GYNECOLOGY

Maternal adaptations in preparation for parturition predict uncomplicated spontaneous delivery outcome

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OBJECTIVE: The objective of the study was to define maternal tissue adaptations in pregnancy associated with uncomplicated spontaneous vaginal delivery using anatomical and biological outcomes.

STUDY DESIGN: Nulliparous gravidas were prospectively enrolled in the first trimester at 2 institutions. Demographic and delivery data were chart abstracted. Vaginal elastase activity (units per milligram of protein) and Pelvic Organ Prolapse Quantification measurements of pelvic organ support were obtained in the first and third trimesters. A subset underwent 3-dimensional ultrasound measures of levator hiatus. Uncomplicated spontaneous vaginal delivery (VD) was defined as no cesarean, forceps, vacuum, shoulder dystocia, third- or fourth-degree perineal laceration, or prolonged second stage labor.

RESULTS: We enrolled 173 women in their first trimester, 50 of whom had ultrasounds. Mean age was 25.5 ± 5.5 years with a body mass index of 28.0 ± 7.3 kg/m^2. Sixty-seven percent were white/Caucasian, 27% black/African American, and 6% Hispanic/Latina. Mean delivery gestational age was 38.5 ± 2.9 weeks, with 23% delivering by cesarean and 59% achieving uncomplicated spontaneous VD. Vaginal support changed significantly over trimesters with posterior vaginal and hiatal relaxation, vaginal lengthening, and increased levator hiatus area during strain. Women achieving uncomplicated spontaneous VD demonstrated significantly greater relaxation on third-trimester Pelvic Organ Prolapse Quantification for anterior, apical, and hiatal measures than those without uncomplicated spontaneous VD. Higher first-trimester vaginal elastase activity was strongly associated with uncomplicated spontaneous VD (geometric mean activity 0.289 ± 0.830 U/mg vs −0.029 ± 0.585 U/mg, $P = .009$). Higher first-trimester elastase, younger age, lower first-trimester body mass index, and more third-trimester vaginal support laxity in points C and GH were predictive of VD success.

CONCLUSION: Significant maternal adaptations occur in the vagina during pregnancy, presumably in preparation for vaginal delivery. Greater adaptation, including vaginal descent and higher first-trimester elastase activity, is associated with an increased likelihood of uncomplicated spontaneous VD.

Key words: childbirth, delivery, elastase, maternal adaptations, pelvic organ prolapse

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Pelvic floor disorders (PFD) including pelvic organ prolapse, urinary incontinence, and anal incontinence are common and costly conditions, with up to one quarter of all adult women endorsing PFD symptoms.[1] Pregnancy, delivery, and associated birth injury are known risk factors for the later development of PFDs. Lifetime risk of suffering from at least 1 symptomatic PFD increases with increasing parity, although first birth seems to have the largest impact.[2-8]

Childbirth injury has long been implicated as the inciting event in the causal pathway of PFDs; however, women exclusively delivering via cesarean section are also affected, suggesting a more complex insult mechanism than birth injury alone.[3,6,8] The association between maternal anal-rectal sphincter injury and new-onset fecal incontinence is perhaps the strongest existent data linking birth injury with pelvic floor

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dysfunction. Direct links between birth injury and urinary incontinence and pelvic organ prolapse are less clear.[2,9] Thus, our current understanding of the relative contributions of pregnancy, birth, and concurrent birth injury to the development of PFDs is incomplete, complicating efforts at prevention.

Limited prior work suggests that the pelvic floor undergoes profound changes during pregnancy, often described as adaptations, presumably in preparation for vaginal delivery. Specifically, the vagina and its supportive tissues relax, as evidenced by a progression of pelvic organ descent across trimesters and persistence of this descent postpartum.[10-12] Animal models demonstrate antenatal mechanical softening of the pelvic tissues, with injury occurring when vaginal distension exceeds the point of failure of these preparatory tissue adaptations.[13-16] Following injury, pathological tissue remodeling ensues, leaving tissues biomechanically weaker than their preinjury state. Mouse models of pelvic organ prolapse containing null mutations for genes involved in elastin synthesis and assembly show that vaginal birth may predispose to pelvic organ prolapse by altering the balance between matrix synthesis, particularly elastin fibers, and protease/elastase activation.[17-19]

Because our understanding of similar maternal pelvic support adaptations in preparation for vaginal birth in humans is limited, we undertook this project to quantify and compare maternal vaginal support adaptations in nulliparas using both anatomical (Pelvic Organ Prolapse Quantification [POP-Q] examination, levator hiatus dimensions) and biological outcomes (vaginal elastase activity) and to identify which specific maternal adaptations are associated with a uncomplicated spontaneous vaginal delivery.

Materials and Methods

Following institutional review board approval, this study enrolled a cohort of nulliparous gravidas in the first trimester. Participants were recruited from June 2011 through July 2012 at 2 academic centers (University of Pittsburgh and University of Utah) from a larger cohort of women participating in larger, multisite perinatology trial, the Nulliparous Pregnancy Outcomes Study—Monitoring Mothers-to-be (nuMoM2b).

The purpose of the ongoing nuMoM2b study is to explore the mechanisms and predictors of adverse pregnancy outcomes in first pregnancies and follows women from the first trimester through delivery, with study visits during each trimester. Women eligible for our ancillary study were 18 years of age or older, with an ultrasound-confirmed, single gestation between 8 and 13 weeks at the time of enrollment, with no prior pregnancy lasting 20 or more weeks, and planned both to deliver at the study site hospital and remain in the area for at least 1 year postpartum.

Exclusion criteria existent for the parent study included no history of 3 or more spontaneous abortions, no known lethal fetal anomaly, no known fetal aneuploidy, no use of donor oocytes for conception, no history of multifetal reduction, and no participation in a conflicting maternal-fetal intervention study. Following enrollment in the parent study, women were approached for enrollment in this ancillary project.

Clinical data

During study visits in the first and third trimesters, study investigators or trained pelvic floor research nurses performed pelvic examinations to measure vaginal support using the POP-Q examination as described by Bump et al.[20] The parent study collected extensive demographic, health, and obstetric data for each subject. Our analysis included the baseline demographics and delivery variables collected via medical record and parent study chart abstraction.

Elastase activity assay

At the first- and third-trimester visits, we collected vaginal fluid swabs from the posterior and lateral fornices to obtain vaginal epithelial cells. After collection, vaginal fluid swabs were processed, the supernatant collected, and the protein concentration determined using the Bio-Rad Protein Assay (Bio-Rad Laboratories, Hercules, CA). Halt proteinase inhibitor cocktail (Thermo Fisher Scientific, Pittsburgh, PA) was added to each sample to preserve proteinase activity. An EnzChek elastase assay kit (Life Technologies, Grand Island, NY) was used to test each sample. This kit contains proprietary DQ elastin labeled with BODIPY FL dye in which the fluorescence has been quenched in the undigested form. When digested by elastase or other proteases that exhibit elastase-like activity, highly fluorescent particles are yielded. This fluorescence is proportional to the amount of elastase activity in the sample and measured at an excitation wavelength of 485 nm and an emission wavelength of 530 nm using a Molecular Devices SpectroMax M2 (Sunnyvale, CA).

Data were analyzed using a 4-parameter regression curve (Masterplex ReaderFit; Miraibio, San Francisco, CA) of purified elastase from pig pancreas and expressed as units per milliliter total elastase, in which 1 unit is defined as the amount of enzyme necessary to solubilize 1 mg of elastin in 20 minutes at pH 8.8 and 37°C. Values are then normalized to protein concentration to yield a final elastase activity value expressed as units of elastase per milligram of protein. We chose to use this noninvasive method to reflect the levels of elastase in the vagina because we previously have found that the levels of active matrix metalloproteinases in vaginal swabs are highly correlated with those in full-thickness vaginal biopsies (obtained from the vaginal apex) in both humans (Spearman's rho $= 0.92$, $P < .001$) and rhesus macaque monkeys (Spearman's rho $= 0.92$, $P = .05$) (data not shown and P. Moalli, personal communication).

Transperineal ultrasonography

A subset of consecutive women at one site also underwent ultrasound measures of the levator hiatus in the first and third trimesters using transperineal 3-dimensional (3-D) technique ultrasound at rest and with maximal strain (Valsalva) as described by Dietz.[21] Transperineal ultrasound was performed by a single unblinded examiner using a Philips IU22 (Philips, Andover, MA) with a 3D6-2 probe with the subject in