nasal correction have been introduced[84-93]. The timing of CL repair generally varies from several days of age to 6 months[75,76,91,94]. The ***"rule of 10s"*** is still used and appropriate: weight of at least 10 pounds, hemoglobin of 10%, and an age of at least 10 weeks. Though, no clear evidence exists to justify early surgery around the neonatal period at this time.

Table 1. *Surgical / Orthodontic treatment protocol for Cleft Lip and Palate patients*

Age of patient	Surgery	Orthodontics
0 - 3 days	Counseling and information to the parents	Counseling
1 - 4 weeks	Regular ENT check until adulthood	Presurgical infant orthopedics if undertaken
2 weeks - 6 months	Primary lip closure	
3 - 9 months	Early soft palate repair if undertaken	
18 - 24 months	Surgical closure of the palate Primary bone grafting if undertaken	
2 - 5 years	Early secondary bone grafting if undertaken	
3 - 6 years	Nasoendoscopy and/or surgical pharyngoplasty	Early orthodontics / Primary dentition treatment
6 - 11 years	Secondary bone grafting Surgical secondary lip closure Surgical closure of fistulae	Mixed dentition treatment
11 – 14 years		Comprehensive orthodontics / Permanent dentition treatment
17 – 19 years	Orthognathic surgery Lip / Nose revision	Orthodontics in conjunction with orthognathic surgery

Surgical closure of the soft and hard palate

(a) ***Periosteoplasty.*** Periosteoplasty was introduced by Skoog as a method of "boneless bone grafting"[95]. (b) ***Surgical closure of the hard palate.*** Following the introduction of the relaxing incisions[96] and the use of mucoperiosteal hard palate flaps[97], a variety of mucoperiosteal flaps have been proposed for closure of the hard palate cleft, such as the Veau-Wardill-Kilner V-Y pushback, the two-flap palatoplasty, and Langenbeck's bipedical flaps[98-101]. (c) ***Surgical closure of the soft palate.*** The procedures concerning soft palate repair included initially lengthening of the palate in order to perform velar closure[98-100]. Later, Kriens (1969) proposed the intravelar veloplasty, an actual repositioning of the abnormally placed muscles to reconstruct the levator sling, and Furlow (1978) presented the double-reversing Z-palatoplasty[102]. It seems that anatomic repositioning of the displaced musculature is an important feature in soft palate repair and can contribute to an improved outcome.

Alveolar bone grafting

While the concept of grafting of the cleft maxilla was introduced in the early 1900s by Lexer[103], only later reports advocated cortical grafting of maxillary clefts in both infancy and later childhood[104]. The goals of this procedure include: (a) the stabilization of the maxillary arch, (b) elimination of oronasal fistulae, (c) creation of bony support for subsequent tooth eruption, and (d) reconstruction of the hypoplastic piriform aperture and soft tissue nasal base support. An important issue in alveolar cleft management remains the timing of bone grafting. Alveolar bone grafting can be performed in patients younger than 2 years of age (primary), between 2 and 5 years of age (early secondary), as well as in patients older than 5 years of age (secondary). Secondary grafting is currently the most commonly used approach.

Surgical pharyngoplasty

Orofacial clefting is the most common cause of velopharyngeal insufficiency (VPI)[105-109]. VPI is the inability to completely close the velopharyngeal port during speech. The resultant leakage of air into the nasal cavity during speech can cause hypernasal vocal resonance and nasal emissions. Possible therapeutic approaches to VPI include palatal lengthening procedures (such as the Furlow double-opposing Z-plasty or various types of pushback palatoplasties), and surgical pharyngoplasty (attachment of a posterior pharyngeal flap or construction of a sphincter pharyngoplasty).

Orthognathic surgery

A significant number of patients with CL/P develop maxillary deficiency. This high incidence of

maxillary retrusion requires orthognathic surgery in approximately 25% of the CLP patients[110-120]. Many factors contribute to the development of maxillary deficiency in cleft patients. Earlier surgical repairs play a significant role in deficient maxillary growth and development[121], due to the mechanical molding action of the muscles and the tight and scarred tissues[122,123]. Treatment of maxillary deficiency by the conventional orthognathic surgical approaches requires waiting until skeletal maturity. However, in some children with CL/P, severe midfacial deficiency can be apparent early in life. For these children maxillary distraction osteogenesis is an alternative approach to the delayed treatment after skeletal maturity is completed[124]. Most authors favor LeFort I osteotomy for the correction of sagittal maxillary deficiency in cleft patients, while the LeFort II osteotomy in some patients with midfacial retrusion, and the LeFort III osteotomy in cleft patients with retrusion of the nose, infraorbital rims, and malar eminences can be applied.

B. Orthodontic treatment procedures for patients with cleft lip and palate

Patients with CLP usually require an extensive and prolonged orthodontic treatment parallel to the surgical treatment. Orthodontic treatment may be required[125]: (a) in infancy, before initial surgical repair of the lip, (b) during the primary dentition period, (b) during the mixed dentition period, (c) during the permanent dentition period and (d) in the late teens after completion of facial growth, in conjunction with orthognathic surgery.

Presurgical orthopedic treatment during infancy

The introduction of passive realignment of the hard palate shelves has been introduced by McNeil and later by Burston[126,127]. This orthopedic approach makes CLP repair easier and may improve the aesthetic outcome of primary CL nasal repair by repositioning the alar base[85,128]. However, unless the appliances used are continued throughout the period of facial growth, their long-term influence on facial growth and dentition remains still a matter of discussion[129,130].

Primary dentition treatment

Orthodontic intervention in the primary dentition has been recommended over the past 60 years, although less in recent years[131-136]. Suggested treatment at that time ranged from full banding[137] to routine arch expansion[133,138-144].

Mixed dentition treatment

Numerous authors have described the beneficial effects on dental and skeletal growth development of cleft patients through the elimination of functional and structural problems at this developmental stage[133,145-149]. The most common procedures for this purpose include: (a) maxillary expansion to correct the reduced transverse dimension, (b) incisor alignment and proclination to remove crowding, rotations, and anterior crossbites, as well as (c) maxillary protraction to reduce maxillary retrusion.

Permanent dentition treatment

Many authors report an increasing frequency of permanent dentition treatment, which is possible using the common orthodontics approaches as for non-cleft patients[133-136,149]. Since the routine use of bone grafting, space closure in the cleft site has become a desirable and achievable goal to eliminate the need for artificial replacement teeth (Fig. 2). In these cases in which space closure is not possible, the use of adhesive bridgeworks[150] or of implants[149,151-155] in the grafted alveolar ridge has become a treatment of choice. A further possibility is the transplantation of a lower premolar to the upper arch[150,156,157].

Orthodontics in conjunction with orthognathic surgery

The development of effective orthognathic surgical techniques in the 1970s and 1980s has provided orthodontics with the means to complete treatment of almost all cleft patients. The use of three-dimensional cephalometry, computed tomography, and scanned dental models[158-160], video imaging[161,162], and computer-generated images[163] have all contributed to the improvement of orthognathic surgery planning. Although initially developed for non-cleft orthognathic surgery, the use of these applications in cleft patients has been increased rapidly.

The influence of treatment procedures on craniofacial growth and development in patients with cleft lip and plate

In addition to any intrinsic growth deficiency, facial growth in CLP may be affected as a result of surgical repair, orthodontic treatment, and functional adaptations. Since the landmark studies of Graber[164-165], which documented severe three-dimensional maxillary collapse in patients with complete clefts following surgical repair, numerous other cephalometric studies have been published describ-

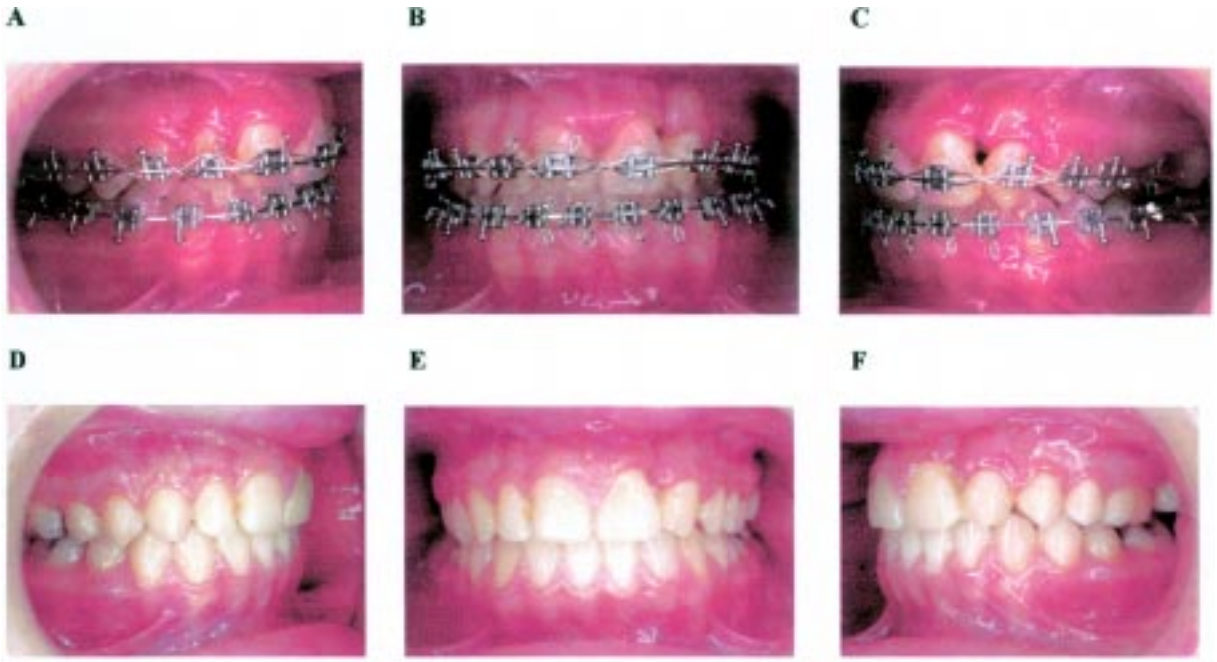


Figure 2. *Intraoral photographs of a patient with UCLP after orthodontic space closure.* ***A-C,*** *With the fixed orthodontic appliances in mouth,* ***D-F,*** *after appliance removal. (Reprinted with permission, Papadopulos NA, Papadopoulos MA. Cleft Lip and Palate. In: Isfer EV, ed., Medicina Fetal: Diagnøstico Pré-Natal e Conduta. (Fetal Medicine: Pre-Natal Diagnosis and Management). 2nd edition, Rio de Janeiro, Brazil: Revinter 2003, in press)*

ing varying degrees of maxillary sagittal deficiency[110,166-174]. It seems that all surgical interventions have an impact on the craniofacial growth of the young patient and their consequences differ according to the extent of the cleft and the techniques used for its correction[14].

By reviewing the literature, it would appear as if relatively little has been accomplished over the past 50 years in resolving the controversies surrounding bone grafting, periosteoplasty, presurgical orthopedics, timing of surgeries and bone and soft tissue healing. However, it is obvious that more research is needed to improve the current status of the clinical management of CL/P patients in order to decrease treatment time and to minimize or avoid the numerous interventions needed for their complete rehabilitation until the 21st year of their lives. Therefore efforts should be done not only in clinical directions, but also in others fields, such as genetics, molecular biology and intrauterine surgery.

Experimental intrauterine surgery for the treatment of cleft lip and palate

According to clinical experience, fetuses with isolated CL have been proposed as the potentially ideal patients for future fetal operations[175], since the scarless wound healing - an intrinsic characteristic of the midgestational skin in animal models, as well as in humans - leave to expect a more normal midfacial growth and an excellent aesthetic result.

Therefore, concerning the clinical application of the intrauterine correction of CLP, it could be possible to reduce or minimize the necessity of secondary operations, as well as of orthodontic treatment and logotherapy, which normally accomplish the postnatal treatment of this malformation. A clear relief of the psyche of the child and of its parents could be further take advantage of the fetal repair. Thus, craniofacial intrauterine surgery might become in the future, due to the promising results, the treatment method of the choice.

However, due to the results achieved until today, it can be stated, that the intrauterine approach cannot be recommended nowadays by CLP malformations on humans. The high morbidity and mortality risk for mother and fetus do not justify under any circumstances a prenatal operation.

A. Fetal wound healing

In 1979 Rowlatt reported that in a 20 weeks old human fetus, skin wounds healed with mesenchymal proliferation and without scar formation[176]. The outstanding properties of fetal wound healing are the absence of polymorphonuclear leukocytes, the absence of an acute inflammation, a prompt re-

epithelialisation and the highly organized wound collagen[177,178]. Unique characteristics of fetal cells, extracellular matrix, cytokine profile, and gene expression contribute to this scarless wound healing, which appears to be intrinsic to the fetal skin and independent of the intrauterine environment. The scarless healing is an advantage, that can prevent functional, as well as aesthetic problems resulting from the healing with scars. This characteristic of the fetus, to be able to heal wounds without scar formation, was examined also in different animal models, such as mouse, rat, rabbit, pig, sheep and monkey[177]. However, substantial differences exist in the scarless wound healing of these animal models. Additionally, a scarless healing procedure depends on a set of various factors as *gestational age*[178,179,180], *wound size*[181], *organ specificity*[182-191], *species*[192-196], *hyaluronic acid and fibroblasts*[178,180,182,197-201], *collagen*[202-204], *oxygen*[192,203], *growth factors*[178,201,205], *homeobox genes*[201,206-208], *tenascin*[195], and *interleukine*[209-220].

In some animal species, like monkey, sheep, rat and the mouse, one can observe a so-called "*transitional phase*". This stage concerns a provisional phase of wound healing, where the collagen architecture is reticular as in the fetal unwounded skin, however, the ability to regenerate epidermal appendices is lost. In the humans this age seems not to be before the 24th gestational week[221].

B. Animal models for intrauterine CLP repair

As the techniques of intrauterine procedures improve, feto-endoscopic surgery for non-life threatening malformations such as the craniofacial disorders will likely occur. Therefore, the experimental intrauterine correction of CLP in the last years has been mainly performed through the endoscopic approach, or after hysterotomy, gaining in this way enough information and experience for a further planed feto-endoscopic approach on the human fetus[191,222-228]. This latter technique has, as mentioned above, two major advantages. First, the inherent characteristics of the fetal wound healing, which is, in contrast to adults, scarless[176,177,202,229,230]. Second, a decreased fetal and maternal morbidity, which means minor PPROM risk (**P**reterm **P**remature **R**upture **O**f the fetal **M**embranes)[231].

The understanding and the investigations in the area of fetal wound healing and CLP repair have been advanced simultaneously with fetal surgery[177,193]. It was also in the field of intrauterine CL repair where the first feto-endoscopic suturing has been reported[232].

In the last two decades, numerous studies report approaches of intrauterine repair of CLP. It is evident that the intrauterine treatment of CLP is a challenging procedure for the surgeon, despite the fact that much progress that has been done in the last 40 years, towards a better understanding of this malformation. Requirements are very pretentious, since lip and palate have to be aesthetically and functionally similar to the normal. For these reasons, intrauterine treatment has captured the interest of craniofacial surgeons, since this method may offer following advantages: scarless wound healing at mid-gestation[177], interruption of the cascade of detrimental secondary effects of this malformation, i.e. no occurrence of secondary maxillary growth restrictions[199,230,233-235], and the decreased need or no need at all for secondary corrections or additional treatments such as orthodontic, dental, logopedical, psychological or other aftercare. These potential advantages of intrauterine surgery would reduce the psychological and economic burden of multiple surgeries on the small patient with a cleft lip and palate, the patient's family, and society in general.

Different animal models have been developed to better understand the etio-patho-physiology of this malformation and to test these hypothesis. Each model has its advantages and disadvantages, and can be classified into one of two principal groups: (a) ***Small, short gestation animals*** such as rats, mouses, and rabbits, with fetal manipulation possible only at late gestation, when the postoperative intrauterine period is short and scarless healing has passed. Interestingly, in 7-12% of A/J mouse (term=19 days) the formation of CLs is intrinsic and can reach nearly 100% if phenytoin is applied[233,234,236]. Histologic confirmation of epithelialization and no gross evidence of scar at 48 to 72 hours was found. In the widespread used *rabbit* model (term=32 days), scarless healing of surgically created clefts has been documented, as well as their long term cephalometric analysis with the evidence of minimal maxillary growth retardation due to the lack of scarring[202,203,229,230,237-242]. (b) ***Large, long gestation animals*** such as the non-primate *sheep* (term=145-150 days) and the primate *monkey* (term=165-180 days), which facilitate fetal manipulation at mid-gestation, providing the possibility of a longer postoperative intrauterine period for observation of scarless wound healing, enabling this way the realization of longterm developmental studies[191,222-228,235,243-248]. The longer intrauterine time period after surgical intervention is crucial for the in-utero treatment of CL, since healing without scars is influenced by gestational age, size, and ten-

sion[180,181]. Finally, these large animals allow multiple fetal procedures during the same gestation, which enables surgical creation of a cleft and its subsequent delayed repair, as well as its long-term maxillary growth analysis[224,248-251].

Endoscopic CLP repair

Feto-endoscopic technology gain increasingly attention by craniofacial surgeons since this method could offer following advantages: high resolution for diagnostic procedures, lower invasiveness to the uterus and the fetus, reduced postoperative premature labour combined with the availability of fetal monitoring, and reproducible access without need of laparotomy. Thus, fetal manipulation can be performed in its natural environment without concern of great risks usually associated to open fetal surgery. Although the risk to traumatize the fetus and the membranes is much lower than in open fetal surgery, it still may have to be dealt with feto-endoscopic surgery, as it is documented in several reports[231].

One of the first demonstrations ever reported, was the feasibility of feto-endoscopic suturing in the mid-gestational pregnant sheep model[232,252,253]. The authors' hypothesis that such minimal invasive procedures might decrease the incidence of preterm labour and fetal and maternal morbidity has been in generally confirmed. This technique has found a widespread acceptance, application, and development in the feto-endoscopic treatment of life threatening malformations[231,252,254].

In the field of CLP repair, this minimal invasive technique has been proposed in combination with the use of microclips in the mice and sheep model, which notably decreased operative time[225,236,255]. After the first reports of Bruner about the use of feto-endoscopic surgery for the coverage of myelomeningocele, the interest of the craniofacial surgeons has increased tremendously, probably because this was the first report of the intrauterine treatment of a non-life threatening malformation in the human fetus[256-258]. Taking advantage of this technique, different studies have been proposed in large, long gestational animal models: the non-primate and the primate models[222-227,259].

Clinically relevant models for intrauterine CLP repair

Since a large animal model with an intrinsic CL malformation is not available, the suggestion by Hedrick et al (1996), who proposed the surgical creation of an 2 mm excisional fetal CL, including the alveolus, in the sheep fetus at 60 days of gestational age and repairing it two weeks later after wound's edges re-epithelialisation, was a significant step to make this animal model clinically relevant[249,250]. A further modification/development of this model came from the team of Stelnicki proposing the application of the endoscopic approach technique in the second stage, following the cleft lip creation in the 60 days old sheep fetus[223,224].

Recently, Weinzweig and his team made another very important step toward a better understanding of the etiopathology and the effects of intrauterine treatment of fetal CP[260-262]. They demonstrated the feasibility of intrauterine CP repair in the congenital caprine model using a modified von Langenbeck technique with elevation of bilateral mucoperiosteal flaps and lateral relaxing incisions. In these studies they proposed the single-layer repair of the mucoperiosteal flaps, which results in the development of a normal palatal architecture by scarless healing, although a minor notch at the repaired side could be demonstrated.

Cephalometric evaluation of intrauterine CLP repair

Dodson and his colleagues presented in 1991 the first model for the measurement of facial length growth after fetal CL repair. A mid-face asymmetry of the skull was shown in the rabbit model, whose lip defect was not repaired during the fetal intervention, whereas the animals with an *in-utero* repair of the CL, revealed a symmetrical mid-face. Manual cephalometric measurements of the length and width of the maxilla, as well as the premaxilla were carried out. No significant inhibition of the frontal maxillary growth could be demonstrated in the animals, which were subject to a fetal surgical lip correction. On the other hand, an increased asymmetry was presented in the non-operated animals, as well as a deviation of the nose septum in the operated *and* not operated animals[229,263].

In an attempt to find a model for the craniosynostosis, Longaker and Kaban used 3D computer tomography for the reconstruction and measurement of the skulls[263]. Only skulls of 28 days old rabbits and of control animals were scanned. By the comparison of the control animals to the operated animals, in which craniosynostosis was created, a difference of the skull form was observed.

Kaban et al. examined in the rabbit model the cephalometric long-term growth of the skulls[230] by means of standardized direct manual measurements. In the animals without repaired CL, they observed a mild to serious asymmetry of the nose, lip, alveolus and the teeth, however no changes at the nasal bones.

The intrauterine operated animals showed a slight asymmetry of the nose and only a minor deviation of the nasal septum.

In order to examine the effect of the scar formation after the intrauterine repair of CL in the craniofacial growth, Canady and his colleagues operated in the sheep fetuses during the period of scarless healing (70th - 77th gestational day) and in fetuses at the period of healing with scar formation (118th - 133rd gestational day)[248]. A group of negative control animals served as comparison during the following evaluation. No significant differences between the 3 groups were observed after the normalization of the measured data. Thus, the results were less statistically significant. The head of the one month old lamb had reached 50 % of an adult skull size, and was estimated to be 300% - 400% larger than the skull at the time of fetal operation. This means that the main growth of the skull takes place after the fetal operation, therefore, allowing a major influence for the scar formation on the postoperative craniofacial growth.

In a long-term study of midfacial growth after different operative methods, Smith et al found firmly that in sheep fetuses, in which a CL was created at the 100th gestational day and not surgically repaired, the midfacial growth resulted in a growth restriction of the premaxilla[222]. On the other hand, the premaxilla showed a normal growth in fetuses in which this defect was surgically repaired endoscopically, as well as using the open hysterotomy technique. The evaluation was completed on the basis of 3D-CT measurements, one week after birth, as well as after 6 months, at the time of the euthanasia. Further, direct manual measurements on the skulls were performed using the same reference points as for the 3D-CT evaluation. These two methods showed a good accordance.

In a further long-term study, Stelnicki and his team examined the maxillary growth of the sheep skull after CL repair[224]. In this case, a CL and an alveolar defect was created at the 65th gestational day. This lip defect was repaired in the half of the animals at the 90th gestational day. This two stages method, first the creation of the defects, and its repair in a later stage, should come more in closer proximity to the clinical conditions of the occurrence of cleft formation. In the other half of the animals the lip was repaired one week after birth. The evaluation of the results was performed 9 months later. Direct measurements of the skulls were made. In the intrauterine operated animals no significant inhibition of the maxillary growth could be observed. In comparison, a significant inhibition of the maxillary growth could be recognized in the group of animals with postnatal lip repair. In addition, the measurement of the total palate length of the postnatal operated group showed a significant reduction of the maxillary development, opposite to the intrauterine operated animals. This study made again clear that the scar formation has a large influence on the growth of the premaxilla and maxilla in postnatal operated CLs.

Fetal bone healing and intrauterine maxillary reconstruction for CLP repair

The fetal surgical treatment of CLP during mid-gestation and its main advantages such as scarless healing and bone healing without callus formation, have to be addressed in malformation's whole entity, which is not only the malformed upper lip soft tissues, but also the maxillary alveolar defect. Bone healing without callus formation has been reported in both large, long gestational animal models, following incisional or excisional bone defects, as well as after fetal bone graft transplantation[187-189].

Nevertheless, in our knowledge there were no previous studies evaluating surgical intervention directed to such an important factor for the developmental midfacial growth of the fetus, as the maxillary alveolar defect[222-226,230,236,242,243,245,249]. Therefore, using a previously described animal model with surgically created CL and underlying maxillary alveolar defect[245], our team attempted the "surgical" repair of a CL malformation in its whole entity[191,235] (Fig. 3). The main purpose of this study was to evaluate possible surgical methods that could be considered for future feto-endoscopic treatment of this malformation in the animal model, as well as in humans, which would prevent an abnormal midfacial development. For these reasons the usefulness of autologous fetal bone grafts, as well as bone-regenerating implant material (Colloss®) in the treatment of maxillary alveolar defect by surgically created CL and alveolar-like defects in sheep fetuses was evaluated. Performing this study, as well as a following feasibility's study on feto-endoscopic incision and repair of surgically simulated CLs in the mid-gestational sheep model[227], we gained valuable experience for a further application that we intend in the delayed animal model described by Hedrick and colleagues[249], as well as the application of the feto-endoscopic approach in this latter model.

At the second look operation of our first study[191], the evaluation of the three-dimensional computer tomography (3D-CT), the two-dimensional maxi-

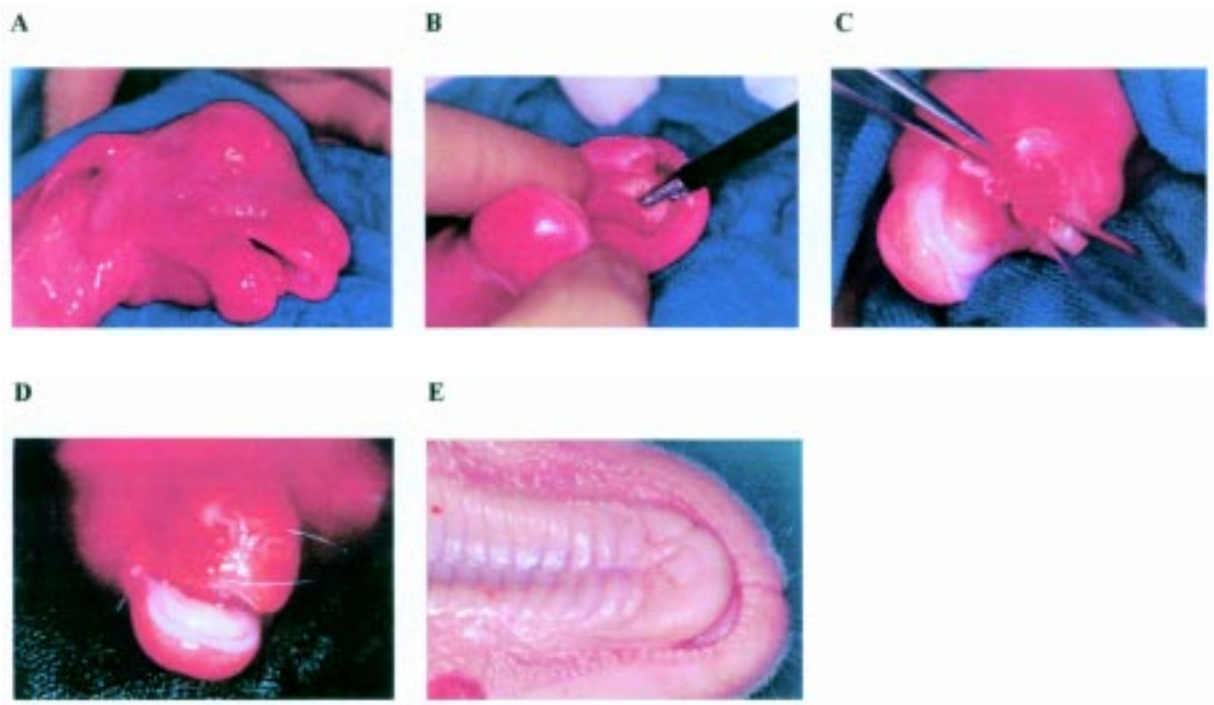


Figure 3. *The fetal sheep head out of the uterus at a GA of 78 days (**A**), and surgical creation of an 2-3 mm wide and 10 mm long unilateral full thickness cleft lip-like defect (**B**).*
*In (**C**) fetal ulnar bone graft fixation into the surgically maxillary alveolar defect with fibrin sealant.*
*Adaptation of the orbicularis oris muscle of the upper lip with polyglactine 6/0 suture (Vicryl ®), and lip skin closure with a nylon 8/0 suture (Prolene®) (**D**). Because of the friability of fetal mucosa, muscle and skin at mid-gestation, the amount of the used suture material was kept to a minimum.*
*(**E**): Photograph of a fetus at 141 days of GA with the repaired cleft lip (left side - upper right). Note the slight asymmetry of the maxilla and upper lip with some notching at the wound closure line.*

mal intensity projection (2D-MIP), and the histologically findings could prove the feasibility of intrauterine reconstruction of the surgical created alveolar defect of the surviving fetuses, by scarless healing of the soft tissues, although the lip soft tissue repair showed poor results, as notching and slight asymmetry, compared to previous studies[225,226,229,230,232,236,242,247-249].

Therefore, further investigations are necessary, since the choice of bone-regenerating implant material and bone graft, as well as its fixation to the maxilla, has to be seriously reconsidered, although in the clinical routine is preferred not to use foreign implant materials. The art of graft fixation to the maxillary defect is also a very important factor, since it is possible nowadays to use human bone, or cartilage bank allografts. Among the possible directions for future research, combination of different techniques, allografts, and bioresorbable bone-regenerating materials such as bone morphogenetic protein-2 (rhBMP-2), as well as tissue engineering may be considered, but additional research should go deeper in the fundamental questions concerning the mechanism of bone healing of the cranial bone defects.

Finally, this attempt showed that intrauterine repair of severe CL-like defects gives poor soft tissue results, but the treatment of the maxillary alveolar defect is feasible. Therefore, we concluded that further intensive research in this area, aiming to treat both the bone and the soft tissue defect in a more clinical relevant animal model is needed, with the long term goal to find ideal and repeatable operative techniques for the human fetus with a CLP, or other craniofacial malformations, which will minimize the need of any additional treatments.

Quality of life in children's with craniofacial malformations and their families

In general, the study of physical health in children with craniofacial malformations has focused on oral health. Children with craniofacial malformations, however, frequently have associated malfor-

mations and conditions that adversely affect other aspects of physical health including sensory, motoric, cardiovascular, and respiratory functions[265]. Little is known about the effects of the child's physical health on the psychological status of either the children with craniofacial malformations or their parents. Although it is not clear that there are higher rates of clinically significant psychological disturbance or behavioral problems in children with craniofacial malformations, many researchers agree that children with craniofacial malformations seem to be at risk for social difficulties and associated problems[266]. The role of development in the association between craniofacial malformations and quality of life indicators, including psychological and behavioral functioning, is complex. There are numerous reasons including the wide range of craniofacial conditions, the prevalence of developmental disabilities and learning disorders in children with craniofacial malformations, and the effects of development over the course of childhood and adolescence.

Children with craniofacial malformations are at risk for teasing and other forms of poor peer acceptance, which may contribute to an increased sense of social isolation and loneliness. In addition, the sense of social isolation may extend to the family as well. The interplay of children's psychosocial adjustment and family functioning is complex, and findings have been inconsistent in this area. However, there are some indications that parent-child attachment problems may occur with greater frequency for children with craniofacial malformations. Parents may struggle with powerful feelings of loss, anger, resentment, guilt, and anxiety after the birth of a child with such a malformation. Furthermore, they have been found to experience less satisfaction with their social networks than comparison parents, and decreased satisfaction with social support networks was associated with less-developed social skills in the child[267].

Because health problems in children are naturally stressful for any parent, factors that may exacerbate that stress are particularly important to understand and address. Psychosocial needs of children with craniofacial malformations and their families may be addressed by having greater involvement of mental health professionals, including psychologists and social workers, on multidisciplinary treatment teams[268].

Discussion

Inadequate wound healing and/or scarring can result in major clinical problems profoundly affecting structure, function and quality of life. Therefore, any potential avenues leading to improved healing and reduced scarring would be of great benefit. In this overview, we show that intrauterine surgery for the treatment of craniofacial malformations, as the cleft lip and palate, results in enhanced cutaneous wound healing as demonstrated by faster wound closure, increased tensile strength, and the reconstitution of a more normal architecture. This characteristic of intrauterine intervention will result to interruption of the malformation's cascade of detrimental secondary effects which will leave to expect a normal growth of the mid-face and an excellent aesthetic result. Additionally, applying this treatment regime it could be possible to reduce or minimize the need of secondary corrections or additional post-natal treatments, such as orthodontic, dental, psychological and logopedical, which normally accomplish the post-natal treatment of this malformation. These potential advantages of intrauterine surgery would **reduce the psychological and economic burden** of multiple surgeries and therapies on the small patient with a cleft lip and palate, its family, and the society in general. Due to these promising results, intrauterine surgery might be a huge relief of the psyche of the child, its parents and its social environment, resulting to a **superior quality of their life**.

Therefore, further research is needed in both directions: to make intrauterine procedures safer, and to achieve such intrauterine operative results that would minimize or even eliminate the need of secondary post-natal treatment; this way we will be able to give an enhanced quality of life to our little patient and its family. But even if these conditions are fulfilled, it is not clear whether we will be able one day to help clinically the human fetus with a cleft lip and palate.

Summary and New Perspectives

After the first successful intrauterine intervention in the pregnant guinea pig animal model reported more than 80 years before[269], an explosive development of sophisticated methods for prenatal diagnosis[160,270], as well as anesthetic, tocolytic and operative management to maximize feto-maternal survival began only in the eighties[271]. Today, the intrauterine diagnosis of human congenital anomalies (by means of high-resolution ultrasound, Magnetic Resonance Imaging (MRI), and other diagnostic procedures) that allows a more earlier and accurate diagnosis through the three-dimensional image reconstruction[160], and also their antenatal

treatment, has become a reality. Not only in case of a life threatening condition but also in the case of a non-life threatening malformation, like myelomeningocele, antenatal treatment has to be considered as a treatment option[257-258]. In addition, recent advances in feto-endoscopic surgery, as a logic consequence of the explosive evolution of adult and pediatric endoscopic surgery, have allowed wider and safer human intrauterine surgery, increasing the number of centers performing such interventions, although the risk of PPROM and preterm labour exists[231]. Thus, the interest of craniofacial surgeons has been renewed intensely, especially after the endoscopic *in-utero* treatment of a non-life threatening malformation such as the myelomeningocele, since it has been speculated that more and more non-life-threatening malformations, such as the craniofacial ones, could be treated antenatal in the near future.

One should not forget that such invasive procedures are associated to the inherent need of membranes' disruption, and therefore, as mentioned before, PPROM might be seriously considered by such complex procedures as the possible "*Achilles' heel*" too[231]. We therefore believe that the craniofacial surgeon has to contribute more than just offering "aesthetic" or "wound healing" results in the treatment of such friable patients, and structures as the fetal membranes, since he is the clinician with the largest experience to handle such friable structures under microscopic control[190,251,259,272].

For these reasons, the mid-gestational rabbit that has been proposed as a model for the evaluation of fetal membrane healing after hysterotomy and fetoscopic exploration of the amniotic sac. In our opinion this inexpensive, readily available animal model, which does not require any special facilities for lodging or anesthesia, and which has been suggested for training in fetoscopy, as well as for research on intrauterine surgery, may be best used as an interesting, and moreover probably important tool to contribute toward the further development of feto-endoscopic surgery, taking further advantage of the experience of the craniofacial surgeons on clinical and experimental wound healing, including the experience of the last years on tissue engineering as well[203,230,231,272-276].

However, further experimental studies are needed not only to this direction. In the field of craniofacial fetal surgery, there is need to achieve excellent surgical results that will not need additional postnatal treatments. Only in such conditions could be possible to help clinically the human fetus with a craniofacial malformation. Therefore, further investigations are necessary to improve fetal CLP surgery in its whole entity; not only in the healing of the soft tissues, but also of the maxillary alveolar bone defect, as well as and other secondary accompanying deformities, as for example the ipsilateral nasal nostril widening and flaring.

Consequently, our team modified a previously described animal model with surgically created CL and underlying maxillary alveolar defect[245], attempting this way the "surgical" repair of a CL malformation in its whole entity[191,235]. In our knowledge this is also the latest development in the intrauterine treatment of CL in the animal model toward a possible future clinical application.

Moreover, the closure technique of the surgically created lip defect might be reconsidered since until today a decrease of the lip volume at the operated cleft side has been observed following intrauterine CL repair[191,224,235,248]. Nowadays we are evaluating the rotation-advancement flap technique[277,278], which is the most common type of lip repair method clinically (not published data); at our knowledge other teams prove the usefulness of similar techniques from the clinical experience as well. The above mentioned technique allows adjustments at the time of surgery, places the scar in an anatomically correct position, and reinforces the nostril sill.

Furthermore, the use of a large congenital animal model of non-surgically, but intrinsically created clefts, would be the ideal model to study better the etio-patho-physiology of the fetal CLP malformation and its treatment/reconstruction in its whole entity, as the congenital caprine model proposed by Weinzweig and his team for the isolated CP[260-262]. In such a model, midfacial growth disturbances of non-operated cleft, as well as long term maxillary growth analysis of *in-utero* treated clefts with the open and later with the feto-endoscopic approach, may be better studied, documented and compared, although it is unclear if similar results could be obtained in genetically abnormal animals after exposure of teratogenic substances.

In the second half of the last century, great advances have been made toward a better understanding of etio-patho-physiology, as well as other aspects of the CLP malformation, but there is still a long way to go before a consensus on the optimal surgical and conservative treatment procedures could be reached. This is due to the great variability in craniofacial morphology and in the patient's response to treatment based on the fact that clefts occur due to the interaction of several genetic and environment factors. Therefore, further research is needed in both

directions: the ante- and neonatal repair surgery of CLP. Common aspect of these two directions is the better understanding of the cleft's etio-patho-physiology. What makes the intrauterine research so important, is not only the best understanding of the intrauterine malformation's development but also the possibility to study the intrauterine treatment of such malformations with the hope to achieve excellent results when dealing with clefts. Additionally, the advantages offered nowadays by the gene therapeutic techniques that can alter the biology of such a condition, have to be better understood, since they may lead in the new millennium to the development of new non-invasive or minimally invasive methods for the treatment of CLP, as well of other craniofacial malformations. Furthermore, an important tool such as tissue engineering and its great advantages have also to be considered in the treatment of such malformations.

As everyone can recognize, there are still many unsolved problems associated with intrauterine surgery, and today, the human fetal surgery for the repair of craniofacial malformations such as CLP is not ethically defendable. Therefore, only if such conditions as described above could be fulfilled, we will be eventually able to help the human fetus with a CLP, although we should not forget that it may not never be possible to find the optimal pre- or postnatal treatment method for this or the others craniofacial malformations!

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ΠΕΡΙΛΗΨΗ

Ν.Α. Παπαδόπουλος, Μ.Α. Παπαδόπουλος. **Μπορεί η ενδομήτρια χειρουργική να βελτιώσει την ποιότητα ζωής των ασθενών με χειλεο-υπερωιο-σχιστίες; Ιπποκράτεια 7 (2): 59-80**

΄Εχει ήδη παρατηρηθεί ότι μερικές από τις συγγενείς ανωμαλίες μπορούν να διορθωθούν με ενδομήτρια χειρουργική αντιμετώπιση, η οποία μπορεί να είναι σωτήρια για τη ζωή. Όμως, ο μετεγχειρητικός πρόωρος τοκετός και ο υψηλός βαθμός τραυματισμού θεωρούνται σαν τα κύρια μειονεκτήματα της "ανοικτής" ενδομήτριας χειρουργικής, εξ' αιτίας κυρίως της πραγματοποιούμενης υστεροτομίας. Πιο πρόσφατα ο συνδυασμός της εμβρυοσκοπίας και της προηγμένης ενδοσκοπικής χειρουργικήςφαίνεται να ανοίγει νέες ελπίδες για πιθανή μελλοντική εφαρμογή εμβρυο-ενδοσκοπικών χειρουργικών μεθόδων ακόμη και για καταστάσεις μη απειλητικές για τη ζωή, όπως οι κρανιοπροσωπικές ανωμαλίες (π.χ. χειλεο-υπερωιο-σχιστίες)

Η ενδομήτρια αντιμετώπιση παρουσιάζει τα ακόλουθα πλεονεκτήματα: (α) επούλωση των μαλακών μορίων χωρίς ουλές κατά τη μέση περίοδο εγκυμοσύνης, (β) διακοπή των δευτερογενών επιπλοκών εξαιτίας της ανωμαλίας (μη εμφάνιση δευτερογενούς αναστολής της αύξησης της άνω γνάθου), (γ) μείωση ή ελάχιστη ανάγκη για δευτερεύουσες διορθώσεις ή επιπρόσθετες μεταγενητικές θεραπείες και (δ) μικρή νοσηρότητα, τουλάχιστον όσον αφορά την ενδοσκοπική τεχνική. Αυτά τα πλεονεκτήματα θα μπορούσαν να μειώσουν την ψυχολογική και οικονομική επιβάρυνση των πολλαπλών χειρουργικών επεμβάσεων και των θεραπειών για τον νεαρό ασθενή με χειλεο-υπερωιο-σχιστία, την οικογένειά του και την κοινωνία γενικότερα.

Παρ' όλα αυτά, χρειάζεται περαιτέρω έρευνα με σκοπό να καταστούν πιο ασφαλείς οι ενδομήτριες διαδικασίες και να επιτευχθούν τέτοια αποτελέσματα που θα μπορούσαν να μειώσουν ή ακόμη και να εξαλείψουν την ανάγκη για επιπρόσθετες μεταγενητικές θεραπείες. Με αυτό τον τρόπο θα μπορούσε να είναι δυνατή η παροχή μιας καλύτερης ποιότητας ζωής σε αυτούς τους ασθενείς και στις οικογένειές τους.

REFERENCES

1. Maerker R. Lippen-Kiefer-Gaumen-Spalten. In: Schumpelich V, Bleese N, Mommsen U, eds. Chirurgie. Stuttgart: Enke Verlag, 1994; 32-4: 352-355
2. Schutte B, Murray J. The many faces and factors of orofacial clefts. Hum Mol Genet 1999; 8: 1853-1859
3. Papadopulos N. La labiopalatoschisi, tecnica chirurgica [Lippen-Kiefer-Gaumenspalte, chirurgische Technik]. MD Thesis, Perugia: Univ. of Perugia 1991
4. Proffit WR, Turvey TA. Special problems in cleft-palate patients. In: Proffit WR, White RP, eds. Surgical orthodontic treatment. St. Louis: Mosby, 1991: 625-659
5. Bianchi F, Calzolari E, Ciulli L. Environment and genetics in the etiology of cleft lip and cleft palate with

reference to the role of folic acid. Epidemiol Prev 2000; 24: 21-27
6. Fogh-Andersen P. Inheritance of harelip and cleft palate. Copenhagen: Munksgaard, 1942
7. Vanderas A. Incidence of cleft lip, cleft palate, and cleft lip and palate among races. A review. Cleft Palate J 1987; 24: 216-212
8. Croen L, Haw G, Wassermann C. Racial and ethnic variations in the prevalence of orofacial clefts in California, 1983-1992. Am J Med Genet 1998; 79: 42-47
9. Tolarova M, Cervenka J. Classification and birth prevalence of orofacial clefts. Am J Med Genet 1998; 75: 126-137
10. Romitti P, Lidral A, Munger R, Daack-Hirsch S, Burns T, Murray J. Candidate genes for nonsyndromic cleft lip and palate and maternal cigarette smoking and alcohol consumption: evaluation of genotype-environment interactions from a population-based case-control study of orofacial clefts. Teratology 1999; 59: 39-50
11. Bender PL. Genetics of cleft lip and palate. J Pediatr Nurs 2000; 15: 242-249
12. Cockell A, Lees M. Prenatal diagnosis and management of orofacial clefts. Prenat Diagn 2000; 20: 149-151
13. Kobayashi J, Kimijima Y, Yamada S. 4p-syndrome and 9p tetrasomy mosaicism with cleft lip and palate. J Craniomaxillofac Surg 2000; 28: 165-170
14. Waite DE, Kersten RB. Residual alveolar and palatal clefts. In: Bell WH, Proffit WR, White RP, eds. Surgical Correction of Dentofacial Deformities. Philadelphia: WB Saunders 1980: 1329-1367
15. American Cleft Palate-Craniofacial Association (ACPA). Parameters for Evaluation and Treatment of Patients with Cleft Lip/Palate or Other Craniofacial Anomalies. Cleft Palate J 1993; 30(suppl 1)
16. Winter RM, Baraitser M. The London Dysmorphology Database: A Computerised Database for the Diagnosis of Rare Dysmorphic Syndromes. Oxford: Oxford University Press 1998
17. Coupland MA, Coupland AI. Seasonality, incidence, and sex distribution of cleft lip and palate births in Trent Region, 1973-1982. Cleft Palate J 1988; 25: 33-37
18. Owens JR, Jones JW, Harris F. Epidemiology of facial clefting. Arch Dis Child 1985; 60: 521-524
19. Shaw GM, Croen LA, Curry CJ. Isolated oral cleft malformations: associations with maternal and infant characteristics in a California population. Teratology 1991; 43: 225-228
20. Derijcke A, Eerens A, Carels C. The incidence of oral clefts: a review. Br J Oral Maxillofac Surg 1996; 34: 488-494
21. Fraser FC. The genetics of cleft lip and cleft palate. Am J Hum Genet 1970; 22: 336-352
22. Lowry RB, Trimble BK. Incidence rates for cleft lip and palate in British Columbia 1952-71 for North American Indian, Japanese, Chinese and total populations: secular trends over twenty years. Teratology 1977; 16: 277-283
23. Coddington DA, Hisnanick JJ. Midline congenital anomalies: the estimated occurrence among American Indian and Alaska Native infants. Clin Genet 1996; 50: 74-77
24. Calzolari E, Milan M, Cavazzuti GB, et al. Epidemiological and genetic study of 200 cases of oral cleft in the Emilia Romagna region of northern Italy. Teratology 1988; 38: 559-564
25. Thomas DB. Cleft palate, mortality and morbidity in infants of substance abusing mothers. J Paediatr Child Health 1995; 31: 457-460
26. Rodriguez-Pinilla E, Martinez-Frias ML. Corticosteroids during pregnancy and oral clefts: a case-control study. Teratology 1998; 58: 2-5
27. Carmichael SL, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. Am J Med Genet 1999; 86: 242-244
28. Park-Wyllie L, Mazzotta P, Pastuszak A, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology 2000; 62: 385-392
29. Khoury MJ, Weinstein A, Panny S, et al. Maternal cigarette smoking and oral clefts: a population-based study. Am J Public Health 1987; 77: 623-625
30. Van Den Eeden SK, Karagas MR, Daling JR, Vaughan TL. A case-control study of maternal smoking and congenital malformations. Paediatr Perinat Epidemiol 1990; 4: 147-155
31. Munger RG, Romitti PA, Daack-Hirsch S, Burns TL, Murray JC, Hanson J. Maternal alcohol use and risk of orofacial cleft birth defects. Teratology 1996; 54: 27-33
32. Wyszynski DF, Duffy DL, Beaty TH. Maternal cigarette smoking and oral clefts: a meta-analysis. Cleft Palate Craniofac J 1997; 34: 206-210
33. Shaw GM, Lammer EJ. Maternal periconceptional alcohol consumption and risk for orofacial clefts. J Pediatr 1999; 134: 298-303
34. Lorente C, Cordier S, Goujard J, et al. Tobacco and alcohol use during pregnancy and risk of oral clefts. Occupational Exposure and Congenital Malformation Working Group. Am J Public Health 2000; 90: 415-419
35. Chung KC, Kowalski CP, Kim HM, Buchman SR. Maternal cigarette smoking during pregnancy and the risk of having a child with cleft lip/palate. Plast Reconstr Surg 2000; 105: 485-491
36. Ardinger HH, Buetow KH, Bell GI, Bardach J, VanDemark DR, Murray JC. Association of genetic variation of the transforming growth factor-alpha gene with cleft lip and palate. Am J Hum Genet 1989; 45: 348-353
37. Mackenzie A, Leeming GL, Jowett AK, Ferguson MW, Sharpe PT. The homeobox gene HOX 7.1 has specific regional and temporal expression patterns during early murine craniofacial embryogenesis, especially tooth development in vivo and in vitro. Development 1991; 111: 269-285
38. Chenevix-Trench G, Jones K, Green AC, Duffy DL,

Martin NG. Cleft lip with or without cleft palate: associations with transforming growth factor alpha and retinoic acid receptor loci. Am J Hum Genet 1992; 51: 1377-1385
39. Damm K, Heyman RA, Umesono K, Evans RM. Functional inhibition of retinoic acid response by dominant negative retinoic acid receptor mutants. Proc Natl Acad Sci USA 1993; 90: 2989-2993
40. Satokata I, Maas R. Msx1 deficient mice exhibit cleft palate and abnormalities of craniofacial and tooth development. Nat Genet 1994; 6: 348-356
41. Culiat CT, Stubbs LJ, Woychik RP, Russell LB, Johnson DK, Rinchik EM. Deficiency of the beta 3 subunit of the type A gamma-aminobutyric acid receptor causes cleft palate in mice. Nat Genet 1995; 11: 344-346
42. LaBorde JB, Pipkin JL Jr, Hinson WG, et al. Retinoic acid-induced stress protein synthesis in the mouse. Life Sci 1995; 56: 1767-1778
43. Proetzel G, Pawlowski SA, Wiles MV, et al. Transforming growth factor-beta 3 is required for secondary palate fusion. Nat Genet 1995; 11: 409-414
44. Asada H, Kawamura Y, Maruyama K, et al. Cleft palate and decreased brain gamma-aminobutyric acid in mice lacking the 67-kDa isoform of glutamic acid decarboxylase. Proc Natl Acad Sci USA 1997; 94: 6496-6499
45. Lidral AC, Murray JC, Buetow KH, et al. Studies of the candidate genes TGFB2, MSX1, TGFA, and TGFB3 in the etiology of cleft lip and palate in the Philippines. Cleft Palate Craniofac J 1997; 34: 1-6
46. Lidral AC, Romitti PA, Basart AM, et al. Association of MSX1 and TGFB3 with nonsyndromic clefting in humans. Am J Hum Genet 1998; 63: 557-568
47. Degitz SJ, Francis BM, Foley GL. Mesenchymal changes associated with retinoic acid induced cleft palate in CD-1 mice. J Craniofac Genet Dev Biol 1998; 18: 88-99
48. Nugent P, Greene RM. MSX-1 gene expression and regulation in embryonic palatal tissue. In Vitro Cell Dev Biol Anim 1998; 34: 831-835
49. Miettinen PJ, Chin JR, Shum L, et al. Epidermal growth factor receptor function is necessary for normal craniofacial development and palate closure. Nat Genet 1999; 22: 69-73
50. Zhao Y, Guo YJ, Tomac AC, et al. Isolated cleft palate in mice with a targeted mutation of the LIM homeobox gene lhx8. Proc Natl Acad Sci USA 1999; 96: 1502-1506
51. Tanabe A, Taketani S, Endo-Ichikawa Y, Tokunaga R, Ogawa Y, Hiramoto M. Analysis of the candidate genes responsible for non-syndromic cleft lip and palate in Japanese people. Clin Sci (Lond) 2000; 99: 105-111
52. Van Den Boogaard MJ, Dorland M, Beemer FA, van Amstel HK. MSX1 mutation is associated with orofacial clefting and tooth agenesis in humans. Nat Genet 2000; 24: 342-343
53. Blanco R, Chakraborty R, Barton SA, et al. Evidence of a sex-dependent association between the MSX1 locus and nonsyndromic cleft lip with or without cleft palate in the Chilean population. Hum Biol 2001; 73: 81-89
54. Beaty TH, Wang H, Hetmanski JB, et al. A case-control study of nonsyndromic oral clefts in Maryland. Ann Epidemiol 2001; 11: 434-442
55. Beaty TH, Hetmanski JB, Zeiger JS, et al. Testing candidate genes for non-syndromic oral clefts using a case-parent trio design. Genet Epidemiol 2002; 22: 1-11
56. Marazita ML, Field LL, Cooper ME, et al. Nonsyndromic cleft lip with or without cleft palate in China: assessment of candidate regions. Cleft Palate Craniofac J 2002; 39: 149-156
57. Ortiz-Monasterio F, Serrano Rebeil A, Valderrama M, Cruz R. Cephalometric measurements on adult patients with nonoperated cleft palates. Plast Reconstr Surg 1959; 24: 53-60
58. Ortiz-Monasterio F, Serrano R A, Barrera P G, Rodriguez-Hoffman H, Vinageras E. A study of untreated adult cleft palate patients. Plast Reconstr Surg 1966; 28: 36-41
59. Ortiz-Monasterio F, Olmedo A, Trigos I, Yudovich M, Velazquez M, Fuentedel-Campo A. Final results from the delayed treatment of patients with clefts of the lip and palate. Scand J Plast Reconstr Surg 1974; 8: 109-115
60. Mestre JC, DeJesus J, Subtelny JD. Unoperated oral clefts at maturation. Angle Orthod 1960; 30: 78-85
61. Innis CO. Some preliminary observations on unrepaired hare-lips and cleft palates in adult members of the Dusan tribes of North Borneo. Br J Plast Surg 1962; 15: 173-181
62. Atherton JD. Morphology of facial bones in skulls with unoperated unilateral cleft palate. Cleft Palate J 1967; 4: 18-30
63. Bishara SE, Krause CJ, Olin WH, Weston D, Van Ness J, Felling C. Facial and dental relationships of individuals with unoperated clefts of the lip and/or palate. Cleft Palate J 1976; 13: 238-252
64. Bishara SE, Jakobsen JR, Krause JC, Sosa-Martinez R. Cephalometric comparisons of individuals from India and Mexico with unoperated cleft lip and palate. Cleft Palate J 1986; 23: 116-125
65. Isiekwe MC, Sowemimo GOA. Cephalometric findings in a normal Nigerian population sample and adult Nigerians with unrepaired clefts. Cleft Palate J 1984; 21: 323-328
66. Mars M, Houston WJ. A preliminary study of facial growth and morphology in unoperated male unilateral cleft lip and palate subjects over 13 years of age. Cleft Palate J 1990; 27: 7-10
67. DeJesus J. A comparative cephalometric analysis of nonoperated cleft-palate adults and normal adults. Am J Orthod 1959; 45: 61-62
68. Boo-Chai K. The unoperated adult bilateral cleft of

the lip and palate. Br J Plast Surg 1971; 24: 250-256
69. Pruzansky S, Friede H. Two sisters with unoperated bilateral cleft lip and palate, age 6 and 4 years. Br J Plast Surg 1975; 28: 251-258
70. Rees TD. Unoperated bilateral cleft lip and palate in a young adult: a thirty three year follow-up. Br J Plast Surg 1991; 44: 378-383
71. American Cleft Palate-Craniofacial Association (ACPA). The Cleft and Craniofacial Team. www.cleftpalate-craniofacial.org/teamcare/, 1996
72. Epker BN, Stella JP, Fish LC. Dentofacial deformities. Integrated Orthodontic and Surgical correction. Vol. III, St. Louis: Mosby 1998: 1487-1713
73. Menard RM, Schendel SA. Rotation-Advancement Repair of Unilateral Cleft Lip: Current Status and Future Horizons. Adv Plast Reconstr Surg Ch 8: 14, 247-278. St. Louis: Mosby-Year Book 1997
74. Delaire J. La cheilo-rhinoplastie primaire pour fente labio-maxillaire congenitale unilaterale. Essai de schematisation d'une technique. Rev Stomat Chir Maxillofac 1975; 76: 193-216
75. Delaire J. The potential role of facial muscles in monitoring maxillary growth and morphogenesis. In: Carlson DS, McNamara JA, eds. Muscle Adaptation in the Craniofacial Region. Ann Arbor: University of Michigan Press 1978a: 157-180
76. Delaire J. Theoretical principles and technique of functional closure of the lip and nasal aperture. J Maxillofac Surg 1978b, 6: 109
77. Joos U. The importance of muscular reconstruction in the treatment of cleft lip and palate. Scand J Plast Reconstr Surg 1987; 21: 109-113
78. Joos U. Muscle Reconstruction in primary cleft lip surgery. J Craniomaxillofac Surg 1989a; 17: 8-10
79. Joos U. Evaluation of the result of surgery on cleft lip and palate and skeletal growth determinants of the cranial base. J Craniomaxillofac Surg 1989b; 17: 23
80. Joos U. Cleft osteoplasty and muscular reconstruction in Cleft lip and palate. Intern. Assoc. of oral and maxillofacial surgeons in training, Luxemburg. 1990
81. Joos U. Skeletal growth after muscular reconstruction for cleft lip and palate. Br J Oral Maxillofac Surg 1995; 33: 139-144
82. Joos U, Friedburg, H. Darstellung des Verlaufs der mimischen Muskulatur in der Kernspintomographie. Fortschr Kiefer - Gesichtschir 1987; 32: 125-127
83. Mpousios V, Ioannidis I, Papadopulos NA, Papadopoulos MA. Muscular reconstruction of the lip in primary cleft lip surgery. Hell Stomatol Chron 2003, (submitted)
84. McComb H. Treatment of the unilateral cleft lip nose. Plast Reconstr Surg 1975; 55: 596-601
85. McComb H. Primary correction of unilateral cleft lip nasal deformity: a 10-year review. Plast Reconstr Surg 1985; 75: 791-799
86. Boo-Chai K. Primary repair of the unilateral cleft lip nose in the oriental person: a 20-year follow up. Plast Reconstr Surg 1987; 80: 185-194
87. Talmant JC. Nasal malformations associated with unilateral cleft lip. Scand J Plast Reconstr Hand Surg 1993; 27: 183-191
88. Noordhoff M, Chen Y, Chen K, Hong K, Lo L. The surgical technique for the complete unilateral cleft lip-nasal deformity. Oper Tech Plast Reconstr Surg 1995; 2: 167-174
89. Thompson HG. Unilateral cleft lip repair. Oper Tech Plast Reconstr Surg 1995; 2: 175-181
90. Bardach J. Unilateral cleft lip/nose repair: Bardach's technique. Oper Tech Plast Reconstr Surg 1995; 2: 187-192
91. McComb H, Coghlan BA. Primary repair of the unilateral cleft lip nose: completion of a longitudinal study. Cleft Palate Craniofac J 1996; 33: 23-30
92. Armstrong GT, Burk RW 3rd, Griffin DW, Howard PS. A modification of the primary nasal correction in the rotation-advancement unilateral cleft lip repair. Ann Plast Surg 1997; 38: 236-245
93. Turdek M, Hrivnateova J, Kudevova J, Smabel Z, Borsky J. Influence of primary septal cartilage reposition on development of the nose in UCLP. Acta Chir Plast 1997; 39: 113-116
94. Nakajima T, Yoshimura Y. Early repair of unilateral cleft lip employing a small triangular flap method and primary nasal correction. Br J Plast Surg 1993; 46: 616-618
95. Skoog T. The use of periosteal flaps in the repair of clefts of the primary palate. Cleft Palate J 1965a; 2: 332-339
96. Dieffenbach JF. Practical Surgery. London: Liston, John Churchill 1837: 471-473
97. Von Langenbeck B. Die uranoplastik mittelst ablosung des mucoes-periostalen gaumenuberzuges. Arch Klin Chir 1861; 2: 205-287
98. Veau V. Division Palatine. Paris: Masson 1931
99. Kilner TP. Cleft lip and palate repair technique. St Thomas Hosp Rep 1937; 2: 127
100. Wardill WEM. The technique of operation for cleft palate. Br J Surg 1937; 25: 117-130
101. Bardach J. Cleft palate repair: two-flap palatoplasty. Research, philosophy, technique, and results. In: Bardach J, Morris H, eds. Multidisciplinary Management of Cleft Lip and Palate. Philadelphia: WB Saunders 1990
102. Furlow LT. Cleft palate repair: preliminary report on lengthening and muscle transposition by Z-plasty. Presented at the annual meeting of the Southeastern Society of Plastic and Reconstructive Surgeons, Boca, 1978
103. Lexer E. Die Verwendung der frien knochenplastic nebst versuchen uber gelenkversteifung and gelenktransplantation. Arch Klin Chir 1908; 86: 939-943
104. Nordin KE, Johansson B. Freie Knochentransplantation bei Defecten in Alveolarkamm nach kieferorthopaedischer Einstellung der Maxilla bei Lippen-Kiefer- Gaumenspalten. In: Schuchardt K,

Wassmund M, eds. Fortschritte der Kiefer- und Gesichts-Chirurgie, Vol. I. Stuttgart: Georg Thieme Verlag 1955
105. Calnan JS. Submucous cleft palate. Br J Plast Surg 1954; 6: 264-282
106. Crikelair GF, Striker P, Cosman B. The surgical treatment of submucous cleft palate. Plast Reconstr Surg 1970; 45: 58-65
107. Weatherley-White RCA, Sakura CY, Brenner LD, Stewart JM, Ott JE. Submucous cleft palate: its incidence, natural history and indications for treatment. Plast Reconstr Surg 1972; 49: 297-304
108. Kaplan EN. The occult submucous cleft palate. Cleft Palate J 1975; 12: 356-368
109. Abyholm FE. Submucous cleft palate. Scand J Plast Reconstr Surg 1976; 10: 209-212
110. Ross RB. Treatment variables affecting facial growth in complete unilateral cleft lip and palate. Part 1: treatment affecting growth. Cleft Palate J 1987a; 24: 5-23
111. Ross RB. Treatment variables affecting facial growth in complete unilateral cleft lip and palate. Part 2: presurgical orthopedics. Cleft Palate J 1987b; 24: 24-30
112. Ross RB. Treatment variables affecting facial growth in complete unilateral cleft lip and palate. Part 3: alveolus repair and bone grafting. Cleft Palate J 1987c; 24: 33-44
113. Ross RB. Treatment variables affecting facial growth in unilateral cleft lip and palate. Part 4: repair of the cleft lip. Cleft Palate J 1987d; 24: 45-53
114. Ross RB. Treatment variables affecting facial growth in unilateral cleft lip and palate. Part 5: Timing of palate repair. Cleft Palate J 1987e; 24: 54-63
115. Ross RB. Treatment variables affecting facial growth in cleft lip and palate. Part 6: Techniques of palate repair. Cleft Palate J 1987f; 24: 64-70
116. Ross RB. Treatment variables affecting facial growth in complete unilateral cleft lip and palate. Part 7: an overview of treatment and facial growth. Cleft Palate J 1987g; 24: 71-77
117. Rosenstein S, Kernahun D, Dado D, Grasseschi M, Griffith BH. Orthognathic surgery in cleft patients treated by early bone grafting. Plast Reconstr Surg 1991; 87: 835-839
118. Mars M, Asher-McDade C, Brattstrom V, et al. A six-center international study of treatment outcome in patients with clefts of the lip and palate: part 3. Dental arch relationships. Cleft Palate Craniofac J 1992; 29: 405-408
119. DeLuke DM, Marchand A, Robeles EC, Fox P. Facial growth and the need for orthognathic surgery after cleft palate repair: literature review and report of 28 cases. J Oral Maxillofac Surg 1997; 55: 694-697
120. Cohen SR, Corrigan M, Wilmot J, Trotrnan CA. Cumulative operative procedures in patients aged 14 years and older with unilateral or bilateral cleft lip and palate. Plast Reconstr Surg 1995; 96: 267-271
121. Herber SC, Lehman JA. Orthognathic surgery in the cleft lip and palate patient. Clin Plast Surg 1993; 20: 755-768
122. Vig KWL, Turvey TA. Orthodontic-surgical interaction in the management of cleft lip and palate. Clin Plast Surg 1985; 12: 735-748
123. Cheung LK, Samman N, Hui E, Tideman H. The 3-dimensional stability of maxillary osteotomies in cleft palate patients with residual alveolar clefts. Br J Oral Maxillofac Sung 1994; 32: 6-11
124. Polley JW, Figueroa AA. Management of severe maxillary deficiency in childhood and adolescence through distraction osteogenesis with an external, adjustable, rigid distraction device. J Craniofac Surg 1997; 8: 181-185
125. Proffit WR. Contemporary Orthodontics. St. Louis: Mosby Inc. 2000
126. McNeil CK. Orthodontic procedures in the treatment of congenital cleft palate. Dent Rec 1950; 70: 126-132
127. Burston WR. The early treatment of cleft palate conditions. Dent Pract 1958; 9: 41
128. Salyer KE. Primary correction of the unilateral cleft lip nose: a 15-year experience. Plast Reconstr Surg 1986; 77: 558-568
129. Huebener DV, Liu JR. Maxillary orthopedics. Clin Plast Surg 1993; 20: 723-732
130. Winters JC, Hurwitz DJ. Presurgical orthopedics in the surgical management of unilateral cleft lip and palate. Plast Reconstr Surg 1995; 95: 755-764
131. Ross RB. The management of dental arch deformity in cleft lip and palate. Clin Plast Surg 1975; 2: 325-342
132. Cooper HK, Long RE Sr, Long RE Jr, Pepek MJ. Orthodontics and oral orthopedics. In: Cooper HK, Harding RL, Krogman WM, Mazaheri M, Millard RT, eds. Cleft Palate and Cleft Lip: A Team Approach to Clinical Management and Rehabilitation of the Patient. Philadelphia: WB Saunders 1979: 358-429
133. Subtelny JD. Orthodontic principles in treatment of cleft lip and palate. In: Bardach J, Morris HL, eds. Multidisciplinary Management of Cleft Lip and Palate. Philadelphia: WB Saunders 1990: 615-636
134. Aduss H, Figueroa AA. Stages of orthodontic treatment in complete unilateral cleft lip and palate. In: Bardach J, Morris HL, eds. Multidisciplinary Management of Cleft Lip and Palate. Philadelphia: WB Saunders 1990: 607-615
135. Olin WH. Orthodontic treatment in different stages of growth and development. In: Bardach J, Morris HL, eds. Multidisciplinary Management of Cleft Lip and Palate. Philadelphia: WB Saunders 1990: 649-662
136. Semb G, Shaw WC. Orthodontics. In: Watson ACH, Grunwell P, Sell D, eds. Management of Cleft Lip

and Palate. London: Whurr Publisher 2000
137. Pierce G, Terwilliger K, Pennisi Jr Y, Klabunde H. Early orthodontic treatment in cleft palate children. Angle Orthod 1956; 26: 110-120
138. Harvold E. Prinsippene for den kjeveortopediske behandling av overkjeven med ensidig total ganespalte. Nor Tannloegeforen Tid 1949; 59: 395-416
139. Pruzansky S. The role of the orthodontist in a cleft palate team. Plast Reconstr Surg 1954; 14: 10-29
140. Pruzansky S. Factors determining arch form in clefts of the lip and palate. Am J Orthod 1955; 41: 827-851
141. Subtelny JD, Brodie A. An analysis of orthodontic expansion in unilateral cleft lip and cleft palate patients. Am J Orthod 1954; 40: 686-697
142. Ross RB, Johnston MC. Cleft Lip and Palate. Baltimore: Williams and Wilkins 1972
143. Olin, WH. Cleft lip and palate rehabilitation. Am J Orthod 1966; 52: 126-144
144. Fishman LS. Dentistry's responsibility to the cleft palate patient. NY State Dent J 1969; 35: 467-479
145. Vargervik K. Orthodontic management of unilateral cleft lip and palate. Cleft Palate J 1981; 18: 256-270
146. Vargervik K. Orthodontic treatment of cleft patients: characteristics of growth and development/treatment principles. In: Bardach J, Morris HL, eds. Multidisciplinary Management of Cleft Lip and Palate. Philadelphia: WB Saunders 1990: 642-649
147. Subtelny JD. The importance of early orthodontic treatment in cleft palate planning. Angle Orthod 1957; 27: 148-158
148. Ohkiba T, Hanada K. Adaptive functional changes in the swallowing pattern of the tongue following expansion of the maxillary dental arch in subjects with and without cleft palate. Cleft Palate J 1989; 26: 21-30
149. Rygh P, Tindlund RS. Early considerations in the orthodontic management of skeletodental discrepancies. In: Turvey TA, Vig KWL, Fonseca RJ, eds. Facial Clefts and Craniosynostosis. Principles and Management. Philadelphia: WB Saunders 1996: 234-319
150. Ramstad T. Fixed prosthodontics in cleft palate. In: McKinstry R, ed. Cleft Palate Dentistry. Arlington: ABI Professional Publications 1998: 236-262
151. Verdi FJ, Lanzi GL, Cohen SR, Powell R. Use of the Branemark implant in the cleft palate patient. Cleft Palate Craniofac J 1991; 28: 301-304
152. Vig KWL, Turvey TA, Fonseca RJ. Orthodontic and surgical considerations in bone grafting in the cleft maxilla and palate. In: Turvey TA, Vig KWL, Fonseca RJ, eds. Facial Clefts and Craniosynostosis. Principles and Management. Philadelphia: WB Saunders 1996: 396-440
153. Takahashi T, Fukuda M, Yamaguchi T, et al. Use of an osseointegrated implant for dental rehabilitation after cleft repair by periosteoplasty, a case report. Cleft Palate Craniofac J 1997; 34: 268-271
154. Kearns G, Perrott DH, Sharma A, Kaban LB, Vargervik K. Placement of endosseous implants in grafted alveolar clefts. Cleft Palate Craniofac J 1997; 34: 520-525
155. Lilja J, Yontchev E, Friede H, Elander A. Use of titanium dental implants as an integrated part of a CLP protocol. Scand J Plast Reconstr Surg Hand Surg 1998; 32: 213-219
156. Hillerup S, Dahl E, Schwartz O, Hjorting-Hansen E. Tooth transplantation to bone graft in cleft alveolus. Cleft Palate J 1987; 24: 137-141
157. Semb G, Schwartz O. The impacted tooth in patients with alveolar clefts. In: Andreasen JO, Petersen JK, Laskin DM, eds. Textbook and Color Atlas of Tooth Impaction. Copenhagen: Munksgaard 1997: 331-348
158. Cutting CB, Bookstein FL, Grayson BH, Fellingham L, McCarthy JG. Threedimensional computer-assisted design of craniofacial surgical procedures: optimization and interaction with cephalometrics and CT based models. Plast Reconstr Surg 1986; 77: 877-887
159. Grayson BH. Planning orthognathic surgery. In: Bardach J, Morris HL, eds. Multidisciplinary Management of Cleft Lip and Palate. Philadelphia: WB Saunders 1990: 494-500
160. Papadopoulos MA, Christou PK, Athanasiou AE, et al. Three-dimensional craniofacial reconstruction imaging. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002b; 93: 382-393
161. Sarver DM, Johnston MW, Matuka VJ. Video imaging for planning and counseling in orthognathic surgery. J Oral Maxillofac Surg 1988; 46: 939-945
162. Sinclair PM, Kilpelainen P, Phillips C, White RP Jr, Rogers L, Sarver DM. The accuracy of video imaging in orthognathic surgery. Am J Orthod Dentofac Orthop 1995; 107: 177-185
163. Gateno J, Teichgraeber JH, Aguilar E. Computer planning for distraction osteogenesis. Plast Reconstr Surg 2000; 105: 873-882
164. Graber TM. Craniofacial morphology in cleft palate and cleft lip deformities. Surg Gynecol Obstet 1949; 88: 359-368
165. Graber TM. Changing philosophies in cleft palate management. J Pediatr 1950; 37: 400-415
166. Graber TM. The congenital cleft palate deformity. J Am Dent Assoc 1954; 48: 375-395
167. Friede H, Pruzansky S. Long-term effects of premaxillary setback on facial skeletal profile in complete bilateral cleft lip and palate. Cleft Palate J 1985; 22: 97-105
168. Enemark H, Bolund S, Jorgensen I. Evaluation of unilateral cleft lip and palate treatment: longterm results. Cleft Palate J 1990; 27: 354-361
169. Paulin G, Thilander B. Dentofacial relations in young adults with unilateral cleft lip and palate. A follow-up study. Scand J Plast Reconstr Surg Hand Surg 1991; 25: 63-72

170. Semb G. A study of facial growth in patients with unilateral cleft lip and palate treated by the Oslo CLP team. Cleft Palate Craniofac J 1991a; 28: 1-21
171. Semb G. A study of facial growth in patients with bilateral cleft lip and palate treated by the Oslo CLP team. Cleft Palate Craniofac J 1991b; 28: 22-39
172. Trotman CA, Ross RB. Craniofacial growth in bilateral cleft lip and palate: ages six years to adulthood. Cleft Palate Craniofac J 1993; 30: 261-273
173. Smahel Z, Mullerova Z. Facial growth and development in unilateral cleft lip and palate during the period of puberty: comparison of the development after periosteoplasty and after primary bone grafting. Cleft Palate Craniofac J 1994; 31: 106-115
174. Heidbuchel KLWM, Kuijpers-Jagtman AM, Freihofer HPM. Facial growth in patients with bilateral cleft lip and palate: a cephalometric study. Cleft Palate Craniofac J 1994; 31: 210-216
175. Lopoo J, Hedrick M, Chasen S, et al. Natural history of fetuses with cleft lip. Plast Reconstr Surg 1999; 103: 34-38
176. Rowlatt U. Intrauterine wound healing in a 20-week human fetus. Virchows Arch 1979; 381: 353-361
177. Longaker MT, Adzick NS. The biology of fetal wound healing: a review. Plast Reconstr Surg 1991; 87: 788-798
178. Longaker MT, Bouhana K, Harrison MR, Danielpour D, Roberts A, Banda M. Wound healing in the fetus, possible role for inflammatory macrophages and transforming growth factor-ß isoforms. Wound Repair Regen 1994; 2: 104-112
179. Sharpe P, Ferguson M. Mesenchymal influences on epithelial differentiation in developing systems. J Cell Sci Suppl 1988; 10: 195-230
180. Mackool RJ, Gittes GK, Longaker MT. Scarless healing. The fetal wound. Clin Plast Surg 1998; 25: 357-365
181. Cass DL, Bullard KM, Sylvester KG, Yang EY, Longaker MT, Adzick NS. Wound size and gestational age modulate scar formation in fetal wound repair. J Pediatr Surg 1997; 32: 411-415
182. Longaker MT, Whitby DJ, Jennings R, et al. Fetal diaphragmatic wounds heal with scar formation. J Surg Res 1991b; 50: 375-385
183. Meuli M, Lorenz H, Hedrick M, et al. Scar formation in the fetal alimentary tract. J Pediatr Surg 1995; 30: 392-395
184. Mast B, Albanese C, Kapadia S. Tissue repair in the fetal intestinal tract occurs with adhesions, fibrosis, and neovascularization. Ann Plast Surg 1998; 41: 140-147
185. Lin KY, Posnick JC, al-Qattan MM. Fetal nerve healing: an experimental study. Plast Reconstr Surg 1994; 15: 811-816
186. Bol´shakova GB. The capacity for regeneration of the myocardium on rat fetuses. Ontogeny 1990; 21: 409-415
187. Michejda M, Bacher J, Kuwabara T, Hodgen GD. In utero allogeneic bone transplantation in primates: roentgenographic and histological observations. Transplantation 1981; 32: 96-100
188. Longaker MT, Moelleken BR, Cheng JC, et al. Fetal fracture healing in a lamb model. Plast Reconstr Surg 1992a; 90: 161-173
189. Goldstein JA, Posnick JC, Wells MD, Slate RK, Thorner PS. An assessment of postnatal growth after in utero long bone osteotomy with fixation. Plast Reconstr Surg 1994; 94: 160-166
190. Papadopulos N. Intrauterine Chirurgie zur fetalen Wundheilung am Beispiel eines operativ erzeugten Lippen-Kieferdefektes (Eine tierexperimentelle Studie). PhD Thesis, Munich: Technical Univ. of Munich, 2002a
191. Papadopulos NA, Papadopoulos MA, Zeilhofer HF, et al. Intrauterine Oberkieferrekonstruktion am Beispiel der Lippen-Kiefer-Gaumenspalten beim Schaffmodell. Chirurgisches Forum 2002b; 31: 557-560
192. Somasundaram K, Prathap K. The effect of exclusion of amniotic fluid on intra-uterine healing of skin wounds in rabbit foetuses. J Pathol 1972; 107: 127-130
193. Longaker MT, Whitby DJ, Adzick NS, Kaban LB, Harrison MR. Fetal surgery for cleft lip: a plea for caution. Plast Reconstr Surg 1991a; 88: 1087-1092
194. Rittenberg T, Longaker MT, Adzick SN, Ehrlich H. Sheep amniotic fluid has a protein factor which stimulates human fibroblast populated collagen lattice contraction. J Cell Physiol 1991; 149: 444-450
195. Ferguson MW, Howarth G. Marsupial models of scarless fetal wound healing. In: Adzick NS, Longaker MT, eds. Fetal Wound Healing. 1st Ed., New York: Elsevier 1991: 95-125
196. Armstrong J, Ferguson M. Ontogeny of the skin and the transition from scar-free to scarring phenotype during wound healing in the pouch young of a marsupial, Monodephis domestica. Dev Biol 1995; 169: 242-260
197. Chen W, Grant M, Schor A, Schor S. Differences between adult and foetal fibroblasts in the regulation of hyaluronate synthesis: correlation with migratory activity. J Cell Sci 1989; 94: 577-584
198. Alaish S, Yager D, Diegelmann R, Cohen I. Biology of fetal wound healing: hyaluronate receptor expression in fetal fibroblasts. J Pediatr Surg 1994; 29: 1040-1043
199. Adzick NS, Longaker MT. Animal models for the study of fetal tissue repair. J Surg Res 1991; 51: 216-222
200. Estes J, Van de Berg JS, Adzick NS, MacGillivray T, Desmoulière A, Gabbiani G. Phenotypic and functional features of myofibroblast in fetal sheep wounds. Differentiation 1994; 56: 173-181
201. Stelnicki EJ, Chin G, Gittes G, Longaker MT. Fetal wound repair: where do we go from here? Semin Pediatr Surg 1999a; 8: 124-130

202. Longaker MT, Whitby DJ, Adzick NS, et al. Studies in fetal wound healing: VI. Second and early third trimester fetal wounds demonstrate rapid collagen deposition without scar formation. J Pediatr Surg 1990a; 25: 63-69
203. Longaker MT, Dodson TB, Kaban LB. A rabbit model for fetal cleft lip repair. J Oral Maxillofac Surg 1990b; 48: 714-719
204. Hallock GG, Rice DC, Merkel J, DiPaolo B. Analysis of collagen content in the fetal wound. Ann Plast Surg 1988; 21: 310-315
205. Stelnicki EJ, Longaker MT, Holmes D, et al. Bone morphogenetic protein-2 induces scar formation and skin maturation in the second trimester fetus. Plast Reconstr Surg 1998c; 101: 12-19
206. Stelnicki EJ, Komuves L, Holmes D, et al. The human homeobox genes MSX-1, MSX-2, and MOX-1 are differentially expressed in the dermis and epidermis of fetal and adult skin. Differentiation 1997; 62: 33-41
207. Stelnicki EJ, Arbeit J, Cass D, Saner C, Harrison MR, Largman C. Modulation of the human homeobox genes PRX-2 and HOXB13 in scarless fetal wounds. J Invest Dermatol 1998a; 111: 57-63
208. Stelnicki EJ, Komuves L, Kwong A, et al. HOX homeobox genes exhibit spatial and temporal changes in expression during human skin development. J Invest Dermatol 1998b; 110: 110-115
209. Poon M, Hsu W, Bogadanov V, Taubman M. Secretion of monocyte chemotactic activity by cultured rat aortic smooth muscle cells in response to PDGF is due predominantly to the induction of JE/MCP-1. Am J Pathol 1996; 149: 307-317
210. Keever-Taylor C, Witt P, Truitt R, Ramanujam S, Borden E, Ritch P. Hematologic and immunologic evaluation of recombinant human interleukin-6 in patients with advanced malignant disease: evidence for monocyte activation. J Immunother Emphasis Tumor Immunol 1996; 19: 231-243
211. Roth M, Nauck M, Tamm M, Perruchoud A, Ziesche R, Block L. Intracellular interleukin 6 mediates platelet-derived growth factor-induced proliferation of nontransformed cells. Proc Natl Acad Sci USA 1995; 92: 1312-1316
212. Franchimont N, Canalis E. Platelet-derived growth factor stimulates the synthesis of interleukin-6 in cells of the osteoblast lineage. Endocrinology 1995; 136: 5469-5475
213. Liechty K, Crombleholme T, Cass D, Martin B, Adzick SN. Diminished interleukin-8 (IL-8) production in the fetal wound healing response. J Surg Res 1998; 77: 80-84
214. Liechty K, Adzick SN, Crombleholme T. Diminished interleukin 6 (IL-6) production during scarless human fetal wound repair. Cytokine 2000a; 12: 671-676
215. Liechty K, Kim H, Adzick SN, Crombleholme T. Fetal wound repair results in scar formation in interleukin-10-deficient mice in a syngeneic murine model of scarless fetal wound repair. J Pediatr Surg 2000b; 35: 866-873
216. Denison F, Kelly R, Calder A, Riley S. Cytokine secretion by human fetal membranes, decidua and placenta at term. Hum Reprod 1998; 13: 3560-3565
217. Cadet P, Rady P, Tyring S, Yandell R, Hughes T. Interleukin-10 messenger ribonucleic acid in human placenta: implications of a role for interleukin-10 in fetal allograft protection. Am J Obstet Gynecol 1995; 173: 25-29
218. Fortunato SJ, Menon R, Swan K, Lombardi SJ. Interleukin-10 inhibition of interleukin-6 in human amniochorionic membrane: transcriptional regulation. Am J Obstet Gynecol 1996; 175(4 Pt 1): 1057-1065
219. Elgert K, Alleva D, Mullins D. Tumor-induced immune dysfunction: the macrophage connection. J Leukoc Biol 1998; 64: 275-290
220. Heyborne K, McGregor J, Henry G, Witkin S, Abrams J. Interleukin-10 in amniotic fluid at midtrimester: immune activation and suppression in relation to fetal growth. Am J Obstet Gynecol 1994; 171: 55-59
221. Samuels P, Tan A. Review Article: Fetal scarless wound healing. J Otolaryngol 1999; 28: 296-302
222. Smith RJ, Xiao H, Jackson IT, Rhee C, Sanus G. Long-term facial growth after endoscopic and in-utero repair of a cleft lip model in the fetal lamb. Eur J Plast Surg 1997; 20: 27-32
223. Stelnicki EJ, Vanderwall K, Hoffman WY, et al. Adverse outcomes following endoscopic repair of a fetal cleft lip using an ovine model. Cleft Palate Craniofac J 1998d; 35: 425-429
224. Stelnicki EJ, Lee S, Hoffman W, et al. A long-term, controlled-outcome analysis of in utero versus neonatal cleft lip repair using an ovine model. Plast Reconstr Surg 1999b; 104: 607-615
225. Oberg KC, Robles AE, Ducsay C, et al. Endoscopic excision and repair of simulated bilateral cleft lips in fetal lambs. Plast Reconstr Surg 1998; 102: 1-9
226. Oberg KC, Robles AE, Ducsay CA, et al. Endoscopic intrauterine surgery in primates: overcoming technical obstacles. Surg Endosc 1999; 13: 420-426
227. Papadopulos NA, Zeilhofer HF, Papadopoulos MA, et al. Experimentelle endoskopische intrauterine Chirurgie bei kraniofazialen Fehlbildungen am Âeispiel der Lippen-Kiefer-Gaumenspalten. Z Mund Kiefer Gesichtschir 2003a; 7: 70-75
228. Papadopulos NA, Papadopoulos MA, Zeilhofer HF, et al. Intrauterine augenous fetal bone transplantation for the repair of cleft-like defects in the midgestational sheep model. J. Cranio-Maxillofac surg 2003c, (In process)
229. Dodson TB, Schmidt B, Longaker MT, Kaban LB. Fetal cleft lip repair in rabbits: postnatal facial

growth after repair. J Oral Maxillofac Surg 1991; 49: 603-611
230. Kaban LB, Dodson TB, Longaker MT, Stern M, Umeda H, Adzick S. Fetal cleft lip repair in rabbits: long-term clinical and cephalometric results. Cleft Palate Craniofac J 1993; 30: 13-21
231. Papadopulos NA, Deprest JA, Dumitrascu I, et al. Endoskopische fetale Chirurgie: Eine neue Perspektive in der fetalen Therapie? [Endoscopic fetal surgery: a new perspective in fetal therapy?] Sozialpaediatrie - Kinder- und Jugendheilkunde 2000; 22: 14-22
232. Estes JM, Whitby DJ, Lorenz HP, et al. Endoscopic creation and repair of fetal cleft lip. Plast Reconstr Surg 1992a; 90: 743-749
233. Hallock GG. In utero cleft lip repair in A/J mice. Plast Reconstr Surg 1985; 75: 785-790
234. Sullivan WG. In utero cleft lip repair in the mouse without an incision. Plast Reconstr Surg 1989; 84: 723-732
235. Papadopoulos MA, Papadopulos NA, Jannowitz C, et al. Drei-dimensionale computertomographische Auswertung des Mittelgesichts-Wachstums nach intrauteriner Wiederherstellung von chirurgisch erzeugten Oberkieferdefekten am Schaffetus. Chir Forum 2003; 32,17-19
236. Oberg KC, Evans ML, Nguyen T, Peckham NH, Kirsch WM, Hardesty RA. Intrauterine repair of surgically created defects in mice (lip incision model) with a microclip: preamble to endoscopic intrauterine surgery. Cleft Palate Craniofac J 1995; 32: 129-137
237. Bardach J, Eisbach KJ. The influence of primary unilateral cleft lip repair on facial growth. Cleft Palate J 1977; 14: 88-97
238. Bardach J, Klausner EC, Eisbach KJ. The relationship between lip pressure and facial growth after cleft lip repair: an experimental study. Cleft Palate J 1979; 16: 137-146
239. Bardach J, Roberts DM, Yale R, Rosewall D, Mooney M. The influence of simultaneous cleft lip and palate repair on facial growth in rabbits. Cleft Palate J 1980; 17: 309-318
240. Bardach J, Mooney M, Giedrojc-Juraha ZL. A comparative study of facial growth following cleft lip repair with or without soft-tissue undermining: an experimental study in rabbits. Plast Reconstr Surg 1982; 69: 745-754
241. Bardach J, Bakowska J, McDermott-Murray J, Mooney MP, Dusdieker LB. Lip pressure changes following lip repair in infants with unilateral clefts of the lip and palate. Plast Reconstr Surg 1984; 74: 476-481
242. Stern M, Schmidt B, Dodson TB, Stern R, Kaban LB. Fetal cleft lip repair in rabbits: histology and role of hyaluronic acid. J Oral Maxillofac Surg 1992; 50: 263-269
243. Hallock GG, Rice DC, McClure HM. In utero lip repair in the rhesus monkey: an update. Plast Reconstr Surg 1987; 80: 855-858
244. Beck GJ, Bruce RA, Fonseca RJ. The effect of antenatal surgery on postnatal palatal growth in sheep. J Oral Maxillofac Surg 1988; 46: 217-223
245. Longaker MT, Stern M, Lorenz P, Whitby DJ, Dodson TB, Harrison MR, et al. A model for fetal cleft lip repair in lambs. Plast Reconstr Surg 1992b; 90: 750-756
246. Stern M, Dodson TB, Longaker MT, Lorenz HP, Harrison MR, Kaban LB. Fetal cleft lip repair in lambs: histologic characteristics of the healing wound. Int J Oral Maxillofac Surg 1993; 22: 371-374
247. Canady JW, Landas SK, Morris H, Thompson SA. In utero cleft palate repair in the ovine model. Cleft Palate Craniofac J 1994; 31: 37-44
248. Canady JW, Thompson SA, Colburn A. Craniofacial growth after iatrogenic cleft palate repair in a fetal ovine model. Cleft Palate Craniofac J 1997; 34: 69-72
249. Hedrick MH, Rice HE, Vander Wall KJ, et al. Delayed in utero repair of surgically created fetal cleft lip and palate. Plast Reconstr Surg 1996; 97: 900-907
250. Hedrick MH, Longaker MT, Harrison MR. A fetal surgery primer for plastic surgeons. Plast Reconstr Surg 1998; 101: 1709-1729
251. Papadopulos NA, Papadopoulos MA, Zeilhofer HF, et al. Intrauterine fetal surgery & cleft lip and palate: Current status and new perspectives. Scand J Plast Reconstr Surg 2003d, (In process)
252. Estes JM, MacGillivray TE, Hedrick MH, Adzick NS, Harrison MR. Fetoscopic surgery for the treatment of congenital anomalies. J Pediatr Surg 1992b; 27: 950-954
253. Estes JM, Szabo Z, Harrison MR. Techniques for in utero endoscopic surgery. A new approach for fetal intervention. Surg Endosc 1992c; 6: 215-218
254. Sylvester KG, Yang EY, Darrell LC, Crombleholme TM, Adzick NS. Fetoscopic gene therapy for congenital lung disease. J Pediatr Surg 1997; 32: 964-969
255. Evans ML, Oberg KC, Kirsch W, Zhu YH, Hardesty RA. Intrauterine repair of cleft lip-like defects in lambs with a novel microclip. J Craniofac Surg 1995; 6: 126-131
256. Bruner JP, Richards WO, Tulipan NB, Arney TL. Endoscopic coverage of fetal myelomeningocele in utero. Am J Obstet Gynecol 1999; 180: 153-158
257. Bruner JP, Tulipan NE, Richards WO. Endoscopic coverage of fetal open myelomeningocele in utero. Am J Obstet Gynecol 1997; 176: 256-257
258. Bruner JP, Tulipan NB, Richards WO, Walsh WF, Boehm FH, Vrabcak EK. In utero repair of myelomeningocele: a comparison of endoscopy and hysterotomy. Fetal Diagn Ther 2000; 15: 83-88
259. Papadopulos NA, Papadopoulos MA, Zeilhofer

HF, et al. Intrauterine Surgery: clinical applications and surgical considerations for the treatment of Cleft lip and Palate. 2nd World Cleft Congress of the International Cleft Lip and Palate Foundation, Munich, Germany, www.cleft 2002.com, 2002c
260. Weinzweig J, Panter KE, Pantaloni M, et al. The Fetal Cleft Palate: I. Characterization of a Congenital Model. Plast Reconstr Surg 1999a; 103: 419-428
261. Weinzweig J, Panter KE, Pantaloni M, et al. The Fetal Cleft Palate: II. Scarless Healing after in Utero Repair of a Congenital Model. Plast Reconstr Surg 1999b; 104: 1356-1364
262. Weinzweig J, Panter KE, Spangenberger A, Harper JS, McRae R, Edstrom LE. The Fetal Cleft Palate: III. Ultrastructural and Functional Analysis of Palatal Development following In Utero Repair of the Congenital Model. Plast Reconstr Surg 2002; 109: 2355-2362
263. Longaker M, Kaban L. Fetal models for craniofacial surgery: cleft lip/palate and craniosynostosis. In: Adzick S, Longaker M, eds. Fetal Wound Healing. New York: Elsevier Scientific Press 1991e; 95-125
264. Stelnicki E, Vanderwall K, Harrison M, Longaker M, Kaban L, Hoffman W. The in utero correction of unilateral coronal craniosynostosis. Plast Reconstr Surg 1998e; 101: 287-296
265. Paul T and Brandt RS. Oral and dental health status of children with cleft lip and/or palate. Cleft Palate Craniofac J 1998; 35: 329
266. Pruzinsky T. Social and psychological effects of major craniofacial deformity. Cleft Palate Craniofac J 1992; 29: 578
267. Benson BA, Gross AM, Messer SC, Kellum G, Passmore LA. Social support networks among families of children with craniofacial anomalies. Health Psychol 1991; 10: 252
268. Warschausky S, Kay JB, Buchmann S, Halberg A. Berger M. Health-related quality of life in children with craniofacial anomalies. Plast Reconstruct Surg 2002; 110: 409-414
269. Mayer A. Über die Möglichkeit operativer Eingriffe beim lebenden Saugtierfötus [About the possibility of operative interventions in alive animal fetus]. Zentralbl Gynäkol 1918; 42: 773
270. Christ JE, Meininger MG. Ultrasound diagnosis of cleft lip and cleft palate before birth. Plast Reconstr Surg 1981; 68: 854-859
271. Harrison MR, Anderson J, Rosen MA, Ross NA, Hendrickx AG. Fetal surgery in the primate I. Anesthetic, surgical, and tocolytic management to maximize fetal-neonatal survival. J Pediatr Surg 1982; 17: 115-122
272. Papadopoulos NA, Jannowitz C, Christou P, et al. Fetal surgical treatment of cleft-lip and palate: A real possibility or an utopia? Hell Plast Surg 2002a; 1: 191-203
273. Papadopulos NA, Van Ballaer PP, Ordonez JL, et al. Fetal membrane closure techniques after hysteroamniotomy in the midgestational rabbit model. Am J Obstet Gynecol 1998; 178: 938-942
274. Papadopulos NA, Dumitrascu I, Ordonez JL, et al. Fetoscopy in the pregnant rabbit at midgestation. Fetal Diagn Ther 1999; 14: 118-121
275. Papadopulos NA, Klotz S, Henke J, et al. Chirurgische Verschlussmethoden von fetoskopisch erzeugten Membrandefekten am mittelträchtigen Kaninchenmodell. Geburtshilfe und Frauenheilkunde 2003b; 63: 1-7
276. Papadopulos NA, Klotz S, Henke J, et al. Successful anatomic repair of feto-endoscopic access sites in the mid-gestational rabbit model. Am J Obstet Gynec 2003e, (in process)
277. Millard DR. Cleft Craft-The Evolution of Its Surgery. The Unilateral Deformity. Vol. 1. Boston: Little, Brown 1976
278. Millard DR Jr, Latham RA. Improved primary surgical and dental treatment of clefts. Plast Reconstr Surg 1990; 86: 856-871

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