Approximately 10% of US births deliver preterm before 37 weeks of completed gestation. Premature infants are at risk for life-long debilitating morbidities and death, and spontaneous preterm labor explains 50% of preterm births. In all cases existing treatments are ineffective, and none are FDA approved. The mechanisms that initiate preterm labor are not well understood but may result from dysfunctional regulation of quiescence mechanisms. Human pregnancy is accompanied by large increases in blood flow, and the uterus must enlarge by orders of magnitude to accommodate the growing fetus. This mechanical strain suggests that stretch-activated channels may constitute a mechanism to explain gestational quiescence.

Human uterine biopsies were obtained with written informed-consent from mothers with singleton pregnancies undergoing Cesarean section. Tissues were dissected under 4x magnification to isolate smooth muscle, then either immediately employed in contractile experiments or snap frozen in liquid nitrogen and stored in a vapor-phase freezer unit at -150 °C. Protein expression was determined by Western blot. Isolated cells were generated from TNL human myometrium as by enzymatic digestion, grown and expanded in primary tissue culture and resulting cells separated over CD31+/CD34+ bead LS columns using a MidiMACS separator. Cells captured by the beads were deemed pregnant human myometrial endothelial cells and CD31- pregnant human uterine smooth muscle cells.

We identify for the first time that Piezo1, a mechanosensitive cation channel, is present in the uterine smooth muscle and microvascular endothelium of pregnant myometrium. Piezo is downregulated during preterm labor, and stimulation of myometrial Piezo1 in an organ bath with the agonist, Yoda1, relaxes the tissue in a dose-dependent fashion. Further, stimulation of Piezo1 while inhibiting PKA, AKT, or eNOS mutes the negative inotropic effects of Piezo1 activation, intimating that actions on the myocyte and endothelial nitric oxide signaling contributes to Piezo1-mediated contractile dynamics. Taken together, these data highlight the importance of stretch-activated channels in pregnancy maintenance and parturition, and identify Piezo1 as a tocolytic target of interest.

Taken together with knowledge that the pregnant human uterus is not regulated by nervous innervation, these data imply an interplay between endothelium and muscle to regulate tone, and that disease can influence the expression of, and ability of Piezo1 channels to mediate contraction. We posit that there is a complex relationship between overlapping and compensatory mechanisms that facilitate the phasic contractile pathways. Such a notion is consistent with our hypothesis that myometrial Piezo1 normally provides a homeostatic function that modulates stretch-activated membrane hyperpolarization by cation influx without inducing contraction.