

PARITY IS A SIGNIFICANT DETERMINANT OF PELVIC ORGAN PROLAPSE IN LOXL1-DEFICIENT MICE

Hypothesis / aims of study

Parity and vaginal delivery are known factors in the development of human pelvic organ prolapse (POP). With the recent introduction of genetic animal models for POP, it is important to characterize what factors significantly contribute to the development of prolapse in these animal models. In contrast to Fibulin 5- deficient mice who develop POP as nulliparous mice [1], LOXL1-deficient mice develop POP post partum. LOXL1 protein levels decrease at the end of pregnancy, and increase quickly after delivery to nonpregnant levels, highlighting LOXL1's essential role in elastin remodeling in the postpartum period of mice [2]. The objective of this study was to describe the development of POP in LOXL1-deficient mice over time. We aim to describe the progression of POP, as well as factor(s) that significantly affect POP.

Study design, materials and methods

LOXL1-deficient mice on a mixed C57Bl/6 and Sv129 background were bred with single pair mating and harem breeding. Female parous mice were observed over a 10 month period. Mouse Pelvic Organ Quantification (MOPQ) was used to measure grade of perineal bulge (0=none, 1=mild, 2=moderate, 3=severe, 4=grossly everted vagina) [1]. Kaplan-Meier Time to Prolapse curves were developed to describe the colony of LOXL1-/- female parous mice. Chi-square test was used with p values <0.05 indicating a significant difference.

Results

Female parous LOXL1^{-/-} mice (n=39) were observed for a mean time of 20 weeks (range 15 to 67 weeks). Of the 39 mice, 25 have developed some degree of POP, and 14 are still being observed for development of POP. Of the 25 who have POP, 11/25 (44%) mice developed POP after the first delivery, 8/25 (32%) mice developed POP after the second delivery, 5/25 (20%) mice developed POP after the third delivery, and 1/25 (4%) mice after the fourth delivery. By 20 weeks of age, 50% of parous mice have developed POP (Fig. 1a). By 20 weeks of age, 15% of parous mice have developed grade 3 POP (Fig. 1b). For each unit increase in parity the estimate for the age at any prolapse decreases by 66.3% (Chi-square=0.0007; Fig. 1c). For each unit increase in parity the estimate for the age at any prolapse decreases by 55% (Chi-square=0.23; Fig. 1d).

Interpretation of results

Parity is the significant factor that triggers POP in LOXL1-deficient mice. This provides further evidence that the LOXL1-deficient mouse model is a relevant genetic animal model for the study of POP because the POP develops and progresses over time after one or multiple pregnancies and deliveries, as is seen clinically.

Concluding Message

Parity is the significant determinant of pelvic organ prolapse in LOXL1-deficient mice.

References

- [1] Int Urogyn J 2006; 17,Supp 3:361-408, P13
- [2] Am J Path 2006; 168 (2): 519.

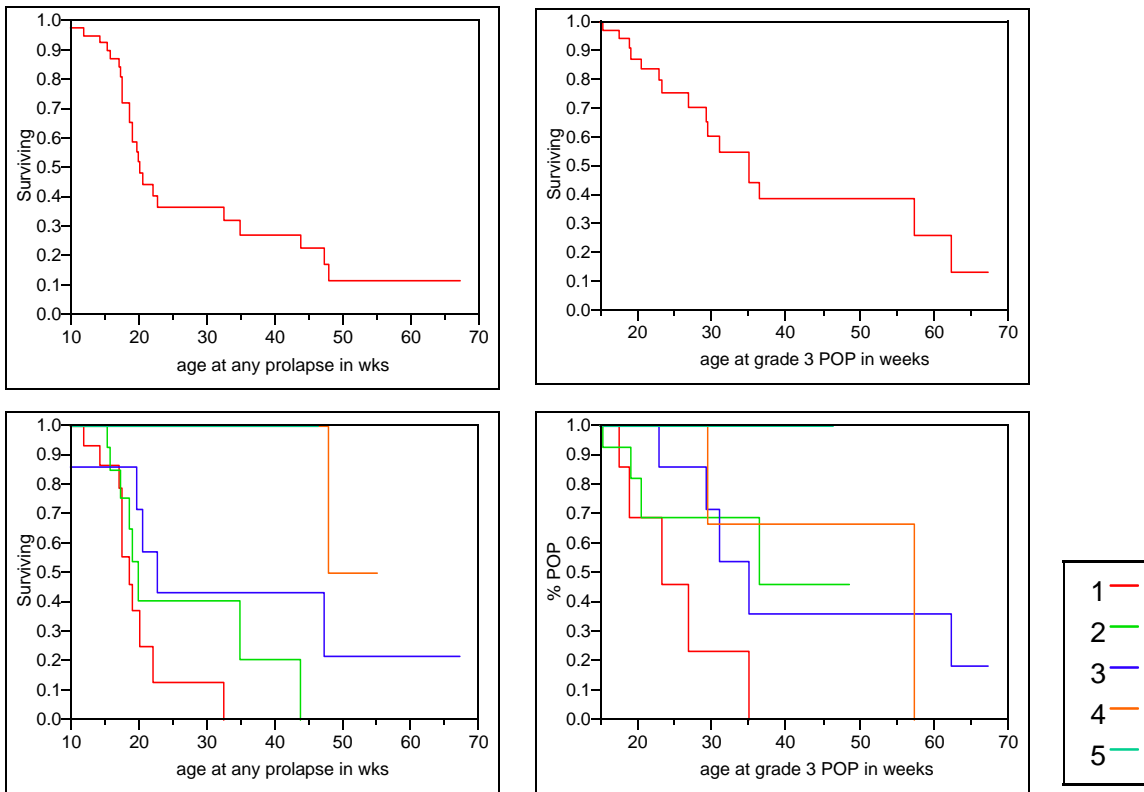


Figure 1. Time to POP for LOXL1-deficient mice expressed as Kaplan-Meier survival curves. **A.** Age of mice at any grade of POP. **B.** Age of mice at grade 3 POP. **C.** Age of mice at any grade of POP by parity. **D.** Age of mice at grade 3 POP by parity. Legend refers to parity in C and D. There is a significant dependence on parity of age at POP.

FUNDING: Cleveland Clinic RPC and Cleveland VA

ANIMAL SUBJECTS: This study followed the guidelines for care and use of laboratory animals and was approved by Cleveland VA IACUC