Uterine injury during diestrus leads to placental and embryonic defects in future pregnancies in mice

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The uterus is central to mammalian reproduction and gynecological health, and yet its capacities to regenerate itself and to interact with the embryo remain poorly understood. While the uterine is capable of scarless regeneration each menstrual or estrous cycle, C-sections and other uterine injuries contribute to scarring, resulting in either infertility or disorders like placenta previa and placenta accreta in subsequent pregnancies. With rates of C-section at approximately 30% of deliveries in the US and projected to continue to climb, a deeper understanding of the mechanisms by which these pregnancy disorders arise and opportunities for intervention are needed. Here we describe a rodent model of uterine injury on subsequent *in utero* outcomes. Using this mouse model, we recapitulated several features of human disorders, including implantation failure, previa-like embryo misspacing, and accreta-like overinvasive placentas. Strikingly, only uteri injured during the diestrus phase of the estrous cycle displayed subsequent embryo misspacing via persistent cyclooxygenase (COX) pathway perturbations following poor wound healing. Using RNA-seq, we identified perturbations in the expression of components of the COX/prostaglandin pathway after recovery from injury, a pathway that has previously been demonstrated to play an important role in embryo spacing. Therefore, we

demonstrate that uterine injury engenders a long-term molecular “memory” of damage that ultimately leads to numerous placental and embryonic developmental defects.