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Risdiplam for transplacental therapy of spinal muscular atrophy: update from the prenatal study group**Mara Rosner, Richard Finkel**

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Introduction: Gene-targeted treatment for spinal muscular atrophy (SMA) has revolutionized patient outcomes, particularly when initiated as soon as possible prior to overt symptomatology. However, multiple studies support that disease progression is occurring already in utero, suggesting an advantage to prenatal treatment.

Methods: Preliminary summary of an informal registry of the first 12 mother-fetus dyads treated with transplacental Risdiplam at a standard oral dose of 5 mg daily. Fetal imaging, fetal monitoring, and newborn testing were not standardized between centers.

Results: All patients had amniocentesis-confirmed SMA with zero copies of SMN1. Eleven patients had 2-copies of SMN2, and one patient had only 1-copy of SMN2. Eight (66%) of patients had a family history of SMA. Risdiplam was started at a median of 32.3 (28.0-35.3) weeks. All patients delivered at full term with a median birth weight of 3.4 (2.7 – 4.3) kg. There have been no apparent drug related maternal or fetal adverse effects. All babies with 2-copies of SMN2 are making good motor gains with favorable neurofilament levels and electrophysiologic results.

Conclusion: Thus far transplacental Risdiplam has proved feasible and safe. Further studies are needed.

[13-133]**The Artificial Placenta Platform**

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Conflicts of Interest:

The authors have no conflicts of interest to disclose.

Background

For two decades we have been developing an extracorporeal artificial placenta to support extremely premature infants. Our work has evolved into three distinct but related applications of the AP platform: 1) AP support of ELGANs; 2) Premie ECMO; and 3) AP CDH treatment.

Methods

All studies were performed using a fetal lamb model at varying gestational ages.

Results

Our laboratory pioneered the Artificial Placenta with a two cannula venovenous (VV) ECMO approach with inflow via the umbilical vein and outflow via the right jugular vein. This resulted in a reproducible model of long-term support, maintaining fetal physiology, organ protection, and development that would be applied preemptively in ELGANs. Subsequently, this work established the foundational prerequisites for Premie ECMO: 1) lung management with perfluorocarbons; 2) development of nonthrombogenic circuits eliminating systemic anticoagulation; 3) demonstration of multiple organ system protection and development; and 4) miniaturization. Lastly, we are leveraging the AP platform to improve survival, promote lung growth, and address the pathophysiology of CDH.

Conclusions

The Artificial Placenta platform has evolved beyond support of ELGANs to encompass Premie ECMO and CDH therapy. Continued development may transform the management of these vulnerable populations by extending physiologic support while promoting growth and organ protection.

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Amniotic fluid stem cell-derived extracellular vesicles enhance the efficacy of tracheal occlusion in congenital diaphragmatic hernia in large animal models**Marianna Scuglia**

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Aim: In selected cases of congenital diaphragmatic hernia (CDH), fetoscopic endoluminal tracheal occlusion (FETO) improves lung growth but incompletely corrects vascular abnormalities. Amniotic fluid stem cell-derived extracellular vesicles (AFSC-EVs) have emerged as a promising antenatal regenerative therapy. We aimed to evaluate the efficacy and safety of AFSC-EVs combined with tracheal occlusion (TO) in two large animal CDH models.

Methods: In CDH lamb model, fetuses received intratracheal injection of AFSC-EVs or saline during FETO at gestational day 95, followed by balloon deflation. In the rabbit model, CDH were induced at pseudoglandular stage, followed by randomization to intratracheal AFSC-EVs or saline with TO. Airway and vascular morphometry, molecular analyses, and off-target organ assessments were performed at term.

Results: TO restored lung size and airway morphometry in both species. However, TO alone failed to normalize pulmonary vascular remodeling. AFSC-EV significantly reduced medial wall thickness and vessel muscularization, restoring vascular architecture to control levels. In lambs, AFSC-EVs reversed TGF- β -related epithelial-mesenchymal-transition alterations. No off-target adverse effects were observed.

Conclusion: AFSC-EVs combined with TO promote antenatal lung regeneration, targeting pulmonary vascular pathology that limits the efficacy of TO alone. These findings support AFSC-EVs as a safe and translatable adjunct therapy for severe pulmonary hypoplasia.

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A Prodrug-Hydrogel System for Sustained Intrafetal Antiviral Delivery: Proof-of-Concept in Congenital Cytomegalovirus Infection

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Delivering therapeutics to the fetus requires drug delivery systems specifically engineered to reach the fetus while minimising maternal exposure. Congenital cytomegalovirus (cCMV) infection illustrates the unmet need: current prenatal management relies on high-dose valaciclovir, raising compliance and nephrotoxicity concerns. We aim to develop a novel injectable formulation for direct fetal administration, designed to bypass the placental barrier and optimise fetal pharmacokinetics and pharmacodynamics while reducing maternal exposure.

To this end, water-soluble polymeric prodrugs of acyclovir and ganciclovir with random and block architectures were synthesized and characterized by nuclear magnetic resonance and size-exclusion chromatography for size, dispersity and drug loading. ¹⁴C-radiolabeled analogues were further synthesized to investigate transplacental transfer using an ex vivo human placental perfusion model. A thermosensitive injectable hydrogel was developed using a biocompatible copolymer, demonstrating sustained drug release and favorable rheological properties including viscosity and injectability compatible with intrafetal administration. Cytocompatibility of the prodrugs was confirmed by MTT assay across multiple human cell lines. Antiviral activity against CMV is currently under evaluation in vitro on fibroblasts.

Together, these results support the feasibility of a combined prodrug-hydrogel platform for sustained intrafetal antiviral delivery, establishing cCMV as a first proof-of-concept for broader in utero pharmacological intervention.

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Fetal Lung Maturation with Low-Dose Antenatal Corticosteroids in a Lamb Ex Vivo Environment

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Background

Artificial placenta support enables lamb survival in an ex vivo environment (EVE) while maintaining fetal circulation, but organ development remains incompletely understood.

Objective

To investigate whether low-dose antenatal corticosteroids (ACS) accelerate fetal lung maturation under EVE.

Methods

Pregnant ewes at 117 days' gestation were assigned to Control (n=7), ACS (n=6), or EVE (n=3). Controls received saline; ACS received two 12 mg intramuscular betamethasone doses 24 hours apart. Lambs were delivered 2 days after the initial treatment. In the EVE group, lambs were connected to an artificial placenta via the umbilical cord and received intravenous betamethasone (18 µg bolus, then 12 µg/h for 50 h; target plasma concentration 2 ng/mL). All lambs underwent 30 minutes of standardized mechanical ventilation.

Results

The EVE group showed consistently higher pH (7.06 [7.00–7.15] vs. 6.90 [6.79–6.91]) and lower pCO₂ (82.6 [44.7–95.8] vs. 127 [105–145]) than Controls, indicating reduced respiratory acidosis. The ACS group showed intermediate values (pH 7.01 [6.83–7.05] and pCO₂ 93.5 [86.7–104]). pO₂ was higher in EVE and ACS than Controls.

Conclusion

Despite small sample size, gas exchange improved in EVE, supporting enhanced lung maturation with low-dose ACS under ex vivo support.

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A new access to the fetal brain: fluoroscopy-guided in utero embolization of a pial arteriovenous fistula

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Pial arteriovenous fistulas may lead prenatally to rapid hemodynamic deterioration due to high-output cardiac failure and cerebral venous hypertension.

We report a fetus diagnosed at 32 weeks with a high-flow pial arteriovenous fistula, causing progressive high-output cardiac failure, without encephalomalacia. After multidisciplinary discussion and parental consent, a rescue fetal intervention was performed at 35 weeks. Percutaneous transuterine access to the fetal superior sagittal sinus was performed using an 18-gauge needle. Retrograde microcatheterization of the venous collector was performed under fluoroscopic guidance, followed by partial coil embolization of the shunt. Immediate doppler ultrasound demonstrated resolution of venous arterialization in the superior sagittal sinus with reduced sinus dilation. Post-intervention MRI showed a limited subdural hematoma without parenchymal injury. Two weeks later, increased cardiac output was again observed without decompensation, and delivery was performed for postnatal management. The neonate remained hemodynamically stable and underwent planned endovascular treatment at 30 hours of life.

This case demonstrates the feasibility of fluoroscopy-guided in utero access to the fetal cerebral venous system, a technique not previously described. Prenatal embolization may offer temporary hemodynamic stabilization in selected cases, allowing prolongation of pregnancy and reducing perinatal morbidity and mortality.

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Percutaneous Ethanol Chemosclerosis of Complicated Giant Chorioangioma

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Objective: Giant chorioangiomas are vascular placental tumors carrying significant risks for fetal-obstetrical complications. Treatment approaches w fetoscopy and injectable sclerosing agents have been reported. We evaluated our experience with a rarely reported treatment of percutaneous alcohol tumor sclerosis of complicated chorioangiomas.

Methods: Cases of complicated chorioangiomas treated with EtOH between 2018-2026 were reviewed. Seven cases underwent ultrasound-guided intratumor injections of 2-3cc of 100% EtOH via 20g or 22g spinal needle.

Results: The mean chorioangioma diameter was 7.2cm. Mean gestational age at treatment was 25.3 weeks. Three required a second EtOH treatment for continued intratumoral blood flow by color Doppler but all showed reduced flow. Three had transient fetal bradycardia. Indications for treatment included: 1) fetal cardiomyopathy (n=5; mean cardiothoracic ratio 0.62; mean combined cardiac output of 741ml/min/kg), 2) fetal anemia requiring IUT (n=4; mean opening hematocrit 25.7%), 3) polyhydramnios (n=5; mean maximal vertical pocket 10.2cm) requiring amnioreduction (mean volume 1483ml), and/or short cervix (n=2; cervical lengths of 2.1 and 2.5cm). Mean gestational age at delivery and latency from treatment were 35.7 weeks and 8.2 weeks, respectively. All newborns survived and were AGA (mean birthweight 2630g).

Conclusion: Intratumor alcohol injection is a feasible, minimally invasive treatment option for complicated giant chorioangiomas.

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Sclerosis of Large Placental Chorioangiomas With Denatured Alcohol – A Viable Fetal Intervention

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Introduction: Placental chorioangiomas (PCs) are rare benign tumors in <1% of pregnancies. Large PCs (>4 cm) are even less common and pose greater risks, including polyhydramnios, high-cardiac-output physiology (HCOP), hydrops, anemia, and fetal demise. We reviewed our experience using denatured alcohol to sclerose the feeding vessel in these cases, given the risks and variable effectiveness of other interventions.

Methods: We retrospectively reviewed fetuses with large PCs treated with denatured alcohol sclerosis at our center (2017–2026). Alcohol was injected into the PC mass near the feeding vessel under local anesthesia. **Results:** Three mothers (two singletons, one twin) presented with large PCs (6–7 cm) and HCOP. One fetus had hydrops; two had anemia. Interventions occurred at 23–26 weeks. In fetuses without hydrops, post-sclerosis blood flow in the PC was absent, CCO decreased, and anemia resolved; both were delivered at term. The fetus with hydrops required a second procedure but developed preterm labor, leading to palliative delivery at 24w5d.

Conclusion: Sclerosis of large placental chorioangiomas with denatured alcohol around the feeding vessel appears to be a viable treatment for fetuses with high cardiac output physiology, with good outcomes except in severe cases with hydrops

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Effect of aspirin and early onset fetal growth restriction Doppler severity

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Objective:

Preeclampsia is a risk factor for placental insufficiency and early onset FGR. Given the use of aspirin to reduce risk of preeclampsia, we hypothesized that aspirin use may reduce risk of early onset FGR.

Study Design:

Retrospective cohort study of singleton, non-anomalous pregnancies with a diagnosis of early onset FGR (<32 weeks) at a single academic institution from 8/10/2016 to 4/17/2024. Association between aspirin use and gestational age at diagnosis, umbilical artery Doppler severity, and gestational age at delivery was assessed using Mann-Whitney and Fisher's exact tests.

Results:

Of 255 patients, 40 were prescribed aspirin (18.6%). Mean gestational age at FGR diagnosis was 26.0 weeks for aspirin users compared to 26.5 for non-aspirin users ($p = 0.256$). The majority of patients had normal UA dopplers at time of diagnosis; rates were not different by aspirin use (92% for non-aspirin users vs 82% for aspirin, $p=0.181$). There was no difference in rates of preterm delivery based on aspirin use, and the majority of patients delivered after 37w (67%).

Conclusions:

Aspirin did not alter the severity of early onset FGR based on gestational age at diagnosis, severity of initial Doppler value, or gestational age at delivery.