Published in final edited form as:

Int Urogynecol J. 2014 August ; 25(8): 1121–1126. doi:10.1007/s00192-014-2363-4.

Lack of association between pelvic outlet diameter and pelvic organ prolapse in squirrel monkeys

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Abstract

Introduction and hypothesis—The aim was to test the hypothesis that the pelvic outlet diameter (POD) is associated with pelvic organ prolapse (POP) in squirrel monkeys.

Methods—Magnetic resonance images (MRI) were obtained from 55 females with and without POP. Commercial software was used by two observers to measure the POD. POD, age, parity, and weight for the two groups were compared using Student's *t* test. Associations of age, parity, and body weight with POD were evaluated with linear regression analysis. Multiple regression

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Content presented as a poster in 2013 at the Annual Meeting of the International Urogynecology Association in Dublin, Ireland.

Financial disclaimer/conflict of interest Funding provided by Enderly Endowment for pelvic floor research and Noble Centennial Endowment (TJK) and NIH P40-RR01254 (JCR and TJK). No commercial conflicts. Research approved by Scott & White Institutional Animal Care and Use Committee (2007–30-R).

analysis examined the relationships of age, parity, and POD with POP. Receiver operating curve methods were used to set thresholds.

Results—Observers concurred on measurements (Cronbach's $\alpha=0.96$ with lower 95 % confidence limit of 0.94). POD was not related to parity ($p=0.10$) or weight ($p=0.053$), but was inversely related to age ($p=0.011$). Animals with POP did not differ from those without POP with regard to age ($p=0.10$), weight ($p=0.17$), or POD ($p=0.99$). The groups differed with regard to parity ($p=0.007$) and multiple regression methods demonstrated that only parity had a significant relationship with POP ($p=0.002$). Parity greater than 2 had 64 % specificity and 89 % sensitivity for POP.

Conclusions—POD size does not contribute to POP in squirrel monkeys. This study confirms that among variables of age, body weight, POD, and parity, only parity appears as a risk factor for POP in squirrel monkeys.

Keywords

Pelvic outlet diameter; Squirrel monkey; Prolapse; Magnetic resonance imaging

Introduction

Historically, variations in the size and shape of the human pelvis have generated hypotheses for the etiology of pelvic floor disorders. The relationship between pelvic organ prolapse (POP) and bony pelvic architecture has been studied in humans to a limited degree [1–3].

It is well accepted that animal research contributes to the study of human disease by allowing hypotheses to be tested in controlled settings that cannot be performed on humans. Squirrel monkeys have unique characteristics that make them useful for pelvic floor research. For example, 50 % of older females demonstrate pelvic support defects [4]. As in humans, these pelvic support defects are associated with childbirth and aging [5]. Since squirrel monkeys deliver large infants (14 % of maternal body weight) relative to maternal size, they are susceptible to pelvic floor injury secondary to labor dystocia. Also, their lifespan is shorter than humans (2 versus 8 decades), which allows for serial observation in a research setting. Because of these characteristics, research on squirrel monkey pelvic anatomy contributes to our knowledge base of POP.

Various modalities for imaging have been used to describe squirrel monkey pelvic anatomy. In 1983, Aksel and Abee [6] used radiographic pelvimetry to evaluate the bony pelvic architecture in females with a focus on predicting the risk of stillbirth in captive breeding programs. Later we used CT imaging to create three-dimensional models of the bony pelvis of a small series ($N=9$) of older animals without detailed obstetric histories [7]. In both studies, of the five pelvic dimensions examined as illustrated in Fig. 1, only the pelvic outlet diameter (POD) was related to stillbirth [6] and prolapse [7]. Recently, magnetic resonance imaging (MRI) has been used to compare levator ani muscle volumes in monkeys with and without prolapse [8], and to compare the effects of delivery [9] and nerve injury [10] on pelvic floor musculature. However, these three articles did not address the risk of prolapse in relationship to bony pelvis dimensions. Therefore, despite this research on muscle

dimensions and contrast changes, the relationship between POD and prolapse in squirrel monkeys has been supported by only the limited observations using CT imaging. Therefore, we undertook this study to use a larger cohort of female squirrel monkeys with known obstetrical histories representing various ages to assess the association between POD and POP in the female squirrel monkey.

Materials and methods

Animals

A colony of squirrel monkeys housed at Scott and White Healthcare was used for this study. The use of these animals and MRI methodology was reviewed and approved by the Scott and White Institutional Animal Care and Use Committee. Nineteen female parous squirrel monkeys with pelvic floor defects based on visual perineal evaluations using methods originally described by Coates et al. [4] and/or the measured descent of the bladder base to greater than 7 mm below bony pelvic landmarks as defined and illustrated by Pierce et al. [10] were included, along with 36 adult females with normal pelvic floor support by both criteria. Animals were of a range of ages, parities, and weights. All animals in the study were initially obtained from the National Squirrel Monkey Breeding and Research Resource, now located at the Michale E Keeling Center for Comparative Medicine and Research of The University of Texas MD Anderson Cancer Center in Bastrop, Texas, USA.

Imaging methods

Magnetic resonance imaging (MRI) of the pelvic floor was performed on all female monkeys using a previously described technique [8–10]. Briefly, animals were sedated, given intravenous contrast medium (0.25 mmol/kg of gadolinium chelate; ProHance; Bracco Diagnostics, Princeton, NJ, USA), and placed inside the MRI unit (3-T Siemens Trios, Erlangen, Germany) with their back and legs supported in a natural position inside an eight-channel wrist coil (model HRW, Philips Medical Systems, Waukesha, WI, USA). Two localizing scans were obtained to set the region of interest for serial images from L7 through C4. A sequence of echo gradient axial images was acquired during a 4.4-min interval. Images were saved as a DICOM series and transferred to a work station with commercial software (3D-Doctor; Able Software, Lexington, MA, USA), which was used to review, manipulate, and measure the POD. The POD, as originally defined by Aksel and Abee [6], is the distance between the inferior lateral margins of the obturator foramina at the level of the pubic arch (Fig. 2). This is the only measure of five previously related to development of prolapse [7]. Two independent reviewers (JSJ, TJK) performed all measurements in anteroposterior views. Bladder position change relative to a skeletal reference line was measured with a dynamic scan where abdominal pressure is applied using a neonatal blood pressure cuff placed around the animal's abdomen using a previously described technique [9, 10]. POP was also directly assessed by an established procedure using perineal visual examination [4].

Statistical analysis

Comparison of POD measurements by two independent observers was made using Cronbach alpha for inter-rater correlation (MediCalc Software, Ostend, Belgium). Prolapse groupings

were compared using Student's *t* test for parametric variables. Linear regression analysis examined the relationship of the outlet dimension to age, parity, and weight. Multiple regression analysis examined the relationships of age, parity, and outlet dimension to the presence or absence of POP. These analyses were performed using Statistica software (StatSoft, Tulsa, OK, USA). Receiver operating curve analysis was performed to establish a threshold criterion level for parity as a predictor of the development of POP (MediCalc Software). *p* values less than 0.05 were interpreted as significant.

Results

The two observers independently performed measurements of 55 PODs in 55 images independently. The measurements were highly correlated (Cronbach's alpha= 0.96 with a lower 95 % confidence limit of 0.94), which implies that there were no differences in measurements between the two observers (Fig. 3). Therefore, the average values for the two observers were used for the remaining analyses.

Table 1 shows independent associations of parity, age, and weight with POD in the 55 subjects. The POD is not related to parity ($p = 0.10$) or weight ($p = 0.053$), but is inversely related to age ($p = 0.011$). Although weight has a tendency to correlate directly with the outlet diameter, the effect is small ($r^2 = 0.07$). Figure 4 illustrates the inverse relationship between outlet diameter and age.

Univariate analyses using Student's *t* test demonstrate that animals with POP do not differ from those without POP with regard to age ($p = 0.10$), weight ($p = 0.17$), or POD ($p = 0.99$). The two groups do differ with regard to parity ($p = 0.002$ using Student's *t* test). Using multiple regression, only parity demonstrated a significant relationship with POP ($p = 0.007$; Table 2). Using receiver-operating curve (ROC) methods, parity as a criterion had a significant ($p < 0.0001$) area under the curve (0.78 with 95 % CI of 0.64 to 0.88; Fig. 5). The optimal criterion for parity as a threshold for the prediction of POP was greater than 2 vaginal deliveries (sensitivity of 64 % and specificity of 89 %); however, greater than 1 vaginal delivery has a similar sensitivity (61 %) and the same specificity (89 %).

Discussion

As previous observations in squirrel monkeys supported the concept that of five boney pelvis measurements, only the POD in the anteroposterior dimension can identify animals with a higher frequency of stillbirths [6] and POP [7], we anticipated that this trial would confirm the risk conferred by a smaller pelvic outlet of the development of POP. As illustrated in Fig. 6, the fetal face is the presenting part as the majority of squirrel monkey deliveries are mentum anterior [11]. However, in the current trial, only parity was shown to be related to the development of POP. Our study in squirrel monkeys showed that PODs do not differ between animals with and without prolapse, which is consistent with the findings by Stein et al. [3]. Stein et al. studied boney landmarks at the level of the pelvic floor in white women and found no association between outlet dimensions and POP [3].

We also reaffirmed earlier observations that parity appears to be the most significant risk factor for prolapse development in squirrel monkeys [5]. However, in the previous study of a

breeding colony, parity and age were highly associated; thus, it was not possible to distinguish which of these characteristics might have the strongest effect. In our current study, age, weight, and outlet diameters were not associated with prolapse, suggesting that parity is the primary risk factor. In spite of a preliminary trial with a cohort of 9 older animals [7], the POD for animals with prolapse in the current study was the same as for animals without prolapse (17.9 ± 1.2 and 17.9 ± 1.5 mm respectively). The measurements made by the two independent observers were precise and valid for this analysis.

The inverse relationship between age and POD is unexplainable at this time. It is possible that the older animals in this cohort had smaller pelvises to begin with, suggesting that the younger animals benefited from improved nutrition in their captive environments. It is also possible that pelvic measurements might change with age. The latter hypothesis is testable in the future by examining serial measurements in animals followed for an extended interval. Although animal weight had a tendency to correlate with outlet diameter, the effect was small.

The advent of sensitive radiographic technology has enticed researchers to study bony pelvic architecture in humans in hopes of addressing various hypotheses pertaining to the risk of the development of pelvic organ prolapse. Using computed tomography, Sze et al. found that women with prolapse had larger transverse inlet diameters than women without prolapse [1]. Using MRI, Handa et al. found that a wider transverse inlet and a shorter obstetrical conjugate were significantly associated with pelvic floor disorders [2]. In previous studies of five measures of the pelvic inlet and outlet in squirrel monkeys, only the POD was found to be related to stillbirth using radiographic projection [6] or POP using CT [7] in a small series of older animals. In squirrel monkeys, the ilium is longer and narrower and the outlet faces more dorsally (Fig. 6). The fetal head does not simultaneously pass the sacral promontory and pubic symphysis; thus, some of the classically defined pelvic diameters may not be relevant to this species [12]. There are no ischial spines as in the human pelvis. The fetal head does become bound circumferentially by the maternal bony pelvis when it reaches the plane of the second sacral vertebra and the superior ramus of the pubic symphysis until it exits at the outlet position [12]. The smallest of the measured diameters is the outlet [4, 7]; thus, while this restriction would seem to be the most important, our study did not support this hypothesis.

It was the initial dilemma of impaired reproductive performance in captivity secondary to a high perinatal mortality rate that encouraged investigators to develop pelvimetry methods as a predictor of pregnancy outcome [6]. This finding led to hypotheses associating traumatic pelvic floor injury from labor dystocia with subsequent prolapse. Despite the suggested relationship between a small POD and prolapse in an earlier and smaller cohort of squirrel monkeys [6], the current study provides data from a different and larger cohort that do not support the earlier preliminary findings. Further investigation of pelvic organ prolapse etiology with a focus on the role of pregnancy and delivery in squirrel monkeys is warranted and in progress.

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Fig. 1.

a Lateral view of a three-dimensional reconstruction of the bony pelvis of an adult female squirrel monkey rotated 18° about the spine with measured inlet and mid-pelvis diameters. **b** Anteroposterior view with inlet, mid-pelvis, and outlet diameters measured

Fig. 2. Magnetic resonance imaging (MRI) of female squirrel monkey pelvis at the level of the pelvic outlet diameter (POD). *Arrow* indicates the POD measured

Fig. 3.

Inter-rater comparison for measurement of POD. No difference between observers was found. Linear regression with 95 % confidence interval. Cronbach's alpha=0.96. Lower 95 % confidence interval of 0.94

Fig. 4.
Linear regression with 95 % confidence interval comparing the POD of 55 animals with ages. Outlet diameter was inversely associated with age ($p=0.011$, $r^2=0.12$)

Fig. 5. Receiver-operating curve with 95 % confidence interval for analysis of the threshold number for parity in relation to pelvic organ prolapse in a cohort of 55 adult squirrel monkey females. Optimal criterion point (*open circle*) is for parity greater than 2

Fig. 6.
a Lateral radiograph of a squirrel monkey fetus entering the birth canal, **b** axial view of three-dimensional reconstruction of CT scan with the tail in front, and **c** artist depiction of mentum anterior presentation to demonstrate that anteroposterior outlet dimension represents a restriction for squirrel monkey vaginal delivery

Table 1

Relationship between pelvic outlet diameter (POD) and parity, age, or weight

Variable	Correlation	R ²	<i>p</i> value [*]
Parity	−0.23	0.05	0.10
Age	−0.34	0.12	0.011
Weight	0.26	0.07	0.053

^{*} Multiple regression model

Table 2

Factors related to pelvic organ squirrel prolapse in the squirrel monkey

Factor	Animals with POP (n=19)	Animals without POP (n=36)	p level*	p level**
Parity	5.0 ± 2.4	2.3 ± 2.4	0.002	0.007
Age (years)	12.0 ± 5.2	9.2 ± 6.3	0.10	0.99
Body weight (g)	750 ± 63	720 ± 84	0.17	0.08
Outlet diameter (mm)	17.9 ± 1.2	17.9 ± 1.5	0.99	0.74

* Univariate comparison using Student's *t* tests

** Multiple regression model