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. 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. Their etiology is complex, including multiple genetic and environmental factors, 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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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, postoperative 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 fetoendoscopic surgical approaches in the future also by non life-threatening conditions, such as the craniofacial malformations (i.e. cleft lip and palate).

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
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 their normal development are not yet well known.

More than 400 syndromes have been already associated with CLP\textsuperscript{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\textsuperscript{2,12,17}. The incidence of CL/P is approximately twice that of CP, thus CL/P is most common in males\textsuperscript{18}, while CP is more common in females\textsuperscript{19}. In addition, the left side is affected twice as often as the right\textsuperscript{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 orofacial clefting\textsuperscript{7,20-23}. Maternal age can also influence the likelihood of children with clefts\textsuperscript{19}.

Children of epileptic mothers have a greater risk than the general population for congenital malformations, possibly including CP\textsuperscript{18,24}. Anti-epileptic, corticosteroid or prednisolone medication during the first trimester of pregnancy has also been implicated in CP\textsuperscript{25-28}. Finally, alcohol consumption and cigarette smoking seems to play also an important role in cleft etiology\textsuperscript{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\textsuperscript{36-56}.

Craniofacial growth and development in patients 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\textsuperscript{57-66}. In addition, many authors have observed normal growth or premaxillary protrusion in patients with unrepaired CLP\textsuperscript{56,60,63,67-70}.

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)
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. 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.

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 follow-up care in a multidisciplinary manner: audiolologic 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. 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. Many authors believe that primary repair of the unilateral CL and nose needs to be performed in conjunction with muscular reconstruction of the lip. 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. The timing of CL repair generally varies from several days of age to 6 months. 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.
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

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

<table>
<thead>
<tr>
<th>Age of patient</th>
<th>Surgery</th>
<th>Orthodontics</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 3 days</td>
<td>Counseling and information to the parents</td>
<td>Counseling</td>
</tr>
<tr>
<td>1 - 4 weeks</td>
<td>Regular ENT check until adulthood</td>
<td>Presurgical infant orthopedics if undertaken</td>
</tr>
<tr>
<td>2 weeks - 6 months</td>
<td>Primary lip closure</td>
<td></td>
</tr>
<tr>
<td>3 - 9 months</td>
<td>Early soft palate repair if undertaken</td>
<td></td>
</tr>
<tr>
<td>18 - 24 months</td>
<td>Surgical closure of the palate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary bone grafting if undertaken</td>
<td></td>
</tr>
<tr>
<td>2 - 5 years</td>
<td>Early secondary bone grafting if undertaken</td>
<td></td>
</tr>
<tr>
<td>3 - 6 years</td>
<td>Nasoendoscopy and/or surgical pharyngoplasty</td>
<td>Early orthodontics / Primary dentition treatment</td>
</tr>
<tr>
<td>6 - 11 years</td>
<td>Secondary bone grafting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgical secondary lip closure</td>
<td>Mixed dentition treatment</td>
</tr>
<tr>
<td></td>
<td>Surgical closure of fistulae</td>
<td></td>
</tr>
<tr>
<td>11 – 14 years</td>
<td></td>
<td>Comprehensive orthodontics / Permanent dentition treatment</td>
</tr>
<tr>
<td>17 – 19 years</td>
<td>Orthognathic surgery</td>
<td>Orthodontics in conjunction with orthognathic surgery</td>
</tr>
<tr>
<td></td>
<td>Lip / Nose revision</td>
<td></td>
</tr>
</tbody>
</table>
maxillary retrusion requires orthognathic surgery in approximately 25% of the CLP patients. 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, due to the mechanical molding action of the muscles and the tight and scarred tissues. 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.

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: (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. This orthopedic approach makes CLP repair easier and may improve the aesthetic outcome of primary CL nasal repair by repositioning the alar base. 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.

Primary dentition treatment

Orthodontic intervention in the primary dentition has been recommended over the past 60 years, although less in recent years. Suggested treatment at that time ranged from full banding to routine arch expansion.

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. 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. 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. In these cases in which space closure is not possible, the use of adhesive bridgeworks or of implants 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.

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, video imaging, and computer-generated images 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, which documented severe three-dimensional maxillary collapse in patients with complete clefts following surgical repair, numerous other cephalometric studies have been published describ-
ing varying degrees of maxillary sagittal deficiency110,166-174. 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 correction14.

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 operations175, 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 formation176. 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[197,198,182,183,184], collagen[192,193,194,195,196,199,200,201], oxygen[192,193,194], growth factors[178,201,202], homeobox genes[203-205], tenascin[196], and interleukine[199-201].

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 with this plane of fetoscopy 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 (Preterm Premature Rupture Of the fetal Membranes)[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 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[179,230,233-235], 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[193,233,234]. 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.[232,233,229,230,237-242]. (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-
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.

**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.

One of the first demonstrations ever reported, was the feasibility of feto-endoscopic suturing in the mid-gestational pregnant sheep model. 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.

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. 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. Taking advantage of this technique, different studies have been proposed in large, long gestational animal models: the non-primate and the primate models.

**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. 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.

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. 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 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.

In an attempt to find a model for the craniostenosis, Longaker and Kaban used 3D computer tomography for the reconstruction and measurement of the skulls. 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 craniostenosis 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 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 - 133th gestational day)246. 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 premaxilla222. 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 repair224. 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 midgestation 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 transplantation247-189.

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 defect222-226,230,236,242,243,245,249. Therefore, using a previously described animal model with surgically created CL and underlying maxillary alveolar defect247, our team attempted the "surgical" repair of a CL malformation in its whole entity219,235 (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 model227, we gained valuable experience for a further application that we intend in the delayed animal model described by Hedrick and colleagues249, as well as the application of the feto-endoscopic approach in this latter model.

At the second look operation of our first study191, the evaluation of the three-dimensional computer tomography (3D-CT), the two-dimensional maxi-
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. 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 bioreabsorbable 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. 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. 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.

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.

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 postnatal 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, an explosive development of Sophisticated methods for prenatal diagnosis, as well as anesthetic, tocolytic and operative management to maximize feto-maternal survival began only in the eighties. 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, 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. In addition, recent advances in fetoscopy, 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. 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. 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.

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 fetoscopy and 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.

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, attempting this way the “surgical” repair of a CL malformation in its whole entity. 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. Nowadays we are evaluating the rotation-advancement flap technique, 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. 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 fetoscopy 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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