Experimental Fetal Uropathy

Alexander Springer
Department of Pediatric Surgery, Vienna
Experimental work for pathogenesis and anatomy

Experimental work for treatment options
(fetal surgery)

Experimental work for molecular basics

Experimental work for fetal transplantation

Experimental work for biomarkers
Experimental work for pathogenesis and anatomy
How can PUV have such a great variety of clinical features?
What is reflux nephropathy, acquired scarring and renal dysplasia?
What is crosstalk?
What is the difference between hyperplasia and hypertrophy?
How can these mechanism play a role in an environment where fetal kidneys do not participate in filtration and elimination process?
Experimental models of fetal obstructive nephropathy
Hinman 1923 renal counterbalance studies in dogs

Jost 1946 fetal rabbit model: removal of testis leads to feminization of fetus

Louw and Barnard 1955 intestinal atresia in fetal dogs

Thomasson 1970 fetal ureteral ligation in rabbits

Beck 1971 fetal ureteral ligation in lambs
Harris 1973 Renal function after release of unilateral ureteral obstruction in rats

Vallancien 1976 Experimental vesico-renal reflux in the sheep fetus

Sauvage 1982 Intra-uterine urologic surgery in the lamb. Development of an experimental protocol
1982 Harrison obstructive uropathy in the fetal lamb
Correction of congenital hydronephrosis in utero. I.
The model: fetal urethral obstruction produces
hydronephrosis and pulmonary hypoplasia in
fetal lambs
Correction of congenital hydronephrosis in utero II.
Decompression reverses the effects of
obstruction on the fetal lung and urinary tract
Correction of congenital hydronephrosis in utero III. Early mid-trimester ureteral obstruction produces renal dysplasia.

Correction of congenital hydronephrosis in utero IV: in utero decompression prevents renal dysplasia.
**Figure 18-1.** Malformations and deformations associated with lower urinary tract obstruction.
Renal Dysplasia

Age of onset (earlier = greater risk)

Duration of obstruction (longer = greater risk)

Early relief of obstruction prevents dysplasia
Kim et al 1992 Acute hemodynamic and endocrinological effects of partial fetal bladder obstruction
Peters et al 1992 The response of the fetal kidney to obstruction

Peters et al 1992 The effect of obstruction on the developing bladder
Gobet et al, 1998 Experimental vesicoureteral reflux in the fetus depends on bladder function and causes renal fibrosis

Gobet et al, 1999 Experimental fetal vesicoureteral reflux induces renal tubular and glomerular damage, and is associated with persistent bladder instability
Experimental work for treatment options (fetal surgery)
Deprest et al 1995 Intrauterine endoscopic creation of urinary tract obstruction in the fetal lamb: a model for fetal surgery
Kitagawa et al, 2003 Optimal timing of prenatal treatment of obstructive uropathy in the fetal lamb
Minimally Traumatic Techniques for In Utero Access and Fetal Surgery

Christopher J. Calvano, PhD, MD, Michael E. Moran, MD, Bryan A. Mehlhaff MD, Pramod P. Reddy, MD, James Mandell, MD

JSLS (1998)2:227-233
Kitagawa et al, 2006 Vesicoamniotic shunt for complete urinary tract obstruction is partially effective
Feasibility of minimally invasive intrauterine fetal access in a monkey model.

Feitz WF, Sleegers EA, de Gier RP, Aarnink RG, Arts T, van der Wildt B.
Department of Urology, University Hospital Nijmegen, The Netherlands.

Abstract

PURPOSE: We evaluated new intervention techniques and surgical instruments in a fetal monkey model to determine improvements that would be useful for early intrauterine intervention. Our findings may be helpful in the future for treating select cases of severe prenatal obstructive uropathology.

MATERIALS AND METHODS: In a series of experiments on 18 pregnant rhesus monkeys (Macaca mulatta) at mid trimester we assessed various endoscopic intra-amniotic access techniques as well as morbidity, mortality and possibilities for fetoscopy.

RESULTS: In all 18 fetuses adequate fetoscopy was possible with no maternal mortality. Of the 18 pregnancies 14 went to term with no early or late postoperative complications. Technical improvements changed the intrauterine access technique from open placement of trocars to the use of the Seldinger technique, gun introduction of needles with small caliber sheets and small caliber introduction trocars, resulting in minimal amniotic membrane separation. Various rigid and flexible endoscopes were evaluated for fetoscopy and up to 3 cannulas were placed. No change in the fetal growth pattern was observed on postoperative ultrasound. Subsequent pregnancies occurred during this study period, and there were no acceptance problems of the newborns by the mothers.

CONCLUSIONS: New techniques have led to improved intrauterine fetal access. Morbidity mainly depends on the disruption of amniotic membranes, which has an important preterm role. Adapted endoscopes and other instruments offer new possibilities for fetal diagnosis and therapy in the future. Our primate model seems to be suitable for evaluating these new techniques before they are used in a clinical setting.
In utero surgery rescues neurological function at birth in sheep with spina bifida

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²Microsurgical Laboratory, Davies Medical Center, San Francisco, California 94114, USA
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We hypothesize that the neurologic deficit associated with open spina bifida is not directly caused by the primary defect but rather is due to chronic mechanical and chemical trauma since the unprotected neural tissue is exposed to the intrauterine environment. We report here that exposure of the normal spinal cord to the amniotic cavity in midgestational sheep fetuses leads to a human-like open spina bifida with paraplegia at birth, indicating that the exposed neural tissue is progressively destroyed during pregnancy. When open spina bifida was repaired in utero at an intermediate stage, the animals had near-normal neurologic function. The spinal cord was deformed but largely preserved. These findings suggest that secondary neural tissue destruction during pregnancy is primarily responsible for the functional loss and that timely in utero repair of open spina bifida might rescue neurologic function.
Percutaneous fetoscopic patch coverage of experimental lumbosacral full-thickness skin lesions in sheep

A minimally invasive technique to minimize maternal trauma from fetal surgery for myelomeningocele

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Percutaneous Fetoscopic Patch Coverage of Spina Bifida Aperta in the Human – Early Clinical Experience and Potential

Thomas Kohl\textsuperscript{a,b} Rudolph Hering\textsuperscript{c} Axel Heep\textsuperscript{d} Carlo Schaller\textsuperscript{e} Bernhard Meyer\textsuperscript{e} Claudia Greive\textsuperscript{c} Gabriele Bizjak\textsuperscript{a} Tim Buller\textsuperscript{b} Patricia Van de Vondel\textsuperscript{a} Wiebke Gogarten\textsuperscript{f} Peter Bartmann\textsuperscript{d} Gisela Knöpfle\textsuperscript{g} Ulrich Gembruch\textsuperscript{a}

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**Objective:** The current operative approach for fetal repair of spina bifida aperta requires maternal laparotomy and hysterotomy. Following technical feasibility studies in sheep, we performed percutaneous fetoscopic patch coverage of this lesion in 3 human fetuses between 23 + 4 and 25 + 3 weeks of gestation. **Methods and Results:** Whereas the patch detached in the first case 3 weeks after the procedure, it covered the exposed neural tissue in the 2 other fetuses beyond their delivery. Two of the three children survived, but 1 unexpectedly died from a ventilation problem in its 3rd week of life. In 1 of the 2 survivors, ventriculoperitoneal shunt insertion was delayed. **Conclusions:** Percutaneous fetoscopic patch coverage of spina bifida aperta is feasible in human fetuses and offers a substantial reduction of maternal trauma compared to open fetal repair. Further clinical experience is now required before the efficacy of the new ap-
Intra-uterine tissue engineering of full-thickness skin defects in a fetal sheep model


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g Department of Pathology, Radboud University Nijmegen Medical Centre, 6500 HB Nijmegen, The Netherlands
SKILL AND TALENT

Bladder changes after several coverage modalities in the surgically induced model of myelomeningocele in lambs

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Abstract

Objective: To assess the presence of early bladder abnormalities in a prenatally corrected and uncorrected animal model of Myelomeningocele (MMC).

Method: A MMC-like lesion was surgically created in 18 fetal lambs between the 60th and the 80th day of gestation. Eight of them did not undergo fetal repair (group A), three were repaired with an open two-layer closure (group B), three using BioGlue® (group C) and four fetoscopically (group D). At term, bladders were examined macroscopically and histopathological changes were assessed using H–E and Masson Trichrome.

Results: Five animals in group A (5/8, 62%), two in group B (2/3, 66%), one in group C (1/3, 33%) and one in group D (1/4, 25%) survived. Macroscopically bladders in group A were severely dilated and showed thinner walls. Microscopically they showed a thin layer of colagenous tissue (Blue layer. BL) lying immediately subjacent to the urothelium. The muscular layers were thinner. Non compliant pattern with thick wall and low capacity was also found in the non corrected model. Group B and the control showed preservation of muscular layers and absence of BL. Groups C and D presented BL but also preservation of muscular layers.

Conclusion: Bladder changes in a surgically induced model of MMC can be described using histopathological data. Both extremes of bladder changes can be observed in the model. These changes were completely prevented with open fetal surgery and partially with other coverage modalities.

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Experimental work for molecular basics
Chronic partial ureteral obstruction and the developing kidney

Robert L. Chevalier
Experimental models of fetal obstructive nephropathy
<table>
<thead>
<tr>
<th>Pathway</th>
<th>Stimulates injury</th>
<th>Interaction</th>
<th>Inhibits injury</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Interstitial inflammation</td>
<td>Angiotensin II</td>
<td>↔</td>
<td>ACEI, ARB</td>
<td>Inhibitors deleterious in fetus and neonate</td>
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<td>CD44&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>CTGF</td>
<td>↔</td>
<td>Pentoxifylline</td>
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Chevalier 2006
Gobe, Axelen 1987 Genesis of renal tubular atrophy in experimental hydrenal nephrosis in the rat. Role of apoptosis
Choi et al, 2000 Mechanism of chronic obstructive uropathy: increased expression of apoptosis-promoting molecules
El-Dahr et al 1993 Upregulation of renin-angiotensin system and downregulation of kallikrein in obstructive nephropathy

Norwood et al 1994 Neonatal ureteral obstruction stimulates recruitment of renin-secreting renal cortical cells
Springer et al 2012  Transcriptomics and bioinformatics analysis of renal damage in fetal unilateral obstructive uropathy

Springer et al, in review  Transcriptional response characterizing compensatory contra-lateral renal growth in fetal unilateral ureteral obstruction
Experimental work for fetal transplantation
Prenatal Diagnosis → Organ failure

Hematopoietic Chimerism

Donor Specific Tolerance

Neonatal Organ Transplantation
In Utero Hematopoietic Stem Cell Transplants Prolong Survival of Postnatal Kidney Transplantation in Monkeys

By George B. Mychaliska, Henry E. Rice, Alice F. Tarantal, Peter G. Stock, Jan Capper, Marvin R. Garovoy, Jean L. Olson, Morton J. Cowan, and Michael R. Harrison
San Francisco, California

The authors hypothesized that in utero transplantation of T-cell-depleted paternal marrow into rhesus monkey fetuses would induce tolerance to postnatal kidney grafts from the marrow donor. T-cell-depleted paternal bone marrow was transplanted intraperitoneally into two female fetal rhesus monkeys at 61 ± 1 days’ gestation. Chimeric monkeys (n = 2) received kidney transplants from paternal donors. Control monkeys (n = 2) underwent kidney transplants without prior in utero stem cell transplants. Both chimeric monkeys demonstrated low level (<0.1% donor cells) engraftment in the bone marrow and peripheral blood using the polymerase chain reaction assay for the Y chromosome. The mixed lymphocyte reaction demonstrated hyporeactivity to the donor. Control animals demonstrated severe acute rejection and graft failure 1 week posttransplant. The first chimeric monkey had no significant clinical or sonographic evidence of renal failure until 7 weeks after the transplant. Biopsy findings showed mild rejection 1 week postoperatively, but rejection did not significantly progress until 5 weeks later. The second chimeric monkey had no significant clinical or sonographic renal deterioration, although biopsy results showed chronic rejection that was confirmed when electively euthanized 8 months later. Our data suggest that in utero transplantation of hematopoietic stem cells can increase the survival of a kidney allograft in the rhesus monkey.

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and complications of immunosuppression. In utero induction of tolerance could potentially solve the problems associated with solid organ transplantation.

Tolerance induction in utero was first demonstrated in genetically different cattle twins who shared a common placenta, which allowed mixing of their blood and the establishment of hematohimeras. Postnatally, the cattle were mutually tolerant and accepted skin grafts from one another. Subsequently, Billingham et al demonstrated the induction of tolerance in mice by transplanting bone marrow and skin grafts from another strain.

Although a variety of cell types have been used to induce tolerance, donor-specific hematopoietic stem cells appear to have advantages as the cellular antigen for the induction and maintenance of tolerance. Stem cells express MHC class I and II antigens that mediate the immune response. Furthermore, their capacity for self-replication, which renders them immortal, may promote the maintenance of tolerance. Hematochimeras have been created postnatally and induced tolerance to solid organs in mice, as well as nonhuman primate models. Unfortunately, the incidence of toxicity was high because of the myeloablative regimens necessary to achieve adequate bone marrow engraftment. Kawai et al reported promising results with a nonmyeloablative prepara-
Hematopoietic chimerism achieved by in utero hematopoietic stem cell injection does not induce donor-specific tolerance for renal allografts in sheep.

Hedrick MH, Rice HE, MacGillivray TE, Bealer JF, Zanjani ED, Flake AW.
Department of Surgery, University of California, San Francisco.
Microchimerism does not induce tolerance and sustains immunity after in utero transplantation.

Donahue J, Gilpin E, Lee TH, Busch MP, Croft M, Carrier E.

Department of Medicine, University of California San Diego School of Medicine, La Jolla, USA.

Abstract

BACKGROUND: To date, over 40 in utero transplants have been performed in humans; the only successes were documented in the treatment of severe combined immunodeficiency syndromes. Hemoglobinopathies and metabolic disorders are candidate diseases for this approach; however, when applied clinically, the results have been discouraging. To address the role of the fetal immune system in the outcome of in utero transplantation, we have developed a murine model of in utero transplantation in immunologically intact murine recipients and have studied chimerism and tolerance/immunity to allogeneic donor cells through the lives of the animals.

METHODS: We have performed experiments in which purified murine sca-1+/-lin- cells and c-kit+/-lin- cells of C57BL/6 (H2b) mice were injected into Balb/c (H2d) fetal recipients at early gestational ages. Chimerism was tested by highly sensitive semiquantitative polymerase chain reaction assay and tolerance/immunity to donor cells was studied by in vivo (skin grafts, responses to postnatal boosts) and in vitro (mixed lymphocyte culture, cytotoxicity, and cytokine release) assays.

RESULTS: One hundred percent (10/10) of mice transplanted with c-kit+ cells and 44% (4/9) of mice transplanted with sca+ cells showed circulating donor cells within the first 6 months of life (P=0.031). Mice in the sca+ group rejected donor skin grafts at a mean time of 9.1 +/- 0.2 days, whereas mice in the c-kit+ group rejected donor skin grafts at a mean time of 15.1 +/- 0.7 days (P=0.001). The difference between the transplanted groups and non-transplanted controls was also significant (P<0.05). All mice transplanted with sca+/lin- cells showed greater response to donor cells than to third-party cells at all effector to target ratios (P=0.002). Differences in response to donor alloantigen between sca+ and c-kit+ groups were significant (P=0.003). Cytokine quantification demonstrated higher TH1 than TH2 cytokine release in all groups, and the response to donor cells was higher in the sca+ compared with c-kit+ mice (P=0.031).

CONCLUSION: These results demonstrate a low level of chimerism and tolerance in mice transplanted in utero with sca+/lin- and c-kit+/lin- cells. The possibility of active in utero immunization to donor cells is supported by accelerated skin graft rejection in mice transplanted with sca+ cells and enhanced in vitro immune responses in mice with persistent microchimerism.
The holy grail of fetal renal disease

Chimerism and immunotolerance

Transplant without immunosuppression
Experimental work for biomarkers
Today low value prognostic markers for fetal obstructive uropathy:

U/S
Urine electrolytes
B2 microglobulin
Amniotic fluid
Fetal MRI?
Urinary biomarkers in prenatally diagnosed unilateral hydronephrosis

Mia Gebauer Madsen a,b,*, Rikke Nørregaard b, Jørgen Frøkiær b, Troels Munch Jørgensen a
<table>
<thead>
<tr>
<th>Urinary biomarkers</th>
<th>Localization in the kidneys</th>
<th>Function in the kidneys</th>
<th>Level in the urine from children with UPJO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transforming growth factor beta 1 (TGF-β1)</td>
<td>Renal tubular epithelial cells, macrophages and interstitial fibroblasts</td>
<td>The main modulator of the healing process after tissue injury</td>
<td>Increased</td>
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<tr>
<td>N-acetyl-beta-D-glucosaminidase (NAG)</td>
<td>Renal tubular epithelial cells</td>
<td>An indicator of tubular damage</td>
<td>Increased</td>
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<tr>
<td>Monocyte chemotactic peptide-1 (MCP-1)</td>
<td>Renal tubular epithelial cells</td>
<td>Chemotactic and activating factor for monocytes</td>
<td>Increased</td>
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<tr>
<td>Epidermal growth factor (EGF)</td>
<td>Renal tubular epithelial cells</td>
<td>Mediator of normal tubulogenesis and tubular regeneration after injury</td>
<td>Decreased</td>
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<tr>
<td>Endothelin-1 (ET-1)</td>
<td>Glomeruli and inner medullary collecting ducts and in the endothelium of renal vessels</td>
<td>Endogenous vasoconstrictor</td>
<td>Increased</td>
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Project: fetal uropathy with placement of safe microcatheters in renal pelvis, bladder, contra-lateral kidney and amniotic cavity in the search of new biomarkers AND correlation to mother
Experimental work for tissue engineering
Intra-uterine tissue engineering of full-thickness skin defects in a fetal sheep model

Nynke A. Hosper\textsuperscript{a,\textdagger,1}, Alex J. Eggink\textsuperscript{b,1}, Luc A.J. Roelofs\textsuperscript{c}, Rene M.H. Wijnen\textsuperscript{d}, Marja J.A. van Luyn\textsuperscript{a}, Ruud A. Bank\textsuperscript{a}, Martin C. Harmsen\textsuperscript{a}, Paul J. Geutjes\textsuperscript{c}, Willeke F. Daamen\textsuperscript{e}, Toin H. van Kuppevelt\textsuperscript{e}, Dorien M. Tiemessen\textsuperscript{c}, Egbert Oosterwijk\textsuperscript{c}, Jane J. Crevels\textsuperscript{f}, Willeke A.M. Blokx\textsuperscript{g}, Fred K. Lotgering\textsuperscript{b}, Paul P. van den Berg\textsuperscript{f}, Wout F.J. Feitz\textsuperscript{c}
Fetal bladder wall regeneration with a collagen biomatrix and histological evaluation of bladder extrophy in a fetal sheep model.


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Abstract

OBJECTIVES: To evaluate histological changes in an animal model for bladder extrophy and fetal repair of the bladder defect with a molecular-defined dual-layer collagen biomatrix to induce fetal bladder wall regeneration.

METHODS: In 12 fetal lambs the abdominal wall and bladder were opened by a midline incision at 79 days' gestation. In 6 of these lambs an uncorrected bladder extrophy was created by suturing the edges of the opened bladder to the abdominal wall (group 1). The other 6 lambs served as a repair group, where a dual-layer collagen biomatrix was sutured into the bladder wall and the abdominal wall was closed (group 2). A caesarean section was performed at 140 days' gestation, followed by macroscopic and histological examination.

RESULTS: Group 1 showed inflammatory and maturational changes in the mucosa, submucosa and detrusor muscle of all the bladders. In group 2, bladder regeneration was observed, with urothelial coverage, ingrowth of fibroblasts and smooth muscle cells, deposition of collagen, neovascularization and nerve fibre formation. This tissue replaced the collagen biomatrix. No structural changes of the bladder were seen in group 2.

CONCLUSIONS: The animal model, as in group 1, for bladder extrophy shows remarkable histological resemblance with the naturally occurring anomaly in humans. This model can be used to develop new methods to salvage or regenerate bladder tissue in bladder extrophy patients. Fetal bladder wall regeneration with a collagen biomatrix is feasible in this model, resulting in renewed formation of urothelium, blood vessels, nerve fibres, ingrowth of smooth muscle cells and salvage of the native bladder.
Outlook/Perspectives:
Experimental work for treatment options (fetal surgery)

Experimental work for molecular basics

Experimental work for fetal transplantation

Experimental work for tissue engineering

Experimental work for biomarkers
Thank you very much!