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Original Contribution

Longitudinal Changes in the Genital Hiatus Preceding the Development of Pelvic Organ Prolapse

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We aimed to explore relationships between changes in genital hiatus (GH) and development of pelvic organ prolapse using data from the Mothers' Outcomes After Delivery (MOAD) Study, a Baltimore, Maryland, cohort study of parous women who underwent annual assessments during 2008–2018. Prolapse was defined as any vaginal segment protrusion beyond the hymen or reported prolapse surgery. For each case, 5 controls (matched on birth type and interval from first delivery to study enrollment) were selected using incidence sampling methods. We used a mixed model whose fixed effects described the initial size and slope of the GH as a function of prolapse status (case vs. control) and with nested (women within matched sets) random effects. Among 1,198 women followed for 1.0–7.3 years, 153 (13%) developed prolapse; 754 controls were matched to those women, yielding 3,664 visits for analysis. GH was 20% larger among the cases at enrollment (3.16 cm in cases vs. 2.62 cm in controls; $P < 0.001$), and the mean rate of increase in the size of the GH was more than 3 times greater (0.56 cm per 5-year period vs. 0.15 cm per 5-year period in controls; $P < 0.001$). Thus, to identify women at highest risk for developing prolapse, health-care providers could evaluate not simply the size of the GH but also changes in the GH over time.

empirical Bayes methods; genital hiatus; mixed-effects models; nested case-control studies; pelvic organ prolapse

Abbreviations: GH, genital hiatus; MOAD, Mothers' Outcomes After Delivery; POP, pelvic organ prolapse; POP-Q, pelvic organ prolapse quantification.

Pelvic organ prolapse (POP) is a disabling, chronic condition in which the uterus and vaginal walls protrude through the vagina, resulting in discomfort as well as bladder and bowel dysfunction. In the United States, more than 300,000 surgical procedures for POP are performed annually (with 1 in 4 women requiring repeat operations) at a cost of $1 billion (1). Thus, the public health burden of disease is substantial. There is strong evidence suggesting a role for levator ani impairment and abnormal connective tissue in POP (2, 3), but prevention strategies have not been identified because the biological mechanisms underlying POP are incompletely understood.

Epidemiologic studies of POP are few, due in part to the difficulty of obtaining pelvic examination data in large cohorts. In cross-sectional studies, vaginal birth, age, and obesity have emerged as risk factors for POP (4). In addition, there is increasing evidence that prolapse is strongly associated with the size of the woman's genital hiatus (GH), which is her vaginal opening as measured on physical examination (5–9). For example, the GH is significantly larger in women with stage 3 POP (i.e., pelvic organs begin to prolapse beyond the hymen) than in women with stage 0 or 1 POP (i.e., pelvic organs are supported) (5, 6).

However, most studies of prolapse are cross-sectional. Thus, the temporal association between GH size and prolapse is unclear. Longitudinal studies in this area are critical to advance our understanding of this association: A temporal relationship would be an important criterion to establish causation (10). Moreover, prevention of POP will remain elusive until the causes and antecedents are accurately identified.

In this analysis, we capitalized on a longitudinal study of parous women to consider changes in GH size several years before the development of prolapse. Specifically, the objective of this research was to explore the relationship between changes in GH size over time and development of POP, using a nested case-control study design.

METHODS

Data for this investigation were derived from the Mothers' Outcomes After Delivery (MOAD) Study, a longitudinal cohort study of POP and other pelvic floor disorders (such as incontinence) among parous women (7, 8, 11). For the MOAD Study, 1,528 participants were recruited from a community hospital in Baltimore, Maryland, 5–10 years after their first delivery (index birth) and were followed annually for up to 9 years (median, 5.1 years (interquartile range, 2.1–7.0)). Participants were identified on the basis of hospital discharge diagnoses; eligibility was confirmed by review of the obstetrical record and telephone interview. Each eligible delivery was classified by mode of delivery (e.g., vaginal birth or cesarean delivery). One of the goals of the MOAD Study was to contrast prolapse and incontinence after cesarean delivery versus vaginal birth; therefore, approximately equal numbers of women in each birth group were recruited for this longitudinal study. Birth groups were matched by age at delivery (in 5-year strata) and the interval from first delivery to recruitment (in 1/4-year strata). Eligible women were randomly selected for recruitment until the desired sample size was achieved. Informed consent was obtained from all participants, and the study was approved by the institutional review boards of the Johns Hopkins University and Greater Baltimore Medical Center.

Prolapse was assessed with the Pelvic Organ Prolapse Quantification (POP-Q) system (12), which uses a structured and validated examination for the quantification of uterine and vaginal support. The POP-Q system requires a gynecological examination, in which the positions of several anatomical points are measured with respect to their position above or beyond the hymen. The positions of these points are measured with straining (while performing the Valsalva maneuver). This allows quantitative description of the support of 3 vaginal segments: the anterior vaginal wall (referred to as point "Ba"), the vaginal apex or cervix (point "C"), and the posterior vaginal wall (point "Bp"). In this study, POP was defined as protrusion of any vaginal segment beyond the hymen (7). Our definition of POP also included patient reports of having undergone surgery for treatment of prolapse (7). Additionally, the POP-Q system includes a measure of GH (12). The size of the GH is defined by the distance (in centimeters) from the external urethral opening to the top of the perineal body. Thus, GH is essentially a measure of the sagittal width of the vaginal opening. The size of the GH was recorded with straining (during the Valsalva maneuver). In this study, the POP-Q examination was performed at each annual visit.

Our objective in this analysis was to compare women with and without POP regarding changes in GH over time. For this analysis, we conducted a nested case-control study (13). Among the 1,528 women in the MOAD cohort, we did not include those who had prolapse at the enrollment examination (n = 28) or those who reported surgery for prolapse prior to enrollment (n = 8), since no data on GH prior to prolapse would have been available. Additionally, we excluded 294 women who attended only 1 study visit (since the primary aim was to assess changes in GH). These exclusions resulted in 1,198 women being eligible for this analysis. Cases were defined at the first visit during study observation at which POP was identified (n = 153). Potential controls for each case must have contributed prolapse-free follow-up in the study for at least the amount of time it took for their respective case to develop POP, plus 6 months. Among potential controls, 5 controls were chosen at random from the pool of women who matched the case on the basis of delivery history (cesarean delivery only vs. $\geq$1 vaginal birth) and interval between first delivery and entry into the MOAD Study (within 6 months). Once incidence sampling had been accomplished, we identified 754 controls.

Data on the outcomes and exposures of interest were collected at study entry and were updated annually. For this analysis, data were derived from all visits prior to the diagnosis of prolapse in the cases and from the corresponding study interval for controls. Body mass index (defined as weight (kg)/height $(m)^2$) was calculated at each study visit and categorized for analyses as $<$25.0 (normal weight), 25.0–29.9 (overweight), or $\geq$30.0 (obese). Each woman's race was self-reported at study entry and was dichotomized as black versus nonblack. Parity was recorded at study entry and was updated for any births recorded between annual study visits; however, only 4.3% of participants in this study had additional deliveries after study enrollment. Because more than 80% of participants had parity less than 3, we categorized parity as 1, 2, or $\geq$3.

A mixed-effects model was used to compare the trajectories of GH in cases versus controls. The model allowed random effects for both the intercepts (corresponding to GH size at study enrollment) and the slopes (annual change in GH). The model's random effects allowed nested effects for 1) women within a matched set and 2) visits within a woman. Specifically, let GH_{ijt} denote the GH of the jth woman in the ith matching set at t years from study enrollment. Thus, i would range from 1 to the total number of prolapse cases. Values for j would typically range from 1 to 6 (i.e., 1 case and 5 controls). Finally, t would range from 2 years to 9 years. We used the following mixed-effects model to describe GH trajectories for cases and controls:

$$\begin{aligned} GH_{ijt} &= \alpha_0 + \alpha_1 \times \text{case} + a_i + u_{ij} \\ &\quad + \left(\beta_0 + \beta_1 \times \text{case} + b_i + v_{ij}\right) t + e_{ijt}. \end{aligned}$$

It follows that the population average values for GH at enrollment correspond to $\alpha_0 + \alpha_1$ for cases and α_0 for controls (i.e., the null hypothesis of no difference in GH at study enrollment corresponds to $\alpha_1 = 0$). Likewise, the population average slopes (i.e., change per year after study enrollment) correspond to $\beta_0 + \beta_1$ for cases and β_0 for controls (i.e., the null hypothesis of no difference in the rate of change in GH corresponds to $\beta_1 = 0$). To incorporate

the nested nature of the random effects describing departures from the population averages, we used (a_i, b_i) for the (random) departures of the initial GH size and slope of the *i*th matching set and (u_{ij}, v_{ij}) for the (random) departures of the initial GH size and slope of the *j*th woman within the *i*th matching set. Lastly, e_{ijt} represent the departures (residuals) from the line of the *j*th woman in the *i*th matching set of the observed GH at the visit occurring *t* years from enrollment. Both (a_i, b_i) and (u_{ij}, v_{ij}) were assumed to follow bivariate normal distributions with mean 0, and e_{ijt} were assumed to follow a standard normal distribution with mean 0, with the 3 stochastic components being statistically independent from one another. Hence, the total number of parameters describing the variance components was 7 (3 for $(a_i, b_i) + 3$ for $(u_{ij}, v_{ij}) + 1$ for e_{ijt}).

Conceptualizing the distribution of random effects as a prior distribution and using the parameter estimates from the maximum likelihood approach of the marginal distribution of the GHs, one can derive the posterior estimates of the initial values and slopes given the data observed on each woman (i.e., the empirical Bayes estimates). We used the "proc mixed" function in the SAS statistical package (SAS Institute Inc., Cary, North Carolina), which offered the empirically based estimates as the best linear unbiased predictions.

To explore possible heterogeneity of the case-control differences by type of delivery, we stratified the data by delivery type (cesarean delivery vs. vaginal birth). For each of these 2 subgroups, a mixed-effects model was used to compare the trajectories of GH in cases versus controls. For this analysis, the model allowed random effects for the intercept (corresponding to GH at study enrollment) only.

Two-tailed *P* values less than 0.05 were considered statistically significant. Analyses were conducted using SAS, version 9.4, and figures were created using R, version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The parent study included 1,198 women who met the inclusion criteria for this analysis (i.e., free of prolapse at enrollment and at least 2 study visits with GH measurements). Among these 1,198 women, who were followed for 1.0–7.3 years, 153 (13%) developed prolapse during follow-up. Among women who gave birth exclusively by cesarean delivery, 6% (36/615) developed POP, while 20% (117/583) of vaginally parous women developed POP. Of the 153 women with prolapse, 132 (86%) had isolated anterior vaginal wall prolapse, 13 (8%) had isolated posterior vaginal wall prolapse, 1 (1%) had isolated apical prolapse, and the remaining 7 (5%) either had mixed prolapse or were classified as having prolapse on the basis of their surgical histories. The analysis focused on these 153 cases and 754 controls who contributed data from a total of 3,664 study visits. For all but 3 cases, we obtained 5 controls per case. For 1 case, we obtained only 2 matched controls, and for 2 cases, we obtained only 1 matched control each.

The characteristics of cases and controls are compared in Table 1. Women who developed prolapse during study observation were similar at study entry to controls with respect to age at first delivery, race, parity, and body mass index. Because of the matching criteria, the two populations were practically identical with respect to interval from first delivery to study entry and proportion with vaginal birth. Furthermore, by design, the durations of follow-up needed to characterize the changes in GH were also very similar. As expected, the state of support (Ba, C, or Bp) among the cases was different at enrollment from that of the controls.

The estimates of the fixed effects of the mixed models with nested random effects are given in Table 2, with an unadjusted model in addition to a model that adjusted for age at first delivery, race, parity, and body mass index. In the model with no adjustment, GH was larger at enrollment among the cases (3.38 cm) than among the controls (2.81 cm) ($P < 0.001$), and the mean rate of change in the size of the GH was also significantly greater for cases (0.55 cm per 5-year period) than for controls (0.14 cm per 5-year period) ($P < 0.001$). In a multivariable model, significant differences persisted. Specifically, for the reference category corresponding to age 30 years at first delivery, nonblack race, parity of 1, and body mass index <25, GH at study entry was 3.16 cm in cases versus 2.62 cm in controls ($P < 0.001$), and the mean change in GH was 0.56 cm per 5-year period in cases versus 0.15 cm per 5-year period in controls ($P < 0.001$). The differences between cases and controls for GH size ($3.16 - 2.62 = 0.54$ cm) and change ($0.56 - 0.15 = 0.41$ cm per 5-year period) were invariant with respect to any case-control pair with the same values in the 4 covariates in the multivariable models.

Figure 1 depicts the empirical Bayes estimates of initial GH sizes and slopes based on the data of each individual woman. To summarize the data of the controls for each case, we calculated the median values of the estimated intercepts and of the estimated slopes of the 5 controls. For both the initial size of the GH and the rate of change in GH, each point in Figure 1 depicts the pairing of the estimate for the case (*y*-axis) with the median of the estimates for that case's matched controls (*x*-axis). Both the initial sizes of the GH (panel A) and the rates of change in GH (panel B) were higher among the cases than among controls (i.e., most points were above the identity (diagonal) line), and there was very little overlap in the distribution of the rate of change in GH. Furthermore, an increase in GH was almost uniformly seen in all women (i.e., only a few had changes below 0).

Finally, in a stratified analysis, the 117 cases who delivered at least 1 baby vaginally (and their 578 vaginally parous controls) were considered separately from the 36 cases of prolapse among women who bore all of their children by cesarean delivery (and their 176 controls). The multivariable models adjusted for age at first delivery, race, parity, and body mass index. As expected (7, 8), the initial GH sizes were higher among the women who had delivered at least 1 baby vaginally (Table 3). In both delivery groups, GH was larger at enrollment among the cases. More importantly, the mean rate of change in the size of the GH was also significantly greater for cases in both delivery groups, and the magnitudes of the changes were very similar among the two groups.

For the multivariable model results presented in Tables 2 and 3, we controlled for overall parity. In order to further

Table 1. Characteristics of Cases and Controls at Study Enrollment, Mothers' Outcomes After Delivery Study, 2008–2018

Characteristic	Controls (*n* = 754)			Cases (*n* = 153)		
	No. of Persons	%	Median (IQR)	No. of Persons	%	Median (IQR)
Age at first delivery, years			31.5 (28.9 to 35.2)			31.6 (28.4 to 35.3)
Black race	99	13.1		19	12.4	
Parity						
1	185	24.5		25	16.3	
2	461	61.1		100	65.4	
≥3	108	14.3		28	18.3	
Body mass index[a]						
<25.0	403	53.4		72	47.1	
25.0–29.9	214	28.4		49	32.0	
≥30.0	137	18.2		32	20.9	
Vaginal support[b], cm						
Ba			−1.5 (−2.0 to −1.0)			−1.0 (−1.5 to −0.5)
C			−6.5 (−7.0 to −5.5)			−6.0 (−6.5 to −5.0)
Bp			−2.5 (−2.5 to −2.0)			−2.0 (−2.5 to −1.5)
Vaginal delivery	578	76.7		117	76.5	
Time since first delivery, years			6.6 (5.6 to 8.8)			6.7 (5.9 to 8.8)
Duration of study follow-up, years			3.1 (2.1 to 4.4)			3.2 (2.1 to 5.0)

Abbreviation: IQR, interquartile range.
[a] Weight (kg)/height (m)^2.
[b] Ba is the position of the anterior vaginal wall, C is the position of the vaginal apex or cervix, and Bp is the position of the posterior vaginal wall. Negative numbers indicate a position proximal to the hymen.

explore the role of vaginal deliveries, we carried out the multivariable analysis presented in Table 3 for vaginally parous women using number of vaginal deliveries (1, 2, and ≥3) in place of overall parity. The results regarding the changes in GH were practically identical to those shown in Table 3 (i.e., 0.11 cm per 5-year period (95% confidence interval: −0.05, 0.28) and 0.47 cm per 5-year period (95% confidence interval: 0.23, 0.71) for controls and cases, respectively).

Table 2. Size of the Genital Hiatus at Study Entry and 5-Year Change in Genital Hiatus During Follow-up (Unadjusted and Adjusted Mixed-Effects Models), Mothers' Outcomes After Delivery Study, 2008–2018

GH Variable and Case/Control Status	Univariable Model		Multivariable Model[a]	
	Estimate	95% CI	Estimate[b]	95% CI
Mean GH size at study entry, cm				
Control	2.81	2.74, 2.88	2.62	2.49, 2.75
Case	3.38	3.26, 3.50	3.16	3.00, 3.33
Mean change in GH per 5-year period, cm				
Control	0.14	0.07, 0.22	0.15	−0.02, 0.32
Case	0.55	0.40, 0.70	0.56	0.34, 0.78

Abbreviations: CI, confidence interval; GH, genital hiatus.
[a] The multivariable model adjusted for age (years) at first delivery, race (black or nonblack), and time-updated parity (1, 2, or ≥3) and body mass index (weight (kg)/height (m)^2).
[b] Estimates are for those women whose covariates corresponded to the reference categories: age 30 years at first delivery, nonblack race, parity = 1, and body mass index <25.

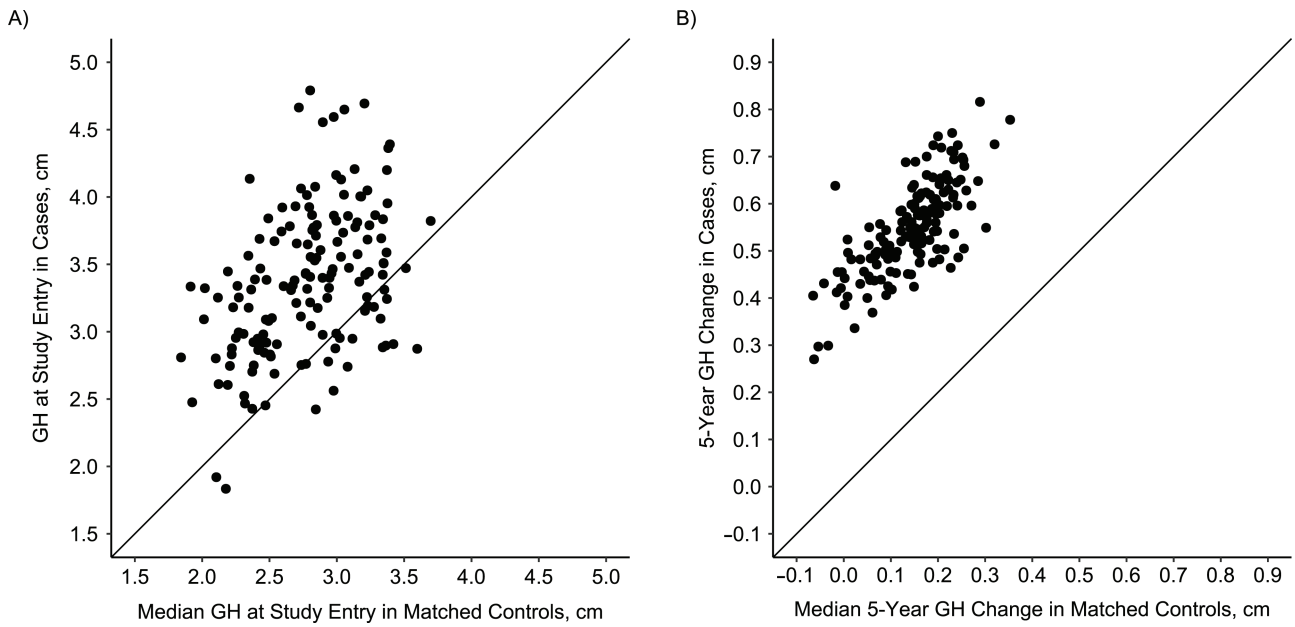

Figure 1. Size of the genital hiatus (GH) at study entry (A) and 5-year change in GH (B), Mothers' Outcomes After Delivery Study, 2008–2018. The graph shows empirical Bayes estimates based on the univariable model presented in Table 2. Each point depicts the pairing of the estimate for the case (*y*-axis) with the median of the estimates for that case's matched controls (*x*-axis).

DISCUSSION

In this analysis, the GH was 20% larger at study enrollment among women who later developed POP, compared with those who did not develop POP. Moreover, GH size increased over time in both groups but increased significantly faster for women who subsequently developed POP: The mean rate of change in the size of the GH was almost 4 times greater for cases (women who later developed POP) than for controls who did not develop POP (0.56 cm per 5-year period vs. 0.15 cm per 5-year period in controls; $P < 0.001$).

Because of the longitudinal design of this study, these data allowed an assessment of the temporal relationship between

Table 3. Size of the Genital Hiatus at Study Entry and 5-Year Change in Genital Hiatus During Follow-up, by Type of Delivery (Adjusted[a] Fixed-Effects (Random Intercept-Only) Model), Mothers' Outcomes After Delivery Study, 2008–2018

GH Variable and Case/Control Status	Cesarean Delivery Only[b]		≥1 Vaginal Delivery[c]	
	Estimate	95% CI	Estimate[d]	95% CI
Mean GH size at study entry, cm				
Control	2.22	2.02, 2.41	2.73	2.59, 2.87
Case	2.70	2.43, 2.97	3.28	3.09, 3.47
Mean change in GH per 5-year period, cm				
Control	0.09	−0.16, 0.33	0.10	−0.10, 0.30
Case	0.59	0.25, 0.93	0.46	0.20, 0.72

Abbreviations: CI, confidence interval; GH, genital hiatus.

[a] Multivariable model that adjusted for age (years) at first delivery, race (black or nonblack), and time-updated parity (1, 2, or ≥3) and body mass index (weight (kg)/height (m)^2).

[b] 36 cases and 176 controls.

[c] 117 cases and 578 controls.

[d] Estimates are for those women whose covariates corresponded to the reference categories: age 30 years at first delivery, nonblack race, parity = 1, and body mass index <25.

GH size and the development of POP. Specifically, the larger GH and more rapid change in GH *preceded* the diagnosis of POP. This relationship remained even after stratifying by delivery mode. Prior research in this study cohort demonstrated that a larger GH at any point in time is associated with a significantly faster rate of deterioration in uterovaginal support (8). In addition, we previously demonstrated that the hazard of POP at any point in time is increased 900% for women with a GH greater than or equal to 3.5 cm versus those with a GH less than or equal to 2.5 cm (7). Together, these findings suggest not only that women develop POP in the setting of a larger GH but also that a progressive widening of the GH is characteristic of women who later develop POP.

A strength of this study was the use of a validated and quantitative physical examination to classify POP and the GH, as well as the masking of examiners to delivery history and prolapse symptoms. Additional strengths of the present analysis included the matching of cases and controls for delivery type, a sufficiently large sample to provide 5 matched controls for almost every case (98%; 150/153), and a sufficient duration of time under study observation. Conversely, a weakness of the study was that the definition of POP did not require the presence of symptoms. We acknowledge that not all prolapse beyond the hymen becomes symptomatic or burdensome. A longitudinal study that follows women to assess the development of impactful prolapse symptoms would shed additional light on the natural history of this condition but may not be feasible.

An unanswered question is whether GH size is causally related to the development of POP. Alternatively, GH may be a marker for other underlying causal factors, such as traumatic disruption to or neurological impairment of the levator ani muscle (14–16). This distinction is important, because the former would suggest that interventions designed to narrow the GH might prevent POP. Conversely, the latter would suggest that the anatomical and functional determinants of GH size would be more appropriate targets for preventative interventions. At present, there is no evidence that such interventions (such as surgical narrowing of the GH via perineoplasty) are appropriate for POP prevention. Nonetheless, given the strong differences in the increase in GH size among those observed to develop POP, assessment of GH may offer information relevant to POP risk and to women's pelvic health. While this measurement is not typically part of clinical care, it is easily performed at the time of gynecological examination. Our results suggest that health-care providers could consider monitoring not simply the current size of the GH but also the pattern of changes in GH over time. An increase of close to 0.5 cm in a 5-year period would be most typical of women observed to develop POP in the current study.

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