REGENERATIVE POTENTIAL OF HUMAN ENDOMETRIAL MESENCHYMAL STEM CELLS IN SHEEP WITH SIMULATED VAGINAL BIRTH INJURY

Abawa A[1], Hennes D[1], Paul K[2], Darzi S[2], Werkmeister J[2], Rosamilia A[3], Gargett C[2], Mukherjee S[1,2]

1. Monash University, 2. Hudson Institute of Medical Research, 3. Monash Health

Background

Vaginal childbirth inflicts substantial trauma to the pelvic floor, emerging as a pivotal risk factor for pelvic floor muscle disorders (PFDs) such as urinary incontinence (UI) and Pelvic Organ Prolapse (POP)[1]. While the damage occurs during childbirth, its enduring impact often becomes evident later in life, marked by complications in bladder, bowel, and sexual functions. This phenomenon affects 25% of women across all age groups, underscoring the profound and lasting consequences of maternal childbirth injury on women's pelvic health[2].

The increasing demand for preventive treatment approaches for POP subsequent to birth injury has led to the exploration of novel biologically active scaffolds such as Aloe Vera-Alginate hydrogel (AV-ALG-Hyd) comprising xenogeneic SUSD2+ human Endometrial Mesenchymal Stem Cells (eMSC)[3]. This study addresses the urgent need for effective birth injury interventions by investigating the therapeutic potential of AV-ALG-Hyd with and without eMSC in promoting healing.

Aim

- The primary aim was to construct and evaluate the efficacy of tissue engineered AV-ALG-Hyd with SUSD2+ eMSC in postpartum tissue healing.
- Furthermore, we aimed to assess for differences in acute inflammatory immune responses, tensile properties of vaginal tissue explants between treatment groups, and to demonstrate optimized eMSC retention for superior immunomodulatory potential.

Method

- Herein, we selected primiparous ewes and simulated birth injury using a balloon catheter that is clinically used to mitigate post-partum uterine bleeding.
- AV-ALG-Hyd, with SUSD2+ eMSC was transplanted directly following simulated vaginal birth injury, while control groups underwent injury without hydrogel and/or eMSC injection.
- Ewes transplanted with AV-ALG-Hyd without eMSCs, and sham injury served as control. Explant analysis at 30 & 90d timepoints encompassed pre-and post-operative POP-Q measurements, eMSC retention, tissue healing, immune response, and tissue tensiometry (**Fig 1**).

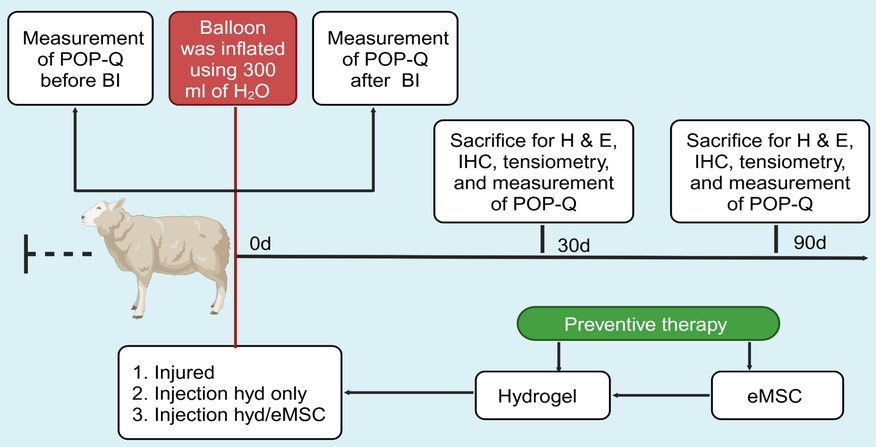

Figure 1. Experimental study design

Results

- Injection of Hyd/eMSC after simulated vaginal birth injury reduces the severity of pelvic organ prolapse at 90d (**Fig 2**).

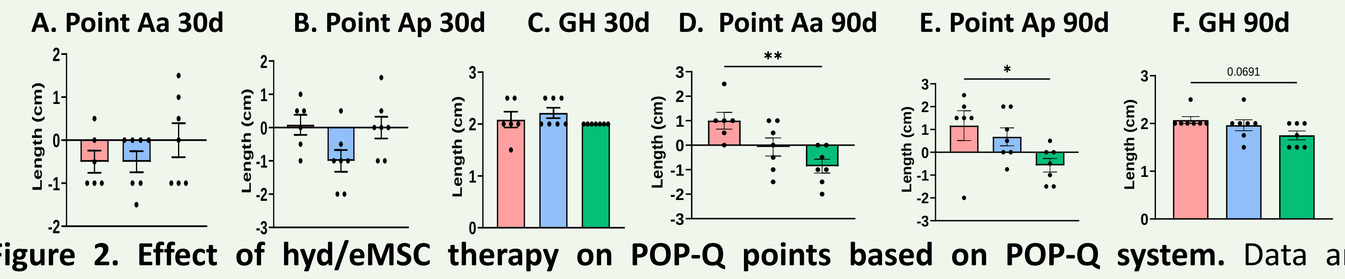

Figure 2. Effect of hyd/eMSC therapy on POP-Q points based on POP-Q system. Data are presented using one-way ANVOA (*p<0.05, **p<0.002), (n=7 per group). GH; Genital Hiatus.

Cell Retention in Tissue

- Delivery of eMSC with Hydrogel enhance the homing and survival of transplanted eMSC at 30d and 90d (**Fig 3**).

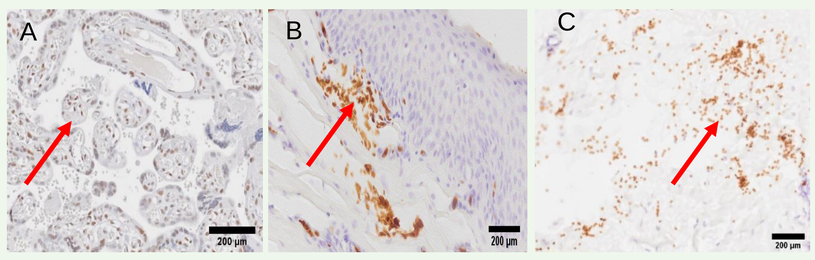

Figure 3. eMSC retention in tissue. (A) Human placenta positive control, (B) 30d, and (C) 90d. Red arrow indicates retention of SUSD2+ eMSC

- Ewes administered Hyd/eMSC showed significant improvement in the smooth muscle of vaginal wall tissue, stabilize elastin and decrease collagen deposition (**Fig 4**).

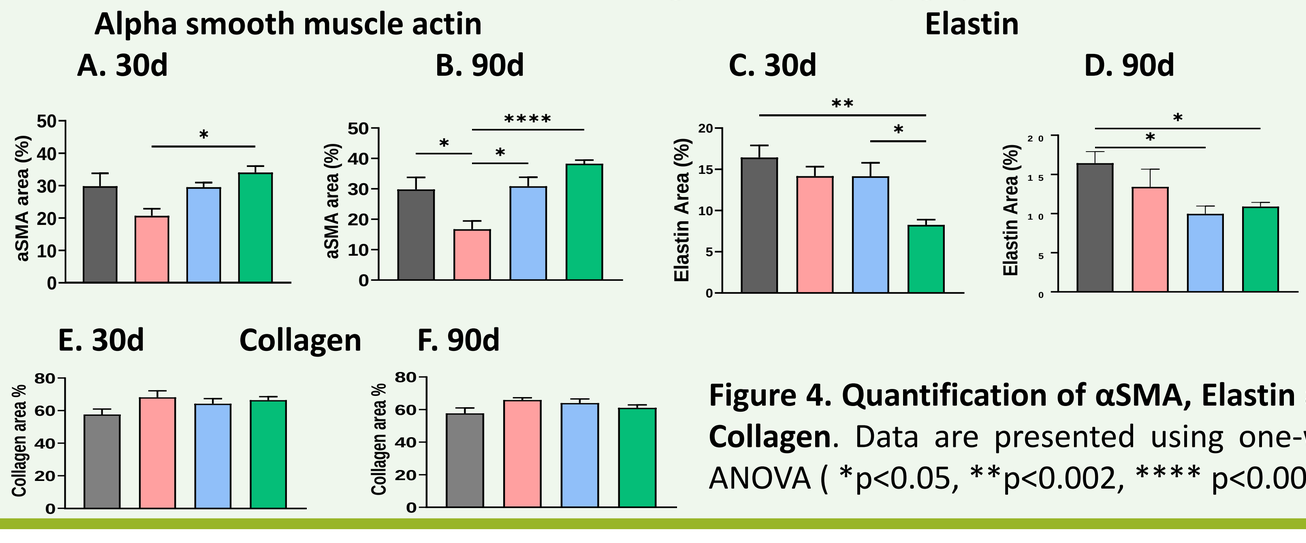

Figure 4. Quantification of αSMA, Elastin and Collagen. Data are presented using one-way ANOVA (*p<0.05, **p<0.002, **** p<0.0001)

Conclusion

- The Hyd/eMSC injection soon after injury significantly decrease the severity of POP as demonstrated by POP-Q system measurements.
- The in vivo delivery of eMSCs via hydrogel effectively improves cell retention within the tissue microenvironment for up to 90 days, indicating an extended therapeutic window for tissue repair.
- Furthermore, transplantation of Hyd/eMSC improve smooth muscle content, stabilize elastin, and collagen deposition which are critical for the structural integrity and function of the female pelvic floor.
- ❖ In summary, the result revealed that the potential of hydrogel/eMSCs therapy as a preventive approach to POP, particularly in mitigating the damage caused by vaginal childbirth injury.

References

1. Memon, H.U. and V.L. Handa, Vaginal childbirth and pelvic floor disorders. Women's health, 2013. 9(3):p. 265-277.
2. Olsen, Ambre L., et al. "Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence." Obstetrics & Gynecology 89.4 (1997): 501-506.
3. Paul, K., et al., Vaginal delivery of tissue engineered endometrial mesenchymal stem/stromal cells in an aloe vera-alginate hydrogel alleviates maternal simulated birth injury. Applied Materials Today, 2021. 22: p. 100890.

Cabrini RESEARCH