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Genital hiatus size and the development of prolapse among parous women

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Abstract

Objectives: In cross-sectional studies, pelvic organ prolapse is strongly associated with genital hiatus size. The objective of this study was to estimate prolapse incidence by the size of the genital hiatus among parous women followed prospectively.

Methods: Data were derived from a longitudinal study of pelvic floor disorders. Participants were followed annually for 2–9 years. Genital hiatus size and prolapse beyond the hymen were assessed with annual POP-Q examinations. Kaplan-Meier methods described prolapse-free survival as a function of genital hiatus size. Accounting for changes over time in genital hiatus size, lognormal models were used to estimate prolapse-free survival by genital hiatus size. This analysis was repeated separately for women who delivered exclusively by cesarean versus those with at least one vaginal birth

Results: Among 1492 participants, median age at enrollment was 38 years; 153 (10.3%) developed POP over 2–9 years. The cumulative probability of prolapse increased substantially as the size of the genital hiatus increased. Lognormal models predicted that the estimated median time to develop prolapse would be 33.4 years for women with a persistent genital hiatus of 3cm; in contrast, the estimated median time to develop prolapse would be 5.8 years for a genital hiatus of ≥4.5 cm. Considering separately women who delivered by cesarean versus those with at least one vaginal birth, genital hiatus size drastically modified prolapse risk in both birth groups.

Conclusions: Prolapse incidence is strongly associated with genital hiatus size, regardless of delivery mode. These findings suggest that a wider GH is an important predictor of future prolapse risk.

Keywords

Prolapse; genital hiatus; Kaplan-Meier; Lognormal models; Longitudinal data; cohort studies

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INTRODUCTION:

Pelvic organ prolapse accounts for more than 300,000 surgical procedures annually in the United States at a cost of $1 billion [1]. Established risk factors for prolapse include parity, vaginal delivery, age, and obesity [2]. Among parous women, prolapse is significantly more common after vaginal versus cesarean birth [3].

There is increasing evidence that prolapse is strongly associated with the size of the genital hiatus (GH), defined as the distance (cm) between the urethral meatus and the posterior hymen [4]. Cross sectional studies have shown that GH is significantly larger in women with stage 3 prolapse compared to women with stage 0 or 1 prolapse [5]. Lowder et al found that a GH of ≥3.75 is highly predictive of apical prolapse [6]. A large GH has also been shown to be associated with prolapse recurrence after reconstructive surgery [7–10]

Our recent longitudinal studies have shown that a larger GH is also associated with incident prolapse [11]. Specifically, the relative incidence of prolapse was nine times higher for women with GH ≥3.5 cm versus ≤2.5 cm (Hazard Ratio= 9.0, 95% confidence interval 5.5–14.8). Also, in a nested case control study from the same population [12], GH was 20% larger at study enrollment and increased at a faster rate among women who ultimately developed prolapse compared to those who did not develop prolapse. However, from a clinical perspective, it would be valuable to understand the likelihood of prolapse across a range of attained GH values. As such, the purpose of this study was to estimate the incidence of prolapse across a spectrum of observed GH size categories.

MATERIALS AND METHODS:

Data for this research were derived from a cohort study of pelvic floor disorders among parous women, the Mothers' Outcomes After Delivery (MOAD) Study [3, 11–13]. Study participants were recruited from a community hospital 5–10 years after a first delivery. A primary goal of the MOAD study was to compare pelvic floor disorders after cesarean versus vaginal birth [3]. Recruitment was based on delivery type, resulting in over-representation of women delivered by cesarean. At enrollment, the delivery groups were matched based on age at delivery and time since first delivery. This study was approved by the institutional review board and all participants provided written informed consent.

Participants were followed for up to 9 years, with an annual assessment for prolapse and other pelvic floor disorders. This analysis focused on prolapse, which was assessed annually using the POP-Q examination system [4]. Prolapse was defined as descent of the vaginal walls or cervix beyond the hymen during forceful Valsalva [11]. Participants who reported surgery for treatment of prolapse were also considered to have prolapse [11]. Prolapse symptoms were not considered. During annual visits, study personnel were blinded to delivery mode, prior examination results, and to current symptoms. Because this analysis considered prolapse that developed during study observation, women who had prolapse at study enrollment and those who reported surgery for prolapse prior to enrollment were excluded.

The genital hiatus (GH), the primary exposure for this analysis, was defined as the distance (cm) from the middle of the external urethral meatus to the posterior midline hymen, measured during Valsalva [4]. For this study, GH was measured to the nearest half-centimeter. GH was reassessed annually. As previously demonstrated in this study population, most study participants demonstrated changes over time in GH [12]. Therefore, each woman may have transitioned across GH categories during study observation. For each woman, we defined her "attained" GH as her GH measurement at any specific point in time.

Other data for this analysis included age, delivery mode, parity, race, and ethnicity. Delivery mode was defined as "cesarean only" for women who delivered all of their children by cesarean; the "vaginal delivery" group included women who had at least one vaginal delivery. Delivery mode was abstracted from the hospital record. For the <5% of deliveries that occurred at nonaffiliated hospitals, patient recall of delivery mode was used to classify birth type [14]. Parity was self-reported. Race was also self-reported and was categorized as American Indian/ Alaska Native, Asian, black or African American, Native Hawaiian / Pacific Islander, white, or other. Participants were also asked if they were of Hispanic origin.

For each value of attained GH, we calculated the proportion of women who developed de novo prolapse. Since participants were at least 5 years from delivery at the time of study enrollment, the origin for the analysis was defined as 5 years after first delivery. As GH may change over time [12], most women provided data for more than one GH category. Each woman either completed the study in her GH category without developing prolapse, developed prolapse, or transitioned to a different GH category. For women who remained POP-free, we censored their times at three months past the last study visit. For women who missed an annual assessment, missing data were imputed with a carry forward method, but only for a single missed visit; data were considered missing otherwise [11]. Thus, the expected prolapse occurrence was imputed using the extended Kaplan-Meier estimator [15]. Applying Kaplan-Meier non-parametric methods extended to incorporate late entries in addition to right censored data, we calculated estimates of proportions of prolapse-free women at different intervals from 5 years from first delivery for a given value or category of GH.

In addition to non-parametric Kaplan-Meier methods to estimate prolapse-free survival, in parallel, we fit lognormal (parametric) models to the observed data. The clinical relevance of the resultant lognormal model is that the parameters for this equation can be used to predict the median time (and any other percentile of interest) to develop prolapse for any GH category. Specifically, the "location" parameter of the lognormal model can be used to estimate the median prolapse-free survival for all categories of attained GH. Also, an important additional use of the lognormal model is that this method can be used to describe dynamic changes in survival estimates according to changes in GH. Specifically, the model was used to estimate the prolapse-free survival as the value of GH changed over time.

In an additional analysis, we stratified the population by delivery history (women with at least one vaginal birth versus women who had delivered exclusively by cesarean). We then fit new lognormal models within each stratum.

Data management was conducted using SAS v9.4 (SAS Institute, Cary, North Carolina). Analyses and figures were created using R v3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). Parametric survival models were fit using the flexsurvreg function from the 'flexsurv' package in R [17]. Additional details of the statistical methods are provided in the Supplement.

RESULTS

Of 1528 study participants for this longitudinal study, 36 were excluded due to prolapse at the time of study enrollment, leaving 1492 for this analysis. Among 1492 women, the median age at enrollment was 38 years (interquartile range: 35–42). Approximately half of the participants had delivered exclusively by cesarean (775, 52%), while 717 (48%) women had at least one vaginal birth. Parity was 1 in 425 (28%), 2 in 834 (56%) and ≥3 in 233 (16%) women. Of 1492 women, 1184 (79%) were Caucasian, 232 (16%) were Black and 61 (4%) were Asian or of other races (race was missing for 15 women (1%)). Additionally, 32 women (2%) were of Hispanic origin.

Participants attended a total of 6977 study visits (range 2–9). As participants were enrolled 5–10 years from delivery and followed for up to 9 years, some participants were almost 2 decades from first delivery at the conclusion of the study. Of 6977 visits, 287 visits included data that were carried forward. In addition, 56 visits with missing GH data were not included in this analysis.

Across all 6977 visits, the range of values for GH was 0.5 cm to 6.5 cm and the most common value for GH was 2.5 cm (Table 1). Two-thirds of GH values were contained in the range between 2 cm and 3 cm. We observed 153 cases of incident prolapse. The incidence of prolapse during 2–9 years of follow-up monotonically increased with GH size (from 0% for GH≤1.5 cm to 11.4% for GH≥4.5 cm).

Parametric lognormal models were used to estimate prolapse-free survival as a function of GH category (≤2.5cm, 3 cm, 3.5cm, 4 cm, and ≥4.5cm). Kaplan-Meier curves are shown in Figure 1 for observation beginning 5 years from first delivery. The corresponding parametric lognormal models are overlaid to demonstrate the goodness-of-fit of the prediction models. As shown, the percent remaining prolapse-free (over >10 years of observation) varied significantly by GH category.

The parameters of the lognormal models are described in the Supplemental Table and results are summarized in Table 2. For women with a GH ≤2.5 cm, the median time to develop prolapse would exceed 45 years from the origin (e.g, 50 years from first delivery). More specifically, the lognormal model estimates that only 16% of women whose GH remains ≤2.5 cm would develop POP within 45 years from the origin. For women with a larger genital hiatus, the estimated median time to develop prolapse would be 33.4 years for a genital hiatus of 3 cm, 14.4 years for a genital hiatus of 3.5 cm, 9.2 years for a genital hiatus of 4 cm, and 5.8 years for a genital hiatus of ≥4.5 cm. The interquartile ranges are shown in Table 2 and provides some information about the dispersion of these data: for example, among women with GH of 3.5 cm, the estimated median time to develop prolapse is 14.4

years from the origin (e.g. 19.4 years from first delivery) but 25% of women are predicted to develop prolapse before 5.7 years from the origin (10.7 years from first delivery) and 25% would be prolapse-free 36.6 years from the origin (41.6 years from delivery).

While the estimates in Table 2 are for women who persistently remain in a given GH category, in most women GH changes over time. Figure 2 illustrates how prolapse-free time would be influenced by hypothetical changes over time in GH size. Survival trajectories representing constant GH size (dashed lines) are contracted with survival trajectories reflecting transitions between GH categories over time (solid lines). The supplemental methods section provide details for how to derive the expected survival functions of women according to their changes in GH.

Finally, we considered the additional impact on prolapse-free survival of vaginal versus cesarean delivery. As shown in Table 1, the distribution of GH sizes was different for the cesarean and vaginal birth groups. Thus, we considered prolapse separately for the two birth groups. In the cesarean group, we compared prolapse-free survival for GH ≤2.5cm versus those with GH ≥3cm. In the vaginal birth group, we considered three GH categories: ≤3cm, 3.5–4 cm and ≥4.5cm. There were too few cases of prolapse at the extremes to further stratify these data. Kaplan-Meier curves and their corresponding lognormal fits are shown in Figure 3. Parameters of the cesarean and vaginal lognormal models are listed in the supplemental table. The findings of these models suggest that GH substantially modifies prolapse risk in both birth history groups.

DISCUSSION

The aim of this study was to estimate prolapse incidence by the size of the attained genital hiatus among parous women. These data demonstrate that the probability of developing prolapse over 2–9 years was strongly and significantly associated with GH size. Prior research has suggested a very strong association between GH size and prolapse [11]. In addition, in a prior case-control study [12], we demonstrated a temporal relationship between GH size and prolapse: specifically, a large GH preceded the incidence of prolapse. The present study builds on those results by demonstrating that prolapse incidence varies significantly across a range of GH values, effectively displaying a “biological gradient”. In epidemiologic research, the strength of the association, temporality, and biological gradient are three classical criteria to distinguish causation from association [18]. Thus, the present study contributes to a growing body of evidence that GH size influences the future development of prolapse.

We created prolapse-free survival curves across a range of GH values, but a limitation of the Kaplan-Meier survival analysis is that this approach assumes that GH is constant over time for an individual woman. In reality, GH changes over time [12]. Specifically, GH increases, on average, by approximately 1/2 centimeter every 5 years among women who subsequently develop prolapse (compared to 0.15 cm per 5-years in control who do not develop prolapse, P<0.001). Thus, the value of the lognormal models presented here is the ability to predict prolapse incidence, not only as a function of time but additionally as a result of a transition to a higher GH category. Lognormal models are often used for skewed distributions (so that

the log-transformed data are amendable to normal based methods). This model is therefore widely used for time-to-event data, as time-to-event data are typically right skewed. In our case, the goodness of fit of the models to the non-parametric estimates (as shown in Figures 1 and 3) clearly supports their adequacy for our data.

A final perspective from the present study is the contrast between prolapse-free survival for women who delivered all their children by cesarean versus those who have delivered vaginally. Vaginal delivery is strongly associated with prolapse [11] and is also associated with a larger genital hiatus [13]. The results of this analysis in which we stratified the population by birth type suggests that GH is associated with prolapse risk even among women who deliver all their children by cesarean. However, among women who delivered exclusively by cesarean, approximately 80% of GH values were less than 3cm. Our results suggest that prolapse incidence remains very low in that subset of this population.

Still unanswered is whether a larger GH is a *cause* of prolapse or a *marker* for the underlying pathophysiology of prolapse. This is a critical question in clinical practice, because GH size can be intentionally modified by surgery. Specifically, posterior colporrhaphy and perineorrhaphy are associated with reduction of the size of the genital hiatus [7,19]. At present, we cannot conclude that such surgical interventions will reduce prolapse risk.

The primary strength of this study was the longitudinal study design. The validity of the annual assessment of these variables was supported both by the use of a quantitative physical examination as well as by the masking of the examiners to each participant's delivery mode, prior examination results, and to current symptoms (to reduce bias). Another notable strength of this analysis is the use of statistical models that account for changes over time in GH category. Finally, the cohort was sufficiently large and followed for a sufficient duration to identify differences in prolapse incidence among GH categories.

A limitation of the study design is that the population was relatively young (median age at enrollment was 38 years). Also, while we followed women for up to 9 years, this duration of follow up may be insufficient to accurately predict outcomes many decades from delivery. In particular, this duration of follow-up was not adequate to look at patterns of prolapse incidence among senior women. Also, the definition of prolapse was based only on physical examination; we acknowledge prolapse beyond the hymen is clinically significant only for women with burdensome symptoms. Also, a dichotomous definition for prolapse is an oversimplification, as worsening of mild prolapse over time may also be clinically relevant.

In conclusion, a larger GH precedes the diagnosis of prolapse [12] and the risk of prolapse varies significantly across a range of GH values. While a causal relationship between GH size and prolapse has yet to be conclusively demonstrated, these findings suggest that a larger GH is an important predictor of future prolapse risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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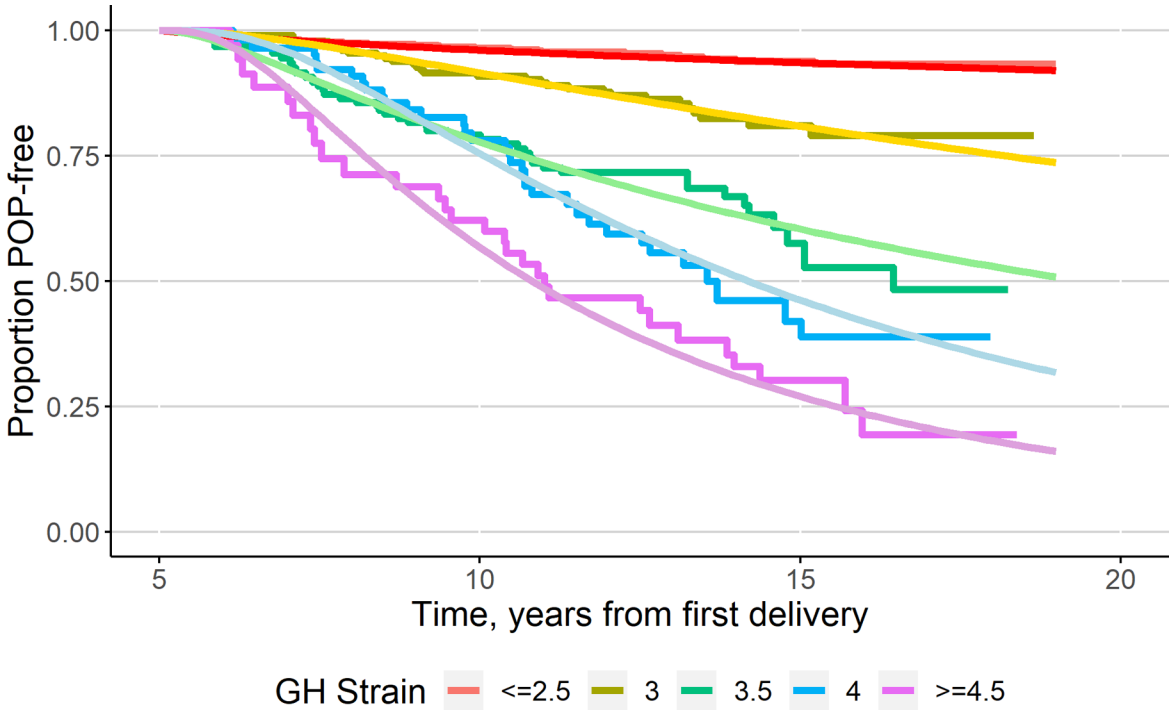

Figure 1:

Kaplan-Meier survival estimates for prolapse-free survival, as a function of GH category. Corresponding lognormal models (described in the Supplemental Table) are overlaid, estimating prolapse-free survival as a function of GH category. P-value for the null hypothesis of no difference between the five GH categories was <0.001.

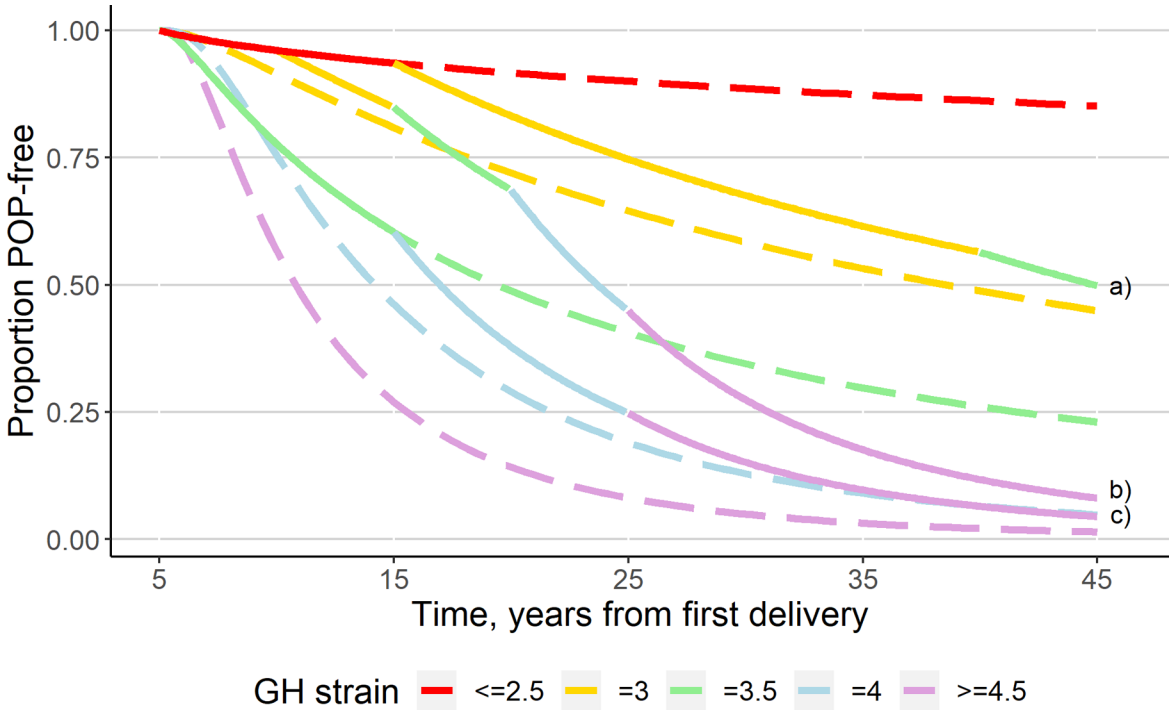

Figure 2:

Lognormal models (fully described in the Supplemental Table), estimating prolapse-free survival as a function of GH category up to 45 years after first delivery. Survival estimates of those persisting in a given GH category over time are represented by dashed lines. Survival estimates for three hypothetical women transitioning between GH categories are represented by solid lines (a, b, and c). Transitions between GH categories are indicated by changes in color of the solid line.

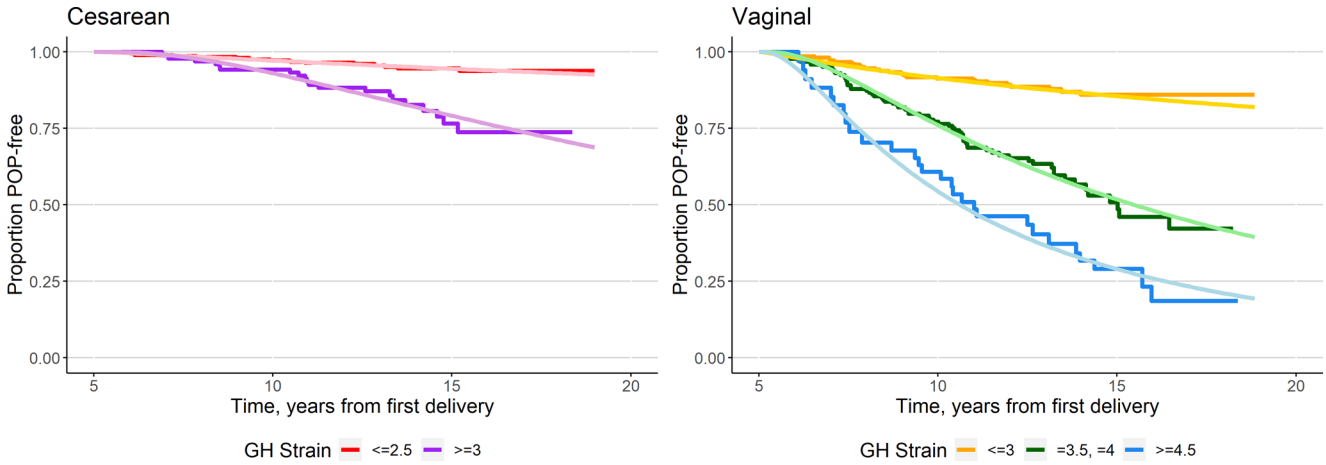

Figure 3:

Kaplan-Meier survival estimates for prolapse-free survival, as a function of GH category, stratified by birth type. Corresponding lognormal models (fully described in the Supplemental Table) are overlaid, estimating prolapse-free survival as a function of GH category. P-values for the null hypothesis of no differences between the GH categories were <0.001 and <0.001 for cesarean only and vaginal delivery groups, respectively.

Table 1:

Prolapse by GH category: New onset of prolapse during study observation, as a function of GH category. Data are presented for 6977 study visits.

GH size (cm)	Prolapse cases (percentage) N=6977 woman-visits	Prolapse cases (percentage), prior cesarean birth only N=3861 woman-visits	Prolapse cases (percentage), at least one prior vaginal birth N=3116 woman-visits
≤1.5	0/1049 (0.0%)	0/901 (0.0%)	0/148 (0.0%)
2	7/1509 (0.5%)	4/1118 (0.4%)	3/391 (0.8%)
2.5	17/1569 (1.1%)	12/986 (1.2%)	5/583 (0.9%)
3	28/1353 (2.1%)	9/599 (1.5%)	19/754 (2.5%)
3.5	39/789 (4.9%)	6/187 (3.2%)	33/603 (5.5%)
4	33/453 (7.3%)	4/56 (7.1%)	29/397 (7.3%)
≥4.5	29/255 (11.4%)	1/14 (7.1%)	28/241 (11.6%)

Table 2:

Estimated median time (in years, from the origin*) and interquartile range (in brackets) to develop prolapse, by GH category. These data are based on the lognormal models of prolapse, as presented in supplemental table.

GH size (cm)	Overall	Cesarean Only	Vaginal Delivery
<=2.5	†	†	†
=3	33.4 [13.2, >45]	23.3 [11.6, >45]	“
=3.5	14.4 [5.7, 36.6]	“	10.5 [5.2, 21.1]
=4	9.2 [5.1, 16.8]	“	“
>=4.5	5.8 [3.2, 10.6]	“	5.6 [2.8, 11.4]

*The origin for these data is 5 years from first delivery.

†For these GH categories, the estimated median time to develop prolapse exceeds 45 years from the origin.