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# Intrauterine Cleft Repair: Step towards Perfection

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**Abstract:**
The old concept of fetal surgeries being limited to life threatening malformations is being replaced by ever increasing research for application in cleft surgeries. Fetal cleft repair is an attractive option for the reconstructive surgeon considering the advantage of scarless wound healing. But its role in non life-threatening malformations is restricted based on lack of feasibility and risk to benefit ratio of intrauterine intervention. In the future, in utero surgical intervention for non life-threatening disease may become possible as fetal surgery becomes safer for the mother and foetus resulting in a major breakthrough in the field of cleft and craniofacial anomalies.
**Keywords:** Intrauterine cleft repair, non life-threatening disease, scarless repair.

**Introduction:**

Clefts of lip and palate vary in their presentations from mild to severe, and may be associated with deficient craniofacial development. Even the most expert and sophisticated methods of surgical repair of these defects are followed by scar contraction and fibrosis with subsequent skeletal defects, dental abnormalities, cosmetic disfigurement, and speech impairment.[1] The continuous refinement and further development of prenatal diagnostics, anesthesia as well as operative techniques have rendered fetal surgery a point of major clinical interest and has raised the possibility of fetal cleft lip and palate repairs.[2]

Fetal cleft repair is an attractive intervention for plastic surgeons as it affords the potential to provide a scarless repair that more closely approximate normalcy owing to the foetus' marked plasticity.[3,4] Furthermore, scarless fetal lip and palate repairs may prevent the ripple effect of postnatal scarring with its resultant

secondary dentoalveolar and midface growth deformities.[4] These potential benefits can dramatically reduce the number of postnatal reconstructive procedures in children with facial clefts. Furthermore, the impact on cost management could be dramatic with a decreased need for extensive postoperative care, orthodontia, and speech therapy. Unfortunately, no long-term outcome studies have been performed to evaluate the efficacy of these repairs.[4] This article reflects on the potential research in this arena and considers intrauterine cleft repair as the next generation surgical advancement.

**Intrauterine Cleft Repair:**

Reliable prenatal diagnosis of anatomic malformations using ultrasonography has led to an interest in fetal surgery to correct conditions that are potentially fatal.[1] Before fetal surgery can be considered for a condition that is not life threatening, such as cleft lip, the benefits must outweigh the risks.[5] Thus a procedure is needed that is rapid, minimally invasive, and provides significant benefit over current protocols.[5]

Fetal cleft lips and palates can be identified in utero prior to 20 weeks gestation.[6-9] Thus the technology exists for fetal surgeries to be performed for cleft lip and palate prior to 20 weeks gestation.[5] It has yet to be demonstrated, however, whether this would be early enough in human development for “regeneration” of the lip and palate following approximation of the cleft edges.[5] Previous experience with fetal cleft lip surgery in mice has shown that mere approximation of the cleft edges during development can lead to fusion and a recapitulation of the normal lip architecture.[5,10]

In utero therapy is attractive to plastic surgeons because it affords the potential to (1) provide a scarless repair, (2) correct the primary deformity, (3) prevent secondary deformities, and (4) give the parents a "normal"-appearing child at birth.[11] A number of studies reviewed by Longaker and Adzick[1,12] using fetal lamb have demonstrated that epidermal wounds heal clinically and histologically without scar formation when repaired in mid gestation. In utero repair of cleft lip and alveolus[13] and endoscopic repair of cleft lip[14,15] have been shown to result in healing without scar formation in fetal lambs operated at 75 days gestation.

The secondary palate is a complex structure, especially with respect to the muscle attachments and the structural associations of these attachments to the hard tissues, with anatomy and function that are different from that of the lip and alveolus.[1] A hypothesis states that fetal palate would heal without scar when repair was performed early in gestation at times similar to that reported for lip and alveolus.[1] It is possible that the tissues of the palate may differentially reach the critical period of scar formation at varying time periods during gestation.[1] Cleft palate repair in utero is technically feasible and results in scarless healing of the mucoperiosteum and velum.

Fetal wound healing has been studied in chick embryos, mice, rats, guinea pig, rabbits, opossum, lambs and monkeys.[1,12] Larger animal models offer the advantage of large fetal size, making fetal manipulation easier and a long gestation allowing for fetal intervention at various times throughout the pregnancy.[15] There is a spectrum to fetal tissue repair as a function of gestational age with a transition from scar-free to scarring as the foetus gets older.[16-18]

**Review of Literature:**

Intrauterine repairs of cleft lips in fetal mice[10,19] and sheep[13] have demonstrated excellent wound healing reminiscent of regeneration. Currently fetal surgery entails an open hysterotomy and fetal exposure, both of which impart significant risks to the mother and foetus.[20] An endoscopic approach would eliminate exposure of the foetus to the outside environment and reduce the risks of a major operation for the mother.[14] However, certain inherent limitations are well recognised when suturing through the endoscope. These include: difficulty in suture placement, external knot tying with subsequent advancement through the endoscope, and knot placement without excessive tissue damage.[5,14]

In other studies on intrauterine cleft lip repair, a paucity of fetal inflammatory response to the repair has been observed. Nylon or nonabsorbable suture has, however, been utilized, which, by its relative inertness, induces less of an inflammatory response than absorbable suture. Moreover, because of its limited absorbability, nylon suture is not the most suitable material for intrauterine cleft lip repair.[5] The absorbable chromic sutures depend upon an inflammatory response to digest the suture. Absorbable sutures such as *vicryl* rely on hydrophobic dissolution and may be better suture candidates for fetal surgery. However, little is known about their dissolution in the fetal environment.[5] Even a relatively inert suture such as nylon stimulates an increased mononuclear cell infiltration and giant cell formation surrounding the suture. Mononuclear component has been reported as a significant player in scar formation.[5,12]

Thus, based on current suturing limitations and the risks associated with open hysterotomy, a newly developed nonpenetrating microclip was utilized that rapidly approximated the tissues and has the potential for percutaneous endoscopic application.[5,21] Tissue remodelling left little histologic evidence of clip application. Microclips provide a more rapid and technically less difficult, method of tissue approximation in fetal cleft lip repair than can be accomplished by traditional suturing. Furthermore, the nonpenetrating nature of the microclip enables impermanent application without the induction of an inflammatory response. Thus, by being technically less difficult and more rapid to apply, the microclip could reduce operative time and the associated risks to the mother and the foetus.[5]

Studies in rats and monkeys[22] support the general principle that there is a critical period in gestation in which there is a change from a regenerative healing pattern without scarring to an adult pattern of collagen deposition and scar formation with contraction. There is evidence that incisional epidermal wounds produced in lambs at 75 and 100 days gestation heal without scar formation[23] Repair of iatrogenically induced cleft lip[12] and cleft lip and alveolus[13] in lambs at 75 days gestation showed healing with no evidence of scar formation. Iatrogenically produced cleft palate was repaired in fetal lamb at 70 days gestation without significant scar formation and the overall normal architecture of the palate was not compromised when examined histologically with only a few loci of fibrous tissue within the surgical area, predominantly at the junction of hard and soft palate in a study by Canady et al.[1] But they concluded that even at the earliest timepoint of fetal surgery in their study (70 days), there was some scarring present in the deeper tissues.

Sheep is an excellent model for fetal surgery due to long gestation period, size of foetus and resistance to spontaneous abortion following surgery. The fetal lamb has proved to be an appropriate and successful model for studies of wound healing and has been shown to be especially applicable to studies of cleft lip and palate repair.[1] After birth, significant craniofacial growth has taken place at 5 to 6 months of age, making the lamb a useful model for craniofacial growth, as well. The influence of surgical repair of the cleft palate on associated abnormal facial growth and development of speech patterns is controversial.[1] Thus far, little has been done using the ovine model to study craniofacial growth. In a few studies,[18,24-26] development of the maxilla was found to be more normal in animals repaired prenatally than those left unrepaired. Studies in other animal models suggest that lip repair postnatally is related to significant midface growth retardation, presumably because of increased lip pressure due to scarring and contracture.[27,28] Histologically, in utero repair of clefts was indeed scarless and there was no diminution in maxillary growth. However, both in utero and postnatal lip repairs produced lips that were significantly shorter than their contralateral noncleft sides.[29] This degree of lip shortening would require a secondary lip revision, thereby defeating the purpose of performing an intrauterine repair.[29]

Although the uterus may be more amenable to manipulation and endoscopic intrusion during the second trimester, thus less likely to incite preterm labour, fetal surgery for nonlife-threatening conditions at this gestational age may evoke justifiable ethical opposition, because the foetus is not yet viable and some risk of fetal loss is inevitable, even with an endoscopic approach. Speculation remains regarding the real potential benefits compared to the risks of fetal surgery for nonlife-threatening malformations.[5] Longaker and co-workers stressed that a great deal of caution and research needs to be employed before attempts at human repairs can be undertaken.[20] Technologic advancements, however, like microclips, which may contribute to the reduction of maternal and fetal risks, are likely to advance our skills in intrauterine surgical intervention of fetal malformations.[5]

**Conclusion:**

Although, the last few decades have seen a plethora of advancements in cleft repair and management, the perspective of inutero therapy remains insufficiently explored. Detailed review of the literature highlights the fact that not much research has been done in the recent past. Inspite of in utero repair of selected life-threatening malformations in the human foetus being a clinical reality, fetal surgery continues to pose significant risks to both the mother and the unborn child. Numerous studies performed in animal models are an evidence to potential benefits of fetal surgery to cleft repairs, yet their application in humans still awaits ethical and technical clearance.[30] Justification of such procedures require many more researches to prove the feasibility and safety of these intrauterine surgeries in humans which can be a major breakthrough and a potential prospective in the field of cleft therapies.

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