Published in final edited form as:

J Med Primatol. 2009 August ; 38(4): 257–262. doi:10.1111/j.1600-0684.2009.00350.x.

Endometrial and cervical polyps in 22 baboons (*Papio* sp.), 5 cynomolgus macaques (*Macaca fascicularis*) and one marmoset (*Callithrix jacchus*)

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Abstract

Background—Endometrial and cervical polyps are masses of endometrium or cervical epithelium that bulge into the uterine or cervical lumen. The physiopathology and contributing factors of endometrial polyps development are still unknown.

Methods—Clinical and pathology records of 28 nonhuman primates with histologically confirmed endometrial and cervical polyps were reviewed. Twenty-one baboons with endometrial polyps were evaluated for age at diagnosis; body weight; menstrual cycle length, presence of endometriosis and adenomyosis; and number of offspring, cesarean sections, and stillbirths.

Results—Endometrial polyps in baboons were associated with increased age, decreased menstrual cycle lengths, endometriosis, and decreased parity. No differences were found for weight, adenomyosis, or number of cesarean sections or stillbirths.

Conclusions—Baboons are a promising model for the study of endometrial polyps because of their similarity to humans in both the development of endometrial polyps and association of many of the same risk factors.

Keywords

endometrium; uterus; mass; cancer; nonhuman primate

Introduction

Endometrial polyps are masses of endometrium that bulge into the uterine lumen, can appear as single or multiple and pedunculated or broad-based [8], and have been reported in humans, nonhuman primates (NHP), dogs, cats, horses, mice, fat sand rats, hedgehogs, elephants, and a horse [3,4,7,8,11,14,16]. Endometrial polyps are composed of endometrial glands, an increased amount of fibrous tissue, and can contain smooth muscle; the endometrial glands can be either normal or cystic and hyperplastic [1,8]. Cervical polyps are

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composed of hyperplastic endocervical endothelium and are often accompanied by inflammation and squamous metaplasia [2,8].

Endometrial polyps have been observed in ovariectomized rhesus macaques following prolonged exogenous estrogen exposure [3]. Endometrial polyps in women can occur at any age, but are most often diagnosed around menopause [22]. In women, endometrial and cervical polyps can cause abnormal uterine bleeding [1,2,8,18] and are associated with infertility [17,24]; pregnancy rates can be improved after polypectomy [24,25]. A significant association between endometrial polyps and pelvic endometriosis has also been published [17,19]. A positive correlation between obesity and the presence, number, and size of endometrial polyps has been identified [21]. Additionally, endometrial polyps have been associated with tamoxifen administration [2,8] and cervical polyps, especially if recurrent, with embryonal rhabdomyosarcoma [1].

Although historically classified as a benign lesion, adenocarcinomas occasionally develop in endometrial polyps [8,13]. Stromal cells within endometrial polyps have been shown to be clonal with chromosome rearrangements [8]. Up to 3.2% of endometrial polyps in women contain malignant areas, suggesting polyps as precursor for endometrial carcinomas [13]. The contributing factors leading endometrial and cervical polyp development, or their malignant transformation are unknown [13].

The baboon (*Papio* spp.) is an excellent model for research in reproduction, the endometrium, endometriosis, and early pregnancy [9,12,20]. The baboon's large size is advantageous for repeated blood analysis and surgeries, the menstrual cycle is easy to monitor by observing changes in the sex skin, and the cervical canal allows easy access to the endometrium [6,10,20]. The baboon's endometrium progresses through changes similar to human endometrium during the menstrual cycle [10]. Although endometrial and cervical polyps have been reported in rhesus and cynomolgus macaques [3,16], to the best of our knowledge, there is only one published report of endometrial polyps in a baboon [4] and none in marmosets.

We report endometrial polyps in 21 baboons, four cynomolgus macaques, and one marmoset. Cervical polyps were found in one baboon and one cynomolgus macaque. We further characterize the 21 endometrial polyps in the baboons with respect to age, weight, menstrual cycle length, reproductive performance, and the presence of concurrent endometriosis or adenomyosis.

Materials and Methods

Animals

The baboons and cynomolgus macaques were housed in indoor-outdoor metal and concrete gang cages. Some baboons were also housed in 6-acre corrals. The marmoset was housed indoors in PVC coated wire caging. All nonhuman primates were fed commercial monkey diets supplemented with grains, vegetables, and fruits. Water was supplied *ad libitum*. The nonhuman primates were usually members of the breeding colony and not generally used experimentally. If there was any question that the pathological lesion could be related to experimental use of an animal, that animal was excluded from the study. All nonhuman primates were cared for in compliance with the Guide for the Care and Use of Laboratory Animals. All procedures were approved by the Institutional Animal Care and Use Committee. The Southwest Foundation for Biomedical Research is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International.

Record Review

A computer search was performed using an internal anatomic pathology database (APATH) for all diagnoses of endometrial and cervical polyps in nonhuman primates over a 26-year period. Endometrial polyps were identified in 21 baboons, four cynomolgus macaques, and a marmoset. Cervical polyps were identified in one baboon and one cynomolgus macaque. Necropsy, histopathology, and computerized medical records were reviewed for all cases.

The 21 baboons with endometrial polyps were compared to a similar, age-matched population of female baboons without polyps ($n=1,275$). We analyzed age at polyp diagnosis, adult weight (from 10 to 15 years of age), weight at necropsy, menstrual cycle length, presence of endometriosis and adenomyosis, and number of offspring, cesarean sections, and stillbirths. Age was estimated when the exact age was unknown. When calculating menstrual cycle data, turgescence scores, vaginal bleeding, and color of sex skin were used to calculate the average cycle duration. Menstrual cycle data did not include periods of pregnancy, 6 months post-parturition, 1 month after cesarean sections or stillbirth, or when the mother was carrying an infant.

Pathology

All nonhuman primates were necropsied and complete tissue sets taken for histologic evaluation. The tissues were fixed in 10% neutral buffered formalin, processed conventionally, embedded in paraffin, cut at 5 μm , stained with hematoxylin and eosin and reviewed by light microscopy. Necropsies were performed and histopathologic diagnoses were made by two board-certified veterinary pathologists. Six cases were referred to the Armed Forces Institute of Pathology (AFIP) for consultation.

Statistics

Statistical analysis was performed using Statistica 6.0 (StatSoft, Inc., 2001). Data are presented as mean $\pm$ standard error of the mean (SEM), unless we indicate the use of standard deviation (SD). Comparison of means was conducted using Student's *t*-test for independent samples adjusted by variance. We considered *p*-values below 0.05 to be statistically significant.

Results

Table 1 lists the clinical information concerning the 28 endometrial and cervical polyps. Endometrial polyps were seen in 21 baboons (average age = $24.1 \pm (\text{SD}) 6.0$ yr, range 11.6 to 31.9 yr). Although there were insufficient numbers for analysis, clinical information for the four cynomolgus macaques and one marmoset with endometrial polyps and for the one baboon and one cynomolgus macaque with cervical polyps are included in Table 1.

All but two baboons with endometrial polyps had a history of weight gain throughout their lifespan. The average weight of all 21 baboons was 17.9 kg. Seven of the 21 (33%) had higher weight when compared with the reported average weight for female baboons in captivity [23].

Menstrual cycle data was available for 19 of the baboons with endometrial polyps. The average menstrual cycle length was 29.8 ± 3 days and was shorter than reported cycle lengths in the literature (32 days, $t = -17.97$, $p < 0.0001$) [10] and our own colony data (35.7 ± 1.2 days, $t = -7.75$, $p < 0.0001$) [15].

Endometriosis was present in six baboons (28.6%) and adenomyosis in four baboons (19.1%); two baboons (9.5%) had endometriosis and adenomyosis.

Pathology

All polyps were identified at necropsy as sessile to pedunculated soft tissue masses ranging from 1-4 cm in size that projected from the mucosal surface of the uterus or cervix and partially to completely filled the uterine lumen (Fig.1, A and B). Histologically, endometrial polyps were composed of loose endometrial stroma and connective tissue supporting and containing multiple typical to irregularly shaped, variably cystic endometrial glands (Fig.1, C and D).

Factors associated with endometrial polyps

Baboons with endometrial polyps were older (24.1 ± 6.2 vs. 18.6 ± 4.8 yr, $p < 0.001$) and more likely to have endometriosis (Odds ratio=3.7; 95% CI 1.4, 9.7; $p < 0.004$). This persisted after adjusting for age and weight (Odds ratio=2.7; 95% CI 1.0, 7.3; $p < 0.054$). Baboons with endometrial polyps had approximately 30% fewer offspring ($p < 0.001$) than those of the same age without polyps (Fig. 2). Differences in weight, presence of adenomyosis, and number of cesarean sections or stillbirths were not observed between baboons with and without endometrial polyps.

Discussion

The finding of endometrial polyps predominantly in older baboons is consistent with the published data in humans, where endometrial polyps are observed most often in perimenopausal women [22].

A positive correlation between obesity and the presence, number, and size of endometrial polyps has been identified in humans [21]. Obesity and hypertension during late menopause are considered to be important factors in endometrial polyp development in women [22]. It is interesting that seven (33%) of the baboons with endometrial polyps were overweight compared with the reported average weight for female baboons in captivity [23]. We evaluated weight in our baboons as a proxy for obesity, but did not find a difference between baboons with and without polyps in our colony. It is possible that captive baboons generally weigh more than baboons in the wild, confounding our ability to identify a weight effect. To the best of our knowledge, the incidence of endometrial polyps in the presumably leaner wild population has not been reported.

Unopposed estrogens have been suggested as a cause of polyps and endometrial cancers [21]. Moreover, the experimental administration of excess estrogens caused endometrial polyps in ovariectomized rhesus macaques [3]. The short cycle lengths found in most of the baboons in our study could indicate that they have increased levels of estrogen [5] or have an irregular cycle with abnormal uterine bleeding. While the retrospective nature of this study does not allow us to make a definite conclusion, our findings are in agreement with the reports of abnormal uterine bleeding in women with endometrial and cervical polyps [1,2,8,18].

The association between endometrial polyps and endometriosis was consistent with reports in women [17,19]. Endometrial polyps in women with endometriosis contributed to the increased frequency of infertility [17,24] and pregnancy rates can be improved after polypectomy [24,25]. Our finding of decreased parity within the group with endometrial polyps suggests that decreased fertility also occurs in baboons with endometrial polyps.

Baboons present a promising animal model for the study of endometrial polyps because of their similarity to humans in both the development of endometrial polyps and association of many of the same risk factors.

Acknowledgments

The authors acknowledge Marie Silva, Michaelle Hohmann and Denise Trejo for pathology support and the expert assistance of the Technical Publications personnel.

Funding: This research was funded in part by NIH/NCRR grant P51 RR013986 to the Southwest National Primate Research Center and conducted in facilities constructed with support from Research Facilities Improvement Program Grant C06 RR014578 and C06 RR015456.

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Figure 1. Endometrial polyps in baboons

A and B, Gross appearance of endometrial polyps in baboons. C and D, Subgross appearance of endometrial polyps in cynomolgus macaques (scanned histologic section, H&E).

Figure 2.
Logistical regression of offspring for baboons with and without endometrial polyps, adjusted by age and weight.

Summary data for nonhuman primates with endometrial or cervical polyps

Table 1

Location of polyp	Species	Age (years)	Weight (kg)	Average Cycle Length (days)	Endometriosis	Adenomyosis	Offspring	Cesarean sections	Stillbirths	Time Between Last Offspring and Death (months)
Uterus	Papio sp.	11.6	15.80	29.0	No	No	4	1	0	10.0
Uterus	Papio sp.	12.0	16.02	27.7	No	No	0	0	0	N/A
Uterus	Papio sp.	13.0	13.30	N/A	No	No	0	0	0	N/A
Uterus	Papio sp.	16.6	18.42	28.3	No	No	4	0	3	52.7
Uterus	Papio sp.	19.1	14.50	29.7	No	No	1	0	0	253.3
Uterus	Papio sp.	22.1	22.95	N/A	Yes	No	11	0	0	44.4
Uterus	Papio sp.	23.0	20.93	28.5	Yes	No	9	0	3	84.1
Uterus	Papio sp.	23.5	17.56	36.4	Yes	Yes	5	1	0	116.5
Uterus	Papio sp.	24.6	16.50	31.5	No	No	9	1	0	113.9
Uterus	Papio sp.	25.6	14.16	37.6	Yes	No	5	3	0	134.4
Uterus	Papio sp.	25.8	20.46	27.0	Yes	No	9	3	0	101.3
Uterus	Papio sp.	26.8	15.31	30.4	No	No	8	2	2	164.6
Uterus	Papio sp.	27.2	18.54	33.4	No	No	5	2	0	131.1
Uterus	Papio sp.	27.5	20.60	31.0	No	Yes	0	0	0	N/A
Uterus	Papio sp.	28.6	12.68	26.4	No	No	13	0	1	132.1
Uterus	Papio sp.	28.7	22.10	26.5	No	No	6	0	0	194.8
Uterus	Papio sp.	29.3	22.60	28.7	No	Yes	6	2	0	169.9
Uterus	Papio sp.	29.3	24.18	28.2	No	No	7	2	0	133.7
Uterus	Papio sp.	29.6	14.12	26.7	Yes	Yes	2	1	0	157.7
Uterus	Papio sp.	30.0	16.18	29.5	No	No	9	0	0	158.8
Uterus	Papio sp.	31.9	18.56	29.4	No	No	7	2	0	152.2
Uterus	Macaca fascicularis	8.2	7.70	UNK	No	No	1	0	0	78.8
Uterus	Macaca fascicularis	12.8	7.00	UNK	No	No	1	0	0	90.2
Uterus	Macaca fascicularis	16.9	7.80	UNK	Yes	No	2	0	1	50.8
Uterus	Macaca fascicularis	17.7	4.40	UNK	No	No	0	0	0	N/A
Uterus	Callithrix jacchus	5.5	UNK	UNK	No	No	UNK	UNK	UNK	UNK
Cervix	Papio sp.	13.6	12.50	27.9	No	No	5	1	0	28.9
Cervix	Macaca fascicularis	26.9	2.80	UNK	No	No	4	0	0	65.0