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Intrapelvic injection of menstrual endometrium causes endometriosis in baboons (*Papio cynocephalus* and *Papio anubis*)

Thomas M. D'Hooghe, MD,[a, c] Charanjit S. Bambra, PhD,[a] Barbara M. Raeymaekers, SCM,[a] Inge De Jonge, MD,[b] Jo M. Lauweryns, MD, PhD,[b] and P.R. Koninckx, MD, PhD[c]
Nairobi, Kenya, and Leuven, Belgium

OBJECTIVE: The Sampson hypothesis of retrograde menstruation as a cause of endometriosis was tested by determining the effect of intrapelvic injection of menstrual versus luteal endometrium on the incidence, peritoneal involvement, and stage of endometriosis.
STUDY DESIGN: Seventeen baboons were injected retroperitoneally with luteal (n = 6) or menstrual (n = 7) endometrium and intraperitoneally with menstrual endometrium (n = 4). Laparoscopies were performed after 2 months in all animals and after 5 and 12 months in six and five primates injected with luteal and menstrual endometrium, respectively.
RESULTS: The peritoneal endometriosis surface area, number of implants, and incidence of typical and red subtle lesions were significantly higher after retroperitoneal injection of menstrual than of luteal endometrium. By use of menstrual endometrium intraperitoneal seeding was more successful in causing endometriosis than was retroperitoneal injection. No significant changes in number or surface area of endometriotic lesions induced with retroperitoneal injection of luteal endometrium after 5 months were observed in the six baboons. At repeat laparoscopy 12 months after intrapelvic injection of menstrual endometrium progression was recorded in three of four regularly cycling animals, whereas regression was evident in one baboon that had become amenorrheic after induction.
CONCLUSION: Intrapelvic injection of menstrual endometrium can cause peritoneal endometriosis and offers experimental evidence supporting the Sampson hypothesis. (Am J Obstet Gynecol 1995;173:125-34.)

Key words: Menstrual and luteal endometrium, retroperitoneal and intraperitoneal injection, endometriosis, baboons, subtle and typical lesions

In 1927 Sampson[1] hypothesized that the pathogenesis of endometriosis could be explained by intrapelvic transplantation of endometrium shed during retrograde menstruation. Only indirect evidence supports this widely accepted hypothesis, as reviewed recently.[2] Retrograde menstruation occurs in most women.[3] Endometrial cells shed during menses are viable[4] and can be found in the fallopian tubes[5] and in the peritoneal fluid.[6, 7] The ability of endometrial cells shed during menses to implant and grow on visceral and parietal peritoneum has not yet been conclusively demonstrated. In women endometrial cells from menstrual effluent can be transplanted to abdominal wall fascia, but the development of endometriosis only occurred in 12% of cases, even after 6 months of shedding.[8] In rhesus monkeys surgical cervical diversion resulted in massive adhesions, but intraabdominal menstruation was not observed and endometriosis was only found in 50% of animals after 10[9] or 35 months.[10] Similarly, intraperitoneal seeding of menstrual endometrium has not been successfully demonstrated to induce en-

From the Institute of Primate Research,[a] the Department of Histopathology, University Hospital St. Rafael,[b] and the Department of Obstetrics and Gynecology, University Hospital Gasthuisberg.[c]
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Reprint requests: Thomas M. D'Hooghe, MD, Fearing Research Laboratory, Brigham and Women's Hospital, Harvard Medical School, 250 Longwood Ave., SGMB 204, Boston, MA 02115.

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Table I. Duration of captivity, number of previous hysterotomies, and endometrial weight used for intrapelvic injection for each of 17 baboons

Animal number	*Duration of captivity (yr)*	*Previous hysterotomies (No.)*	*Endometrial weight (mg)**
Luteal RP (group 1)			
1	2	0	200
2	2	0	60
3	12	3	750 (315)
4	12	3	1000 (60)
5	11	6	490 (Unknown)
6	12	7	500
Menstrual RP (group 2)			
7	2	0	1350
8	11	6	400
9	2	0	870
10	7	3	620
11	2	0	1000
12	1	0	480
13	2	0	Unknown
Menstrual IP (group 3)			
14	12	3	Unknown
15	12	3	Unknown
16	1	0	Unknown
17	5	1	Unknown

RP, Retroperitoneal; *IP*, intraperitoneal.
*Number in parentheses indicates endometrial weight used for first unsuccessful induction.

dometriosis in other nonhuman primates.[10-12] However, nonmenstrual (luteal or follicular) endometrial cells injected retroperitoneally or intraperitoneally in monkeys have been reported to cause endometriosis in 17%,[13] 75%,[9, 12, 14] and 100%[15] of cases.

The purpose of this study was to test the Sampson hypothesis by comparing the effect of intrapelvic injection of menstrual versus luteal endometrium on the incidence, peritoneal involvement, stage, and evolution of endometriosis.

Material and methods

Animals. This study was performed on 17 adult female baboons (16 *Papio anubis*, one *Papio cynocephalus*) weighing 12 ± 3 kg. Their exact age was not known, but they had been at the Institute of Primate Research for 6 ± 5 years. All were of proved fertility in the wild, had normal menstrual cycles, and were without endometriosis, as laparoscopically demonstrated before the onset of this study.[16, 17] Pelvic adhesions, resulting from previous hysterotomies performed for termination of pregnancy in captivity, were present in seven animals. Detailed information regarding duration of captivity and number of hysterotomies for each animal can be found in Table I. Perineal staging was used to diagnose the luteal phase on the basis of earlier observations that perineal inflation and deflation correspond with the follicular and luteal phases, respectively.[18] This project had been reviewed and was approved by the Institute Scientific Resources Evaluation and Review Committee.

Retroperitoneal and intraperitoneal injection of endometriosis. Preparation of animals, anesthesia, and laparoscopic procedures were accomplished as previously described.[16] All laparoscopically observed peritoneal fluid was aspirated. In eight baboons endometrium was obtained by transcervical biopsy with an adapted 2 mm Novak curette (curved tip, small opening) (Belge de Gembloux, Gembloux, Belgium), and peritoneal injection was performed during laparoscopy. In the other nine animals the uterus could not be probed under laparoscopic guidance, and a laparotomy had to be performed (low midline incision) to obtain endometrium. To prevent adhesion formation, a uterine incision was not made, but the fundus was penetrated with an 18-gauge needle followed by a Verress needle. Subsequently the adapted Novak curette was introduced through the small opening in the fundus. In each animal a curettage was performed, and all endometrial biopsy specimens were pooled together to obtain an appreciable quantity of endometrial tissue. The endometrial tissue used for retroperitoneal or intraperitoneal injection was not standardized with respect to weight or cell number. When used for retroperitoneal injection (n = 13), the endometrium obtained was placed in a sterile Petri dish; its color was assessed; and it was weighed, minced with small scissors, resuspended in 1 to 2 ml of sterile 0.9% saline solution, and injected with an 18-gauge needle beneath the peritoneum. When intraperitoneal seeding was performed (n = 4), the objective was to assess the implantation potential of freshly obtained and unmanipulated menstrual endometrium. Therefore the endometrial tissue was not weighed, minced, or resuspended in solution but immediately aspirated in

Table II. Summary of different variables for groups 1, 2, and 3

	Group 1 (n = 6): Luteal endometrium, retroperitoneal injection	*Group 2 (n = 7): Menstrual endometrium, retroperitoneal injection*	*Group 3 (n = 4): Menstrual endometrium, intraperitoneal injection*
Endometrial weight (mg)	500 ± 345 (495*)	787 ± 358 (745*)	Unknown
No. of lesions (mean, median, range)	40 (6 ± 3, 5, 4-11)	85 (12 ± 5, 10, 8-21)	106 (26 ± 13, 25, 16-41)
No. of lesions (typical, subtle red plus white, suspicious)	40 (2, 1 ± 34, 3)	85 (8, 30 ± 39, 8)	106 (14, 18 ± 63, 11)
No. of biopsy specimens (typical, subtle red plus white, suspicious)	25 (3, 1 ± 19, 2)	20 (1, 8 ± 9, 2)	13 (3, 4 ± 5, 1)
No. of positive biopsy specimens (typical, subtle red plus white, suspicious)	14 (2, 1 ± 11, 0)	13 (1, 7 ± 5, 0)	8 (2, 4 ± 2, 0)
Surface lesions (mm^2) (mean, median, range)	140 (23 ± 18, 17, 9-56)	362 (52 ± 30, 46, 21-110)	720 (180 ± 135, 140, 70-370)
Surface lesions (typical, subtle red plus white, suspicious)	140 (5, 2 ± 99, 34)	362 (12, 182 ± 127, 41)	720 (454 ± 151, 38)

*Median.

a 5 ml syringe with assessment of volume and color,[5] fragmented through an 18-gauge needle, and, because it had a pastelike consistency, "placed" on top of the peritoneum. Both retroperitoneal injection and intraperitoneal seeding were done in the uterosacral ligaments, uterovesical fold, posterior uterine peritoneum, cul-de-sac, broad ligament, and ovaries. Each site of retroperitoneal injection was inspected for intraperitoneal leakage during 1 to 2 minutes. The places of retroperitoneal injection and intraperitoneal seeding were carefully recorded on a pelvic map for each baboon.

Retroperitoneal injection with endometrium obtained during the late luteal phase was performed in six baboons. After 2 months three baboons underwent a second retroperitoneal injection with luteal endometrium, because the first attempt had not been successful (see Results). All six animals with biopsy-proven endometriosis after injection with luteal endometrium were included in group 1. Retroperitoneal injection with endometrium obtained during the first or second day of menstruation was performed in seven animals (group 2). Intraperitoneal seeding of menstrual endometrium was performed in four primates (group 3). Intraperitoneal seeding of luteal endometrium was not done because the results of group 1 were disappointing (see Results).

To determine the effect of peritoneal trauma on the implantation of ectopic endometrium, superficial scarification of the lower right area of the posterior uterus (1 × 1 cm) was performed in four baboons with lesions induced with menstrual endometrium (three retroperitoneal and one intraperitoneal method). This was done with either a surgical knife during laparotomy ($n = 3$) or with laparoscopic scissors during laparoscopy ($n = 1$).

Follow-up laparoscopies. A first laparoscopy was performed to assess the success of retroperitoneal or intraperitoneal endometrial injection after 2.2 ± 0.4 months (group 1, $n = 6$, range 1.5 to 2.5 months), 2 ± 0.4 months (group 2, $n = 7$, range 1.5 to 2.5 months), and 1.5 ± 0.4 months (group 3, $n = 4$, range 1 to 2 months). Follow-up laparoscopies were repeated to evaluate the spontaneous evolution after 5 ± 2 months in group 1 ($n = 6$, range 3 to 9 months) and after 12 months in group 2 ($n = 2$) and group 3 ($n = 3$). The other baboons were not available for follow-up because they were pregnant (group 2, $n = 5$; group 3, $n = 1$).

Endometriosis screening. The internal genitalia and pelvic peritoneum were evaluated for the presence of endometriosis as previously described.[16] Briefly, typical lesions were defined as white plaques with pigmented spots or blue-black cysts. Subtle lesions included red lesions (red-orange vesicles, red polyps, hemorrhagic zones, petechia) and white lesions (plaques with or without vesicles, vesicles only, or nodules). Peritoneal orange zones or irregular blood vessel patterns were considered as suspicious lesions.

During each laparoscopy the number, size, and surface area of the endometriotic lesions were recorded on a pelvic map made for each animal. All induction sites were specifically screened by palpation with a laparoscopic probe for the presence of retroperitoneal involvement. Because the majority of implants were circular, the lesional surface area was calculated with the formula πr^2 and expressed as number per square millimeter. In animals that underwent reinduction the number, size, and surface area of lesions were corrected for the few implants present from the first induction.

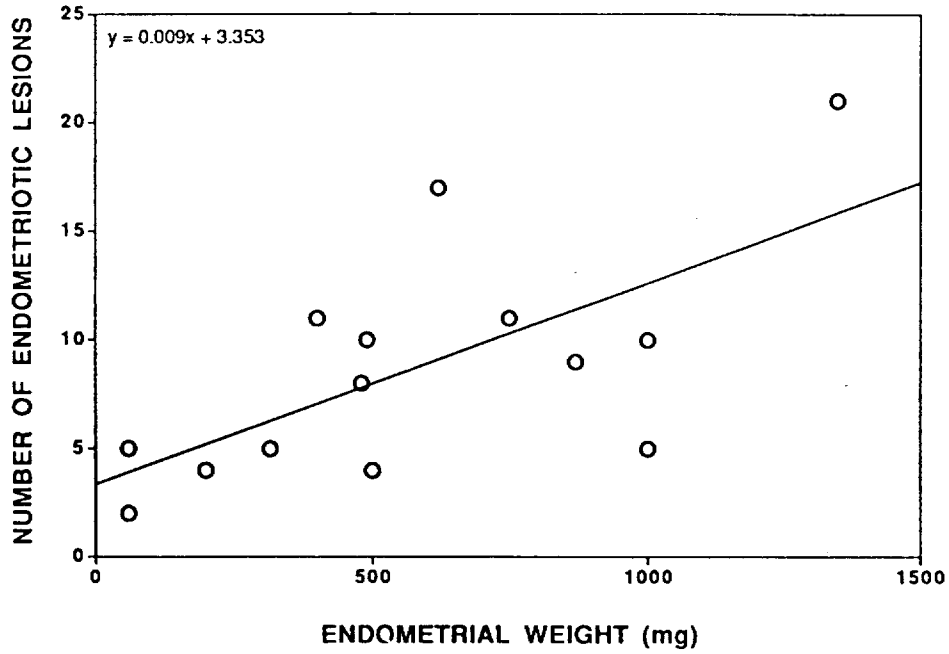

Fig. 1. Significant linear correlation ($p < 0.01$) between endometrial weight used for induction and number of endometriotic lesions.

The American Fertility Society classification for pelvic endometriosis[19] was used to stage the disease in the animals without preexisting adhesions ($n = 10$), after modification to correct for the smaller size of the pelvic organs in baboons compared with humans.

Histologic study. Fifty-eight biopsies were taken from typical ($n = 7$), red ($n = 13$), white ($n = 33$), and suspicious ($n = 5$) endometriotic implants, immediately fixed in 10% phosphate-buffered formalin, dehydrated, and embedded in paraffin. Four micrometer sections were stained with hematoxylin and eosin and histologically evaluated. In biopsies from macroscopically positive- but microscopically initially negative-appearing lesions, serial sections through the whole lesion were made. Endometriosis was diagnosed by pathologic criteria of the human disease (presence of endometrial glands together with stroma at ectopic pelvic sites).

Statistics. Mean ± SD were used where indicated. Statistical significance ($p < 0.05$) was analyzed with parametric (Student t test, analysis of variance) or nonparametric (Kruskal-Wallis, Mann-Whitney) and χ^2 (Fisher's exact) tests when appropriate. A linear regression analysis was performed to determine the effect of endometrial weight on the development of endometriosis.

Results

Initial induction with luteal endometrium resulted in biopsy-proven endometriosis in only three of six baboons of group 1. However, reinduction with luteal endometrium in the three baboons with initially failed induction was successful (histologic confirmation in all animals). Intrapelvic injection of menstrual endometrium resulted in biopsy-proved endometriosis in all baboons of groups 2 and 3. No differences were observed in the incidence or location of endometriosis between baboons that were injected with endometrium harvested during transcervical (laparoscopy) and transfundal (laparotomy) aspiration.

Endometrial tissue: color, weight, volume (Tables I and II, Fig. 1). Endometrium obtained during the luteal phase was pink or light red with only a little blood, whereas endometrial specimens obtained during the menstrual phase were usually dark red and heavily embedded in blood. The weight of luteal endometrium used for the first induction ($n = 6$, 227 ± 186 mg) was significantly lighter ($p = 0.02$) than that used for reinduction ($n = 3$, 747 ± 255 mg) and than menstrual endometrium ($n = 7$, 787 ± 358 mg). However, the weight of luteal endometrium used for successful retroperitoneal injection (group 1, $n = 6$, 422 ± 333 mg, median 402 mg) was not significantly lower than that of endometrial tissue obtained in the menstrual phase (group 2, $n = 7$, 787 ± 358 mg, median 745 mg). There was a significant linear correlation (Fig. 1) between the weight of endometrium used for induction and the number of lesions ($y = 3.3 + 0.009x$, $p < 0.01$) but not between endometrial weight and the surface area of implants ($y = 4.8 + 0.06x$, $p > 0.5$).

The volume of the mixture of menstrual endome-

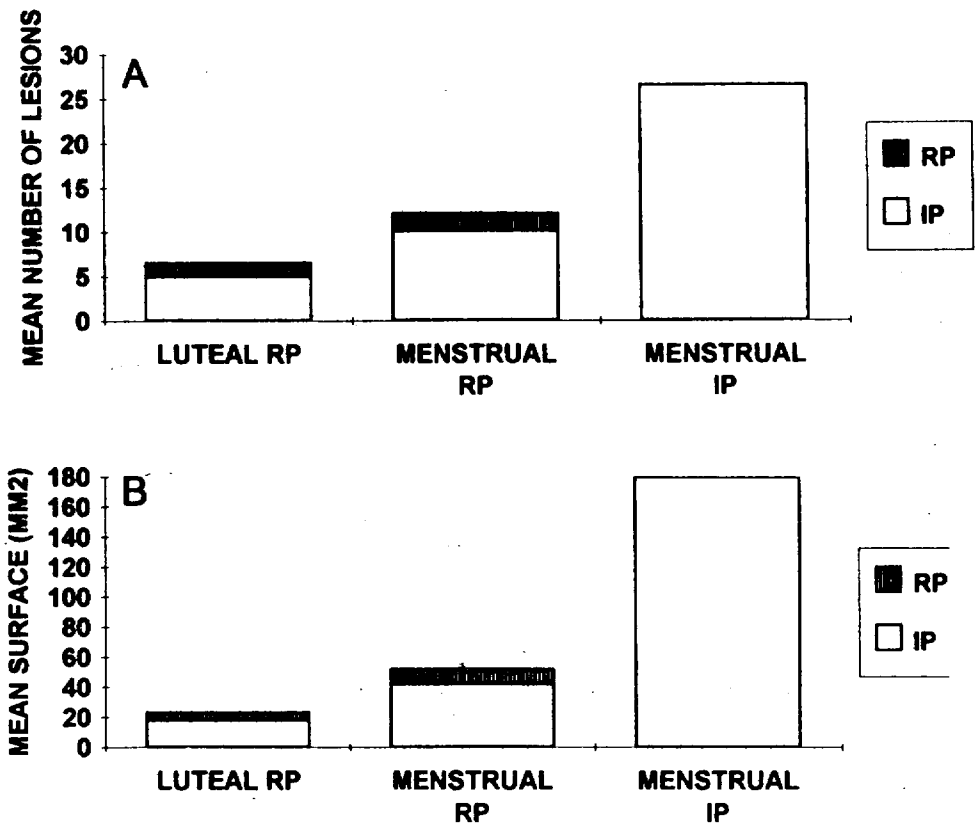

Fig. 2. Mean number **(A)** and mean surface area (square millimeters) **(B)** of endometriosis lesions after retroperitoneal *(RP)* injection with luteal (n = 6, group 1) or menstrual (n = 7, group 2) endometrium and after intraperitoneal *(IP)* seeding with menstrual endometrium (n = 4, group 3). *Striped area,* Lesions located on spot of retroperitoneal injection. **A,** All groups, $p < 0.01$; luteal retroperitoneal versus menstrual retroperitoneal, $p < 0.05$; luteal retroperitoneal versus menstrual intraperitoneal, $p = 0.001$; menstrual retroperitoneal versus intraperitoneal, $p < 0.05$. **B,** All groups, $p < 0.01$; luteal retroperitoneal versus menstrual retroperitoneal, $p < 0.05$; luteal retroperitoneal versus menstrual intraperitoneal, $p = 0.001$; menstrual retroperitoneal versus intraperitoneal, $p = 0.01$.

trium and blood used for intrapelvic injection varied between 1 and 1.5 ml.

Comparison of groups 1, 2, and 3. Significantly more lesions ($p = 0.03$) and a larger endometriosis surface area ($p < 0.05$) were observed in baboons retroperitoneally injected with menstrual endometrium (group 2) compared with the animals that had experimental endometriosis after retroperitoneal injection of luteal endometrium (group 1, Fig. 2). Considerable intraperitoneal leakage was noted at most sites of induction during and immediately after the retroperitoneal injection. The majority of endometriotic lesions (66% in group 1 and 84% in group 2) and the endometriosis surface area (72% in group 1 and 74% in group 2) were observed outside the site of retroperitoneal injection (Fig. 2). Intraperitoneal seeding of menstrual endometrium (group 3) was more effective than retroperitoneal injection (group 2), as evidenced by significantly more lesions ($p < 0.05$) and a larger endometriosis surface area ($p = 0.01$, Fig. 2).

Typical and subtle lesions (Figs. 3 and 4, Table II). The laparoscopic appearance of endometriosis was dependent on the method used. There were significantly more ($p = 0.003$) subtle red lesions (Figs. 3 and 4) occupying a significantly larger surface area ($p < 10^{-6}$) after injection with menstrual (groups 2 and 3) than with luteal endometrium (group 1). Injection of menstrual endometrium caused 96% of the total number of red lesions and 99% of their surface area. The peritoneal surface area covered by typical lesions was significantly greater ($p < 10^{-6}$) with menstrual (groups 2 and 3) than with luteal endometrium (group 1). Menstrual endometrium was responsible for 92% of the total number of typical lesions and for 94% of their surface area.

Follow-up evaluations. In group 1 the number and surface area of endometriotic lesions had not changed significantly 5 months after induction. In group 2 the number and surface of endometriotic implants had decreased in one baboon and increased in the other 12

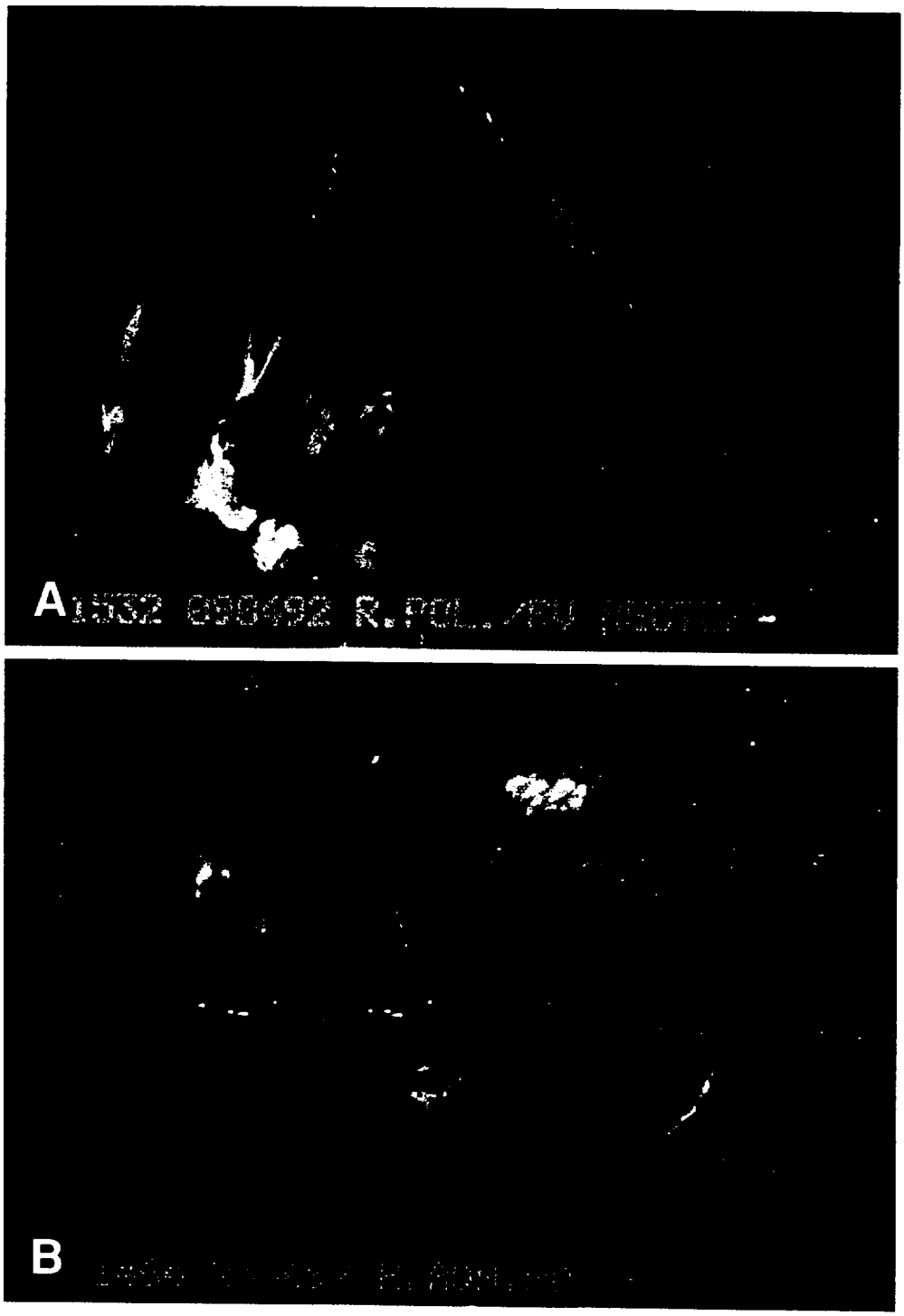

Fig. 3. A, Red polypoid lesion in baboon retroperitoneally injected with menstrual endometrium. **B,** Red hemorrhagic area with pelvic adhesions in baboon intraperitoneally seeded with menstrual endometrium.

months after induction. The number and surface area of typical lesions significantly increased ($p < 0.025$ and $p < 2 \times 10^{-6}$, respectively) in this group. In group 3 the number of lesions increased after 12 months in two baboons but decreased in one animal that had become amenorrheic immediately after induction. In group 3 the surface area occupied by subtle red lesions decreased ($p < 10^{-6}$), whereas the surface area of typical and white lesions increased ($p < 10^{-5}$, Fig. 5). Remodeling and transformation of lesions from subtle to

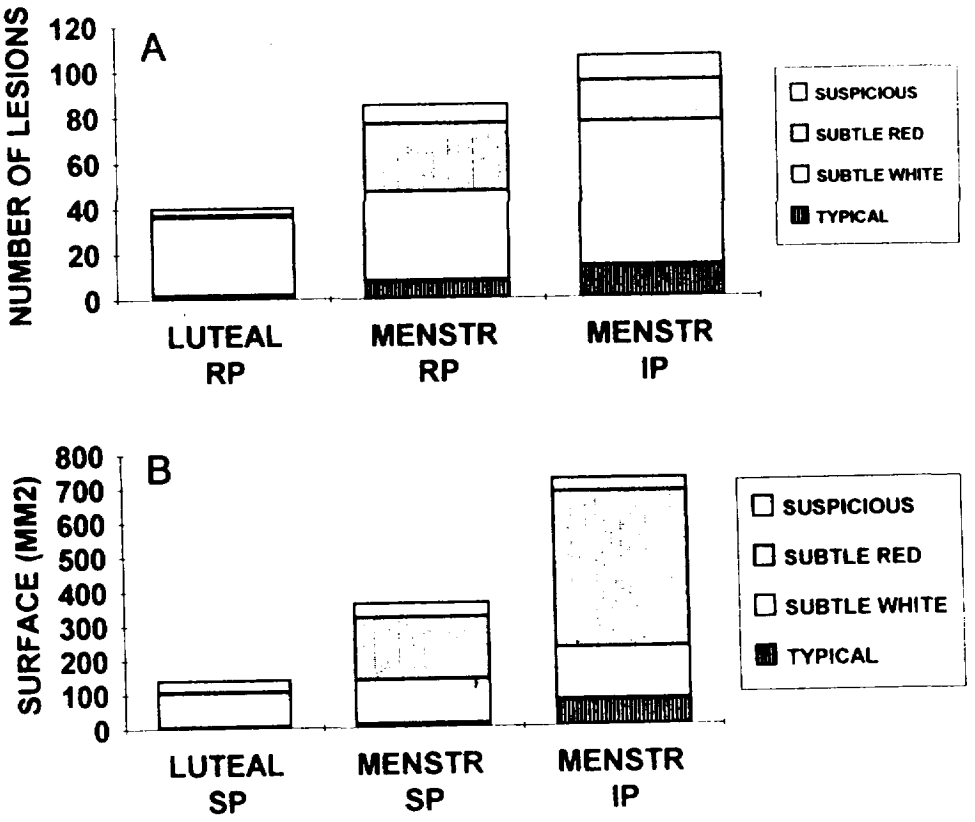

Fig. 4. Total number **(A)** and total surface area (square millimeters) **(B)** of typical, subtle (white, red), and suspicious endometriotic lesions retroperitoneally *(RP)* induced with luteal (n = 6, group 1) or menstrual (n = 7, group 2) endometrium and induced after intraperitoneal *(IP)* seeding with menstrual endometrium (n = 4, group 3). **A,** Higher number of red lesions after intraperitoneal or retroperitoneal injection of menstrual endometrium than after retroperitoneal injection of luteal endometrium (p = 0.003). **B,** Larger surface area of red lesions after intraperitoneal or retroperitoneal injection of menstrual endometrium than after retroperitoneal injection of luteal endometrium ($p < 0.000001$).

typical and from white plaque to white vesicle, red vesicle to white implant, or vice versa was observed.

American Fertility Society classification. Endometriosis could be classified in 10 baboons of groups 1 (n = 2), 2 (n = 6), and 3 (n = 2). Only minimal endometriosis was found in group 1. The animals in group 2 had minimal (n = 1), mild (n = 3), moderate (n = 1), and severe (n = 1) endometriosis. The animals in group 3 had either moderate (n = 1) or severe endometriosis (n = 1). The American Fertility Society score was more influenced by adnexal and cul-de-sac adhesions than by degree of peritoneal involvement. Adnexal adhesions were more related to endometriotic implants, especially red subtle lesions and typical lesions, than to surgical artifacts. Significant adnexal adhesions induced during laparotomy were found in 50% of the AFS classified animals and were absent in those animals that underwent induction during laparoscopy. Adhesions between uterus and omentum or rectum, but no typical or subtle endometriotic lesions, were also found in all four baboons with scarification of the posterior lower right side of the uterus at induction.

Histologic confirmation. Thirty-five of the 58 biopsy specimens (60%) contained histologic evidence of endometriosis. The confirmation rate was higher for typical (71%) and subtle red lesions (92%) than for subtle white lesions (55%). Suspicious lesions (n = 5) were histologically negative for endometriosis.

Comment

This study presents experimental evidence that intrapelvic injection of menstrual endometrium can cause endometriosis and is in agreement with studies reporting an increased prevalence of endometriosis in women with outflow obstruction and therefore increased retrograde menstruation.[20, 21]

In this study it was impossible to standardize the endometrial tissue used for injection with respect to endometrial weight or cell number, because all the endometrium obtained during curettage was used for

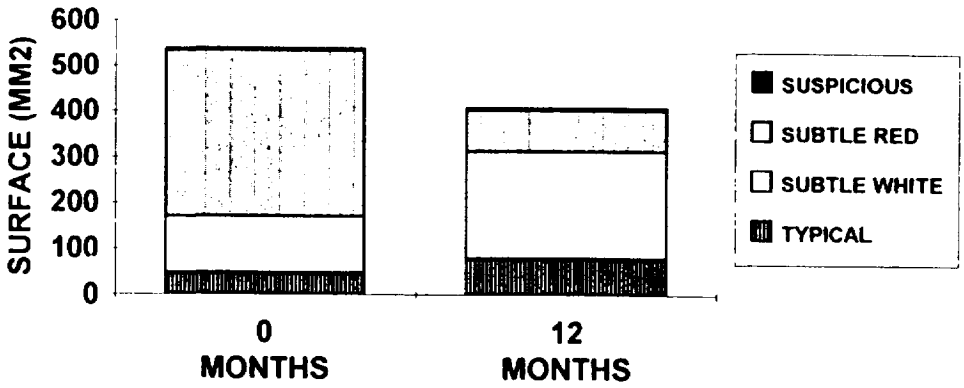

Fig. 5. Spontaneous evolution over 12 months: Significant decrease in total surface area occupied by red lesions ($p < 10^{-6}$) and increase in area covered by typical and white implants ($p < 10^{-5}$) in baboons induced after intraperitoneal seeding with menstrual endometrium ($n = 2$, group 3).

intrapelvic injection. Therefore this study did not allow any conclusions regarding the minimal endometrial weight (or cell number) required for successful induction. However, the significant linear relationship of endometrial weight with number of endometriotic implants suggests that quantity is an important factor determining implantation and may explain the successful reinduction with luteal endometrium. Endometriosis was more efficiently caused by injection with menstrual than with luteal endometrium, as shown by the higher number and larger surface area of endometriotic lesions and the more advanced stages of endometriosis. It is unlikely that this difference can be explained by the endometrial weight used for induction, because it was comparable in the baboons retroperitoneally injected with luteal and menstrual endometrium. It is likely that basal endometrial cells were also obtained during endometrial biopsy, because multiple biopsies were taken in each animal to have a large amount of tissue for induction. However, the proportion of basal cells is a confounding variable for any endometrial biopsy whether taken during the menstrual or the luteal phase. It is known that shedding of the functional layer of the endometrium is most prominent during the first 2 days of menses.[22] Because endometrial biopsy specimens were taken on the first or second day of menses, the obtained tissue used for injection contained the bulk of degenerated functional endometrium. We hypothesize that menstrual endometrium contains unknown factors (cytokines, growth factors, integrins) that enhance its implantation potential in the female pelvis.

Subtle red and typical lesions were caused more frequently by injection of menstrual than of luteal endometrium. Red lesions have been reported to have more vascularization and higher mitotic activity than typical or white lesions, suggesting that they are metabolically active.[23]

Intraperitoneal seeding of menstrual endometrium caused both a higher number of lesions and a larger endometriosis surface area than did retroperitoneal injection. Because the menstrual endometrium was not weighed or manipulated before intraperitoneal seeding, it cannot be excluded that intraperitoneal seeding was more successful because more tissue was injected, because the injected tissue was unminced or more viable. However, even in the retroperitoneally injected groups the majority of endometriosis was found outside the injection sites. This can be explained by intraperitoneal leakage of endometrial fragments after retroperitoneal injection. Other investigators[15] have successfully induced endometriosis by retroperitoneal injection of luteal endometrium. However, these investigators neither described leakage nor reported the use of pelvic mapping to compare the location of the endometriotic lesions with the retroperitoneal injection sites. Therefore it is possible that the observation of endometriosis made in the previous study[15] was the consequence of intraperitoneal leakage rather than retroperitoneal injection. Our data suggest that endometrium injected beneath pelvic peritoneum has a lower implantation potential than endometrium seeded by direct intraperitoneal instillation.

Peritoneal fluid was removed before induction in all animals, suggesting that gonadal steroids, growth factors, and cytokines present in peritoneal fluid[24] may not be essential for implantation and growth of endometrial cells on pelvic surfaces. However, peritoneal fluid can promptly reaccumulate, and removal at surgery does not guarantee that materials in this fluid are not critical to allow implantation and progression of endometriosis. Furthermore, it is important to recognize that the amount of endometrium used for retroperitoneal or intraperitoneal injection in this study was large when compared with the normal volume of retrogradally shed endometrium and could have overwhelmed local immunologic factors within the peritoneal environment that may be important in physiologic conditions.

Neither ovarian implants nor endometriomas were

observed in our study after either intraperitoneal seeding of menstrual endometrium on the ovarian surface or retroperitoneal injection of luteal and menstrual endometrium in the ovarian capsule, even 1 year after induction. This was surprising, because endometriosis was observed at several peritoneal sites. In previous studies on baboons with spontaneous endometriosis ovarian lesions have not been observed.[16, 17] It is possible that ovarian endometriomas take a longer time to develop after induction. Ovarian endometriosis has been reported to occur after induction in only four nonhuman primates. After subcapsular ovarian injection of nonmenstrual endometrium, ovarian endometriosis was obtained in one of two rhesus monkeys after 12 months.[12] In another study[15] ovarian endometriosis was observed 1 month after induction in two of 11 cynomolgus monkeys (18%) without subcapsular or intracapsular injection of luteal endometrium, suggesting that these endometriomas were formed after invagination of endometrial fragments that had intraperitoneally leaked from other retroperitoneal injection sites. Diversion of the cervix in another study resulted in ovarian endometriosis in only one of eight animals after 2 years.[10]

The adhesions found in the current study were primarily related to typical or subtle red lesions. They were found in only 50% of the baboons that had undergone laparotomy and were absent after laparoscopy. However, the small number of animals studied does not exclude the possibility that endometriotic lesions may also cause adnexal adhesions after laparoscopy.

It has been suggested that tissues derived from coelomic epithelium, such as peritoneum and ovarian surface epithelium, may potentially differentiate into mullerian-directed epithelium, mediated by unknown factors contained in retrograde menstruation.[25] Our results suggest that such unknown irritative factors in the menstrual fluid, if present, have less potential to induce metaplasia in peritoneum when they are injected retroperitoneally rather than intraperitoneally. Further studies are needed to determine whether irradiated menstrual endometrium that is incapable of mitosis could implant and "induce" peritoneal metaplastic change.

The spontaneous evolution of endometriosis in our study revealed that endometriosis remained unchanged in all primates undergoing induction with luteal endometrium after 5 months and increased in three of four regularly cycling baboons undergoing induction with menstrual endometrium after 12 months. These findings support our earlier observation that injection of menstrual endometrium is more successful than luteal endometrium in inducing endometriosis. The incidence of red lesions decreased and typical lesions increased during the follow-up period in all animals. This finding supports the hypothesis that red lesions represent early manifestations, whereas typical implants represent late manifestations of pelvic endometriosis[22, 26, 27] and confirms our previous observation that remodeling and transformation of typical and subtle lesions occur.[17]

In conclusion, the results of this study indicate that menstrual endometrium can cause endometriosis more effectively than can luteal endometrium and that intraperitoneal seeding is more successful than subperitoneal injection in causing disease. These findings provide evidence in support of the Sampson hypothesis that viable endometrial tissue regurgitated through the oviducts during menses can implant in the pelvis. The decrease in subtle red lesions and the increase in typical implants during follow-up laparoscopies support the concept that these implants represent early and late manifestations of endometriosis, respectively.

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Estrogenic activity of RU 486 (mifepristone) in rat uterus and cultured uterine myocytes

Khaled I. Dibbs, MD,[a] Yoel Sadovsky, MD,[a] Xue-Jun Li, PhD,[b] Samuel S. Koide, MD, PhD,[b] Stuart Adler, MD, PhD,[a] and Anna-Riitta Fuchs, DSc[c]

St. Louis, Missouri, and New York, New York

OBJECTIVE: Our purpose was to determine whether RU 486 (mifepristone) has direct estrogenic activity in uterine myocytes.

STUDY DESIGN: Ovariectomized adult rats were treated with RU 486, and its effect on uterine oxytocin receptor concentration, as a marker of estrogenic activity, was measured. Results were compared with the induction by RU 486 of an estrogen-responsive reporter gene in a cultured Syrian hamster uterine myocyte cell line.

RESULTS: Baseline oxytocin receptor concentration was 58.8 ± 7.2 fmol/mg protein (mean ± SEM) and increased to 227 ± 49 fmol/mg with 17β-estradiol (2.5 μg/kg) and to 145 ± 18 fmol/mg after RU 486 (5 mg/kg) treatment, an effect that was inhibited by the antiestrogen ICI 182,780 (1.5 mg/kg). In the cultured Syrian hamster uterine myocyte cell line cells RU 486 (10^{-6} mol/L) caused a 2.17 ± 0.17–fold increase in the expression of the reporter gene versus 113.0 ± 7.4–fold with 17β-estradiol (10^{-8} mol/L). The estrogenic activity of RU 486 was dependent on the presence of both estrogen receptor and the promoter's estrogen response element.

CONCLUSION: RU 486 has a weak estrogen-like activity in uterine myocytes. This activity may partly explain the therapeutic effects of RU 486 on this target organ. (Am J Obstet Gynecol 1995;173:134-40.)

Key words: RU 486, estrogenic activity, myocytes, ovariectomized rats, oxytocin receptor

From the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Washington University School of Medicine,[a] the Center for Biomedical Research, the Population Council,[b] and the Department of Obstetrics and Gynecology, Cornell University Medical College.[c]

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Reprint requests: Yoel Sadovsky, MD, Department of Obstetrics and Gynecology, Washington University School of Medicine, 4911 Barnes Hospital Plaza, St. Louis, MO 63110.

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