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Endometriosis, retrograde menstruation and peritoneal inflammation in women and in baboons

Thomas M.D'Hooghe[1] and Sophie Debrock

Leuven University Fertility Center and Department of Obstetrics-Gynecology, University Hospital Gasthuisberg, 3000 Leuven, Belgium

[1]To whom correspondence should be addressed. E-mail: thomas.dhooghe@uz.kuleuven.ac.be

The aim of this review was to assess critically the importance of the frequency, quantity and quality of retrograde menstruation and its relationship to peritoneal inflammation. The basis was the current evidence in women and in baboons supporting the Sampson hypothesis that retrograde menstruation is a key factor in the pathogenesis of endometriosis. It is not proven that retrograde menstruation is a universal phenomenon occurring similarly in women with and without endometriosis. A more thorough understanding of the physiological, cytological and immunological events in peritoneal fluid, peritoneum, endometrium and uterus during menstruation in women with and without endometriosis is critical in order to understand the pathogenesis of this enigmatic disease.

Keywords: baboon/endometriosis/endometrium/peritoneal inflammation/retrograde menstruation

TABLE OF CONTENTS

Introduction

According to the Sampson hypothesis (Sampson, 1927), endometriosis is caused by retrograde menstruation with intraperitoneal spilling of endometrial cells and subsequent adhesion to and implantation on the peritoneal surface. Retrograde menstruation is known to occur only in women and in non-human primates, and in a few exceptional species, such as the elephant shrew and the bat. Menstruation is hypothesized to be the result of millions of years of Müllerian duct evolution (Finn, 1987). This process started with a transition from external fertilization to internal fertilization. Later, increasing embryo demands for nourishment and protection resulted in a highly invasive implantation process in women and in non-human primates. This resulted in a highly differentiated endometrium in anticipation of pregnancy, with endometrial breakdown and menstruation in the absence of pregnancy (Finn, 1987).

Clinical relevance of the baboon model for the pathogenesis of endometriosis

Baboons are well-established models for the study of human reproduction (Stevens, 1997) as they have a reproductive cycle comparable with the menstrual cycle in women, with a cycle interval of 33 days. The perineum can be used to diagnose the cycle phase in female baboons. Perineum turgescence occurs during the follicular phase, while perineum deturgescence is observed during the luteal phase. Ovulation has been estimated to occur about 2 days before the onset of perineal turgescence. Furthermore, the reproductive anatomy of the internal genitalia in female baboons is similar to the situation in women. Female baboons also have about 2 ml of peritoneal fluid in the luteal phase (D'Hooghe *et al*., 1991). In parous animals, the cervix can be cannulated to perform an endometrial biopsy or to obtain pre-implantation embryos by flushing the endometrial cavity (D'Hooghe, 1997) Female baboons are physically strong, which allows for repetitive blood sampling and repetitive surgery, if needed (D'Hooghe *et al*., 1999). Furthermore, baboons are not an endangered species but are abundant in many parts of Africa, and are even considered a threat to agriculture by most African farmers. Hence, baboons can be considered as a natural resource for various African countries. At the Institute of Primate Research (IPR), Nairobi, Kenya, about 500 female baboons are kept in a colony for various studies in reproduction and infectious diseases. Baboons are mostly kept outside in group-cages close to their natural environment. For specific research purposes, they can be housed in single cages (Isahakia and Bambra, 1990).

Spontaneous endometriosis occurs in baboons (Merrill, 1968). In several publications, severe obstructive bowel endometriosis has been described as an important cause of death for female baboons in captivity (Lapin and Yakovleva, 1963; Folse and Stout, 1978; Da Rif *et al*., 1984).

Between 1990 and 1993, the baboon has been developed at IPR Nairobi, Kenya, as a model for the study of endometriosis (for review, see D'Hooghe, 1997). The prevalence of spontaneous endometriosis in the baboon colony at IPR is ~20%, mostly minimal disease, mostly located on the uterosacral ligaments, uterine peritoneum and uterovesical fold (D'Hooghe *et al*., 1991). Ovarian cystic endometriosis was not observed, except in one animal during severe immunosuppression (D'Hooghe *et al*., 1995a). Microscopic endometriosis was very rare. In two prospectively controlled studies (D'Hooghe *et al*., 1994a, 1996a) it was shown that fertility was reduced in baboons with mild, moderate or severe endometriosis, but not in baboons with minimal disease. A comprehensive review of the studies developing the baboon as a model for the study of endometriosis has been published recently (D'Hooghe, 1997).

Does retrograde menstruation occur more frequently in individuals with endometriosis?

The prevalence of retrograde menstruation has been described in 76% (Liu and Hitchcock, 1986), 82% (Blumenkrantz *et al*., 1981) and in 90% (Halme *et al*., 1984) of the investigated women. Although some investigators did not find a difference in the prevalence of retrograde menstruation between women with and without endometriosis (Halme *et al*., 1984), others reported that the prevalence of retrograde menstruation was higher in women with endometriosis (97%) when compared with women without endometriosis (60%) (Liu and Hitchcock, 1986). In baboons, the prevalence of retrograde menstruation has been reported in 62% of the investigated animals, and this prevalence was significantly higher in baboons with spontaneous endometriosis (83%) than in baboons without endometriosis (51%) (D'Hooghe *et al*., 1996b).

The problem with laparoscopic studies evaluating the prevalence of retrograde menstruation, is that they observe the phenomenon only during one cycle. In women, no data are available recording the recurrence of retrograde menstruation in the same woman during consecutive cycles. In baboons, recurrent retrograde menstruation during two subsequent cycles has been observed in all baboons with spontaneous endometriosis, and only in 25% of baboons with a normal pelvis or induced endometriosis (D'Hooghe *et al*., 1996b).

In published reports (Blumenkrantz *et al*., 1981; Halme *et al*., 1984; Liu and Hitchcock, 1986), the diagnosis of retrograde menstruation was made only qualitatively, that is by the observation of red-stained peritoneal fluid, but not quantitatively, namely by measurement of endometrial cell numbers in the peritoneal fluid. Red-stained peritoneal fluid can be observed not only during menstruation, but also during the first 5 days after ovulation (Scheenjes *et al*., 1990) and during other phases of the cycle (Halme *et al*., 1984). It also has been reported that there is only a weak correlation between the colour of peritoneal fluid and the presence of endometrial cells in the peritoneal fluid (Reti *et al*., 1983).

Endometriosis, menstruation and peritoneal inflammation

Endometrial cells in the peritoneal fluid have been observed in 59–79% of women during menstruation or the early follicular phase (Koninckx *et al*., 1980; Bartosik *et al*., 1986; Kruitwagen *et al*., 1991). According to these studies, no difference was found in the presence of endometrial cells in women with and without endometriosis. However, fundamental differences in the quantity or quality of peritoneal fluid endometrial cells between women with and without endometriosis have not been investigated.

Does endometriosis develop after a sufficient number of menstrual cycles with retrograde menstruation?

It is difficult to answer this question in women, since it is impossible to perform serial laparoscopies in women for ethical reasons. Retrograde menstruation has been documented in the baboon model for endometriosis (D'Hooghe *et al*., 1996b), and the effect of cumulative retrograde menstruation on the prevalence and incidence of endometriosis has been evaluated using three different approaches (D'Hooghe *et al*., 1996c,d,e).

In the first study, increased duration of captivity was associated with increased prevalence of spontaneous endometriosis (D'Hooghe *et al*., 1996c). The prevalence of biopsy-proven endometriosis was 10%, and 27% in baboons undergoing a laparoscopy within 1–2 years in captivity, and after more than 2 years in captivity respectively. It was concluded that increased duration of captivity without interrupting pregnancy is associated with a higher number of consecutive menstrual cycles and with increased exposure to retrograde menstruation (D'Hooghe *et al*., 1996c).

In a second study, spontaneous endometriosis was found to be a progressive disease in baboons when followed by laparoscopy every 6 months during 2 years (D'Hooghe *et al*., 1996d). The disease was progressive in nearly all animals. Progression was seen especially in the number and surface area of subtle lesions. Some animals developed mild to moderate endometriosis, based on the extent of peritoneal endometriotic lesions and adhesions related to these lesions (D'Hooghe *et al*., 1996d).

In the third study, 64% of baboons with an initially normal pelvis developed histologically proven minimal endometriosis after 32 months, as documented by laparoscopies every 6 months (D'Hooghe *et al*., 1996e). In this study, a baboon was considered to have endometriosis if a laparoscopic diagnosis could be made, and if the biopsy of at least one peritoneal lesion showed ectopic endometrium at histological examination.

Based on these three studies, it seems that most baboons will develop some degree of endometriosis if they are maintained long enough in captivity with regular menstrual cycles (exposure to retrograde menstruation) and without intervening pregnancy. It can be questioned whether the serial diagnostic laparoscopies performed in the latter two studies might have caused peritoneal trauma, potentially facilitating the development of endometriosis. Indeed, it has been shown *in vitro* (Van der Linden *et al*., 1996) using an amniotic membrane model, that intact intra-epithelial lining can prevent adhesion of endometrial fragments (but not of an endometrial carcinoma cell line). Diagnostic laparoscopy in baboons can indeed cause a transient subclinical pelvic inflammation (D'Hooghe *et al.*, 1999). If a repeat laparoscopy was carried out within 5 days after the initial laparoscopy, the following observations have been reported at the second

laparoscopy: (i) a 10-fold increase in the volume of peritoneal fluid; (ii) a 2-fold increase in peritoneal fluid white blood cell (WBC) concentration; (iii) a 10-fold increase in peritoneal fluid interleukin-6 (IL-6) concentration; and (iv) a 2-fold increase in peritoneal fluid transforming growth factor (TGF)-β concentration (D'Hooghe *et al*., 1999). When the follow-up laparoscopy was carried out 1 month after the initial diagnostic laparoscopy, no evidence was found for any local peritoneal inflammation. These results suggest that a diagnostic laparoscopy can cause a short self-limiting subclinical pelvic inflammation (D'Hooghe *et al*., 1999).

Furthermore, it can be hypothesized that repeat laparoscopies—by causing repetitive trauma—increase the implantation potential of peritoneal fluid endometrial cells on the peritoneum. In our opinion, this seems unlikely for several reasons. First, many reports have shown that successful endometrial autologous transplantation is possible in (nude) mice, rats, rabbits and non-human primates without prior trauma to peritoneum (Dunselman *et al*., 1991). Second, studies in captive baboons (D'Hooghe *et al*., 1996c) have shown that the prevalence of endometriosis increased with the duration of captivity without any intervening laparoscopies. Third, in rhesus monkeys the prevalence or severity of endometriosis was not correlated with the number of previous laparoscopies (Hadfield *et al*., 1997). Fourth, most repeat laparoscopies in the above-mentioned baboon studies were performed in the early luteal phase about 10 days before the next menstruation. It is known that pelvic peritoneum heals rapidly, usually within about 6 days. Therefore, in these studies, peritoneal healing could be hypothesized to have been completed before the next menstrual period and exposure to retrograde menstruation. However, it can not be excluded that other laparoscopy-associated effects unrelated to endometriosis (e.g. CO_2 insufflation, intra-abdominal pressure, general anaesthesia) could independently affect the development of endometriosis.

Why do not all women develop endometriosis?

Quantity of retrogradely flushed endometrial cells

Epidemiological studies have clearly shown that there is an increased risk for endometriosis if there is a short cycle length (Cramer *et al*., 1986; Arumugam and Lim, 1997), or a longer menstrual flow (Cramer *et al*., 1986; Vercellini *et al*., 1997). Furthermore, endometriosis has been observed in 66% (Olive and Henderson, 1987) or 77% (Pinsonneault and Goldstein, 1985) of women with obstructed menstrual outflow. Similarly, three baboons with experimentally obstructed menstrual outflow (supracervical ligation of uterus during laparotomy) developed spontaneous endometriosis within 3 months (D'Hooghe *et al*., 1994b). Experimental in-vivo data in baboons have shown that there is a positive correlation between the weight of endometrial tissue used for intrapelvic seeding and the extent of peritoneal endometriosis in baboons (D'Hooghe *et al*., 1995b). Furthermore, experimental in-vitro data suggest that endometrial fragments with intact microstructure express several adhesion molecules and adhere more easily to amniotic epithelium (Van der Linden *et al*., 1996) and to extracellular matrix (Wild *et al*., 1994) than isolated or single endometrial cells. Based on these epidemiological and experimental data, it can be hypothesized that the quantity of retrogradely flushed endometrial cells may be important in the development of endometriosis and in the spontaneous evolution of the disease.

Retrograde menstruation and peritoneal inflammation

In-vivo evidence exists that endometrium obtained during the menstrual phase can cause more extensive and active peritoneal endometriosis than endometrium obtained during the luteal phase (D'Hooghe *et al*., 1995b). So far, it is not well known to what extent menstrual endometrium is different in women or baboons with and without endometriosis. In baboons, it has been reported recently that retrograde menstruation increases inflammatory parameters in peritoneal fluid (D'Hooghe *et al*., 2001). During menstruation, the peritoneal fluid WBC concentration was increased significantly, as was the proportion of peritoneal fluid cells staining positive for tumour necrosis factor (TNF)-α, TGF-β-1, and intracellular adhesion molecule (ICAM)-1, and the peritoneal fluid concentration of TGF-β-1 and IL-6, when compared with non-menstrual phases of the cycle. Similarly, after intrapelvic injection of endometrium, the peritoneal fluid WBC concentration, and the proportion of peritoneal fluid cells positive for TNF-α, TGF-β-1, and leukocyte markers CD3 and HLA-DR significantly increased. These data suggest that subclinical peritoneal inflammation occurs in baboons during menstruation and after intrapelvic injection of endometrium (D'Hooghe *et al*., 2001). In women, a preliminary report (Debrock *et al*., 2000) described that the peritoneal fluid concentration of leukocytes and erythrocytes was increased during menstruation in women with endometriosis, but not related to the degree of endometriosis

It can be hypothesized that various growth factors, cytokines, adhesion molecules and matrix metalloproteinases (MMPs) can be expressed differently in the menstrual endometrium of women with and without endometriosis, though further studies are necessary to investigate this hypothesis.

Immunological hypothesis

It has been hypothesized that endometriosis can be caused by decreased clearance of peritoneal fluid endometrial cells due to reduced natural killer (NK) activity, and/or decreased macrophage activity (Oosterlynck *et al*., 1991). However, endometriosis can also be considered as a condition of immunological tolerance versus ectopic endometrium which essentially is self tissue (D'Hooghe and Hill, 1996). Indeed, it can be questioned why viable endometrial cells in the peritoneal fluid would be a target for NK cells or macrophages. Autotransplantation of blood vessels, muscles, skin grafts and other tissues is known to be extremely successful in humans. Furthermore, there is no in-vitro evidence that peritoneal fluid macrophages actually attack and perform phagocytosis of viable peritoneal fluid endometrial cells. It is also controversial whether women have decreased NK activity in peripheral blood and decreased cytotoxic activity against autologous endometrial cells, as reviewed recently (D'Hooghe *et al*., 1997). Finally, high-dose immunosuppression can slightly increase the progression of spontaneous endometriosis in baboons (D'Hooghe *et al*., 1995a), though there is no clinical evidence that the prevalence of endometriosis is increased in immunosuppressed patients. The fact that women with kidney transplants under chronic immunosuppression are not known to

have increased infertility problems (Armenti *et al.*, 1994) can be considered as indirect evidence that these patients do not develop extensive endometriosis

Peritoneal fluid factors potentially affecting attachment of endometrial cells onto the peritoneum

In vitro, it has been reported that TNF-α can promote the adhesion of human endometrial stroma cells to peritoneum mesothelial cells (Zhang *et al.*, 1993). The importance of other adhesion molecules in the adhesion process between endometrium and peritoneum has also been extensively investigated (Dunselman *et al*., 2001).

The role of MMPs and their inhibitors still needs further elucidation. In cynomolgus monkeys (Sillem *et al*., 1996), it has been shown that intraperitoneal seeding of endometrial fragments pretreated with proteinase inhibitor resulted in decreased ectopic growth when compared with intraperitoneal seeding of untreated intact endometrial fragments. In nude mice (Bruner *et al*., 1997), estradiol treatment of human endometrial tissue in culture maintained secretion of MMPs and promoted establishment of ectopic lesions when injected into recipient nude mice. This establishment of ectopic lesions was inhibited after progesterone suppression of MMP secretion from human endometrial tissue or after blocking MMP enzyme activity with natural inhibitors. In women, it has been observed that early endometriosis invades the extracellular matrix (Spuijbroeck *et al.*, 1992), that MMPs are highly expressed in menstrual endometrium (Rodgers *et al.*, 1994), and that MMP-1 is highly expressed in red-active peritoneal and ovarian endometriosis (Kokorine *et al.*, 1997). These data from studies in women and in animal models all suggest that proteinase/metalloproteinase activity is important in the early establishment of endometriotic lesions.

Conclusions

From retrograde menstruation to endometriosis: an hypothesis

Many data from studies in women and in baboons reviewed in this article support the hypothesis that the process from retrograde menstruation to the establishment of endometriosis is determined by the quantity of retrograde menstruation, by the subclinical peritoneal fluid inflammation occurring during retrograde menstruation, and by local peritoneal factors such as TNF-α, MMPs, growth factors and (potentially) other substances that promote the adhesion of endometrium on the peritoneum.

Future studies should quantify the amount of endometrial cells in the peritoneal fluid in women with and without endometriosis during menstruation in relation to uterine contractility and to menstrual characteristics, in order to determine the real role of retrograde menstruation in the pathogenesis of endometriosis. The adhesion potential of menstrual endometrial cells to pelvic peritoneum needs to be quantified *in vitro* in women with and without endometriosis, which may lead to the development of a non-invasive test in the diagnosis of endometriosis. Finally, the attachment of menstrual endometrial cells to pelvic peritoneum needs to be assessed, stimulated and blocked in the baboon, which provides an excellent in-vivo culture model to test new preventive and therapeutic medical agents that might inhibit the development of endometriosis

References

Armenti, V.T., Ahlswede, K.M., Ahlswede, B.A., Jarrell, B.E., Moritz, M.J. and Burke J.F. (1994) National Transplantation Pregnancy Registry in cyclosporine-treated female kidney transplants. *Transplantation*, **57**, 502–506.

Arumugam, K. and Lim, J.M. (1997) Menstrual characteristics associated with endometriosis. *Br. J. Obstet. Gynaecol*., **104**, 948–950.

Bartosik, D., Jacobs, S.L. and Kelly, L.J. (1986) Endometrial tissue in peritoneal fluid. *Fertil. Steril.*, **46**, 796–800.

Blumenkrantz, M.J., Gallagher, N., Bashore, R.A. and Tenckhoff, H. (1981) Retrograde menstruation in women undergoing chronic peritoneal dialysis. *Obstet. Gynecol*., **57**, 667–670.

Bruner, K.L., Matrisian, L.M., Rodgers, W.H., Gorstein, F. and Osteen, K.G. (1997) Suppression of matrix metalloproteinases inhibits establishment of ectopic lesions by human endometrium in nude mice. *J. Clin. Invest*., **99**, 2851–2857.

Cramer, D.W., Wilson, E., Stillman, R.J., Berger, M.J., Belisle, S., Schiff, I., Albrecht, B., Gibson, M. Stadel, B.V. and Schoembaum, S.C. (1986) The relation of endometriosis to menstrual characteristics, smoking and exercise. *JAMA*, **355**, 1904–1908.

Da Rif, C.A., Parker, R.F. and Schoeb, T.R. (1984) Endometriosis with bacterial peritonitis in a baboon. *Lab. Anim. Sci*., **34**, 491–493.

Debrock, S., Drijkoningen, R., Goossens, W., Meuleman, C., Hill, J.A. and D'Hooghe, T.M. (2000) Quantity and quality of retrograde menstruation: red blood cells, inflammation and peritoneal cells. Abstract presented at the Annual Meeting of the American Society for Reproductive Medicine, Toronto, Canada, October 24th, 2000. *Fertil. Steril.*, **74**, 3S.

D'Hooghe, T.M. (1997) Clinical relevance of the baboon as a model for the study of endometriosis. *Fertil. Steril.*, **68**, 613–625.

D'Hooghe, T.M. and Hill, J.A. (1996) Immunobiology of endometriosis. In: Bronson, R.A., Alexander, N.J., Anderson, D.J., Branch, D.W. and Kutteh, W.H. (eds), *Immunology of Reproduction*. Blackwell Science, Cambridge, MA, USA, pp. 322–358.

D'Hooghe, T.M., Bambra, C.S., Cornillie, F.J., Isahakia, M. and Koninckx, P.R. (1991) Prevalence and laparoscopic appearance of spontaneous endometriosis in the baboon (*Papio anubis-Papio cynocephalus*). *Biol. Reprod*., **45**, 411–416.

D'Hooghe, T.M., Bambra, C.S. and Koninckx, P.R. (1994a) Cycle fecundity in baboons of proven fertility with minimal endometriosis. *Gynecol. Obstet. Invest*., **37**, 63–65.

D'Hooghe, T.M., Bambra, C.S., Suleman, M.A., Dunselman, G.A., Evers, J.H.L. and Koninckx, P.R. (1994b) Development of a model of retrograde menstruation in baboons (*Papio anubis*). *Fertil. Steril.*, **62**, 635–638.

D'Hooghe, T.M., Bambra, C.S., Raeymaekers, B.M., Hill, J.A. and Koninckx, P.R. (1995a) Immunosuppression can increase progression of spontaneous endometriosis in baboons. *Fertil. Steril.*, **64**, 172–178.

D'Hooghe, T.M., Bambra, C.S., Raeymaekers, B.M., De Jonge, I., Lauweryns, J.M. and Koninckx, P.R. (1995b) Intrapelvic injection of menstrual endometrium causes endometriosis in baboons (*Papio cynocephalus*, *Papio anubis*). *Am. J. Obstet. Gynecol*., **173**, 125–134.

D'Hooghe, T.M., Bambra, C.S., Raeymaekers, B.M., Riday, A.M., Suleman, M.A. and Koninckx, P.R. (1996a) The cycle pregnancy rate is normal in baboons with stage I endometriosis but decreased in primates with stage II and stage III-IV disease. *Fertil. Steril.*, **66**, 809–813.

D'Hooghe, T.M., Bambra, C.S., Raeymaekers, B.M. and Koninckx, P.R. (1996b) Increased prevalence and recurrence of retrograde menstruation in baboons with spontaneous endometriosis. *Hum. Reprod*., **11**, 2022–2025.

D'Hooghe, T.M., Bambra, C.S., De Jonge, I., Lauweryns, J.M. and Koninckx, P.R. (1996c) The prevalence of spontaneous endometriosis in the baboon increases with the time spent in captivity. *Acta Obstet. Gynecol. Scand*., **75**, 98–101.

D'Hooghe, T.M., Bambra, C.S., Raeymaekers, B.M. and Koninckx, P.R. (1996d) Serial laparoscopies over 30 months show that endometriosis is a progressive disease in captive baboons (*Papio anubis*, *Papio cynocephalus*). *Fertil. Steril.*, **65**, 645–649.

D'Hooghe, T.M., Bambra, C.S., Raeymaekers, B.M. and Koninckx, P.R. (1996e) The cumulative incidence rate of endometriosis in baboons (*Papio anubis*, *Papio cynocephalus*) with an initially normal pelvis is 70% after 30 months. *Obstet. Gynecol*., **88**, 462–466.

D'Hooghe, T.M., Bambra, C.S. and Hill, J.A. (1997) A very sticky riddle. *Fertil. Steril.*, **67**, 182–183.

D'Hooghe, T.M., Bambra, C.S., Raeymaekers, B.M. and Hill, J.A. (1999)

Pelvic inflammation induced by diagnostic laparoscopy in baboons. *Fertil. Steril.*, **72**, 1134–1141.

D'Hooghe, T.M., Bambra, C.S., Ling Xiao, L. and Hill, J.A. (2001) The effect of menstruation and intrapelvic injection of endometrium on peritoneal fluid parameters in the baboon. *Am. J. Obstet. Gynecol.*, **184**, 917–925.

Dunselman, G.A., Dumoulin, J.C.M., Land, J.A. and Evers, J.L. (1991) Lack of effect of peritoneal endometriosis on fertility in the rabbit model. *Fertil. Steril.*, **56**, 340–342.

Dunselman, G.A.J., Groothuis, P.G., de Goeij, A.F.P.M. and Evers, J.L.H. (2001) Debate: the mesothelium, Teflon or Velcro? *Hum. Reprod.*, **16**, 605–607.

Finn, C.A. (1987) Why do women and other primates menstruate? *Perspect. Biol. Med.*, **30**, 566–574.

Folse, D.S. and Stout, L.C. (1978) Endometriosis in a baboon. *Lab. Anim. Sci.*, **28**, 217–219.

Hadfield, R.M., Yudkin, P.L., Coe, C.L., Scheffler, J., Uno, H., Barlow, D.H., Kemnitz, J.W. and Kennedy, S.H. (1997) Risk factors for endometriosis in the rhesus monkey (*Macaca mulatta*): a case-control study. *Hum. Reprod. Update*, **3**, 109–115.

Halme, J., Becker, S., Hammond, M.G., Raj, S.G. and Talbert, L.M. (1984) Retrograde menstruation in healthy women and in patients with endometriosis. *Obstet. Gynecol.*, **64**, 151–154.

Isahakia, M.A. and Bambra, C.S. (eds) (1990) Primate models for research in reproduction. In: *Gamete Interaction: Prospects for Immunocontraception*. Wiley-Liss, Inc., New York, NY, USA, pp. 487–500.

Kokorine, I., Nisolle, M., Donnez, J., Eeckhout, Y., Courtoy, P.J. and Marbaix, E. (1997) Expression of interstitial collagenase (MMP-1) is related to the activity of human endometriotic lesions. *Fertil. Steril.*, **68**, 246–251.

Koninckx, P.R., Ide, P., Vandenbroucke, W. and Brosens, I.A. (1980) New aspects of the pathophysiology of endometriosis and associated fertility. *J. Reprod. Med.*, **24**, 257–260.

Kruitwagen, R.F.P.M., Poels, L.G., Willemsen, W.N.P., de Ronde, I.J.Y., Jap, P.H.K. and Rolland, R. (1991) Endometrial epithelial cells in peritoneal fluid during the early follicular phase. *Fertil. Steril.*, **55**, 297–303.

Lapin, B.H. and Yakovleva, L.A. (1963) Endometriosis. In: Thomas, C.C. (ed.), *Comparative Pathology in Monkeys*. Springfield, pp. 202–206.

Liu, D.T.Y. and Hitchcock, A. (1986) Endometriosis: its association with retrograde menstruation, dysmenorrhoea and tubal pathology. *Br. J. Obstet. Gynaecol.*, **93**, 859–862.

Merrill, J.A. (1968) Spontaneous endometriosis in the Kenya baboon. *Am. J. Obstet. Gynecol.*, **101**, 569–570.

Olive, D.L. and Henderson, D.Y. (1987) Endometriosis and Mullerian anomalies. *Obstet. Gynecol.*, **69**, 412–415.

Oosterlynck, D., Cornillie, F.J., Waer, M., Vandeputte, M. and Koninckx, P.R. (1991) Women with endometriosis show a defect in natural killer cell activity resulting in a decreased cytotoxicity to autologous endometrium. *Fertil. Steril.*, **56**, 45–51.

Pinsonneault, O. and Goldstein, D.P. (1985) Obstructing malformations of the uterus and vagina. *Fertil. Steril.*, **44**, 241–247.

Reti, L.L., Byrne, G.D. and Davoren, R.A.M. (1983) The acute clinical features of retrograde menstruation. *Aust. N. Z. J. Obstet. Gynaecol.*, **23**, 51–52.

Rodgers, W.H., Matrisian, L.M., Giudice, L.C., Dsupin, B., Cannon, P. and Svitek, C. (1994) Patterns of matrix metalloproteinase expression in cycling endometrium imply different functions and regulation by steroid hormones. *J. Clin. Invest.*, **94**, 946–953.

Sampson, J.A. (1927) Peritoneal endometriosis due to menstrual dissemination of endometrial tissue into the pelvic cavity. *Am. J. Obstet. Gynecol.*, **14**, 422–469.

Scheenjes, E., te Velde, E.R. and Kremer, J. (1990) Inspection of the ovaries and steroids in serum and peritoneal fluid at various time intervals after ovulation in fertile women: implications for the luteinized unruptured follicle syndrome. *Fertil. Steril.*, **54**, 38–41.

Sillem, M., Hahn, U., Coddington, C.C., Gordon, K., Runnebaum, B. and Hodgen, G.D. (1996) Ectopic growth of endometrium depends on its structural integrity and proteolytic activity in the cynomolgus monkey (*Macaca fascicularis*) model of endometriosis. *Fertil. Steril.*, **66**, 468–473.

Spuijbroek, M.D.E.H., Dunselman, G.A.J., Menheere, P.P.C.A. and Evers, J.L.H. (1992) Early endometriosis invades the extracellular matrix. *Fertil. Steril.*, **58**, 929–933.

Stevens, V.C. (1997) Some reproductive studies in the baboon. *Hum. Reprod. Update*, **3**, 533–540.

Van der Linden, P.J.Q., de Goeij, A.FP.M., Dunselman, G.A.J., Erkens, H.W.H. and Evers, J.L.H. (1996) Endometrial adhesion in an in vitro model using intact amniotic membranes. *Fertil. Steril.*, **65**, 76–80.

Vercellini, P., De Giorgi, O., Aimi, G., Panazza, S., Uglietti, A. and Crosignani, P.G. (1997) Menstrual characteristics in women with and without endometriosis. *Obstet. Gynecol.*, **90**, 264–268.

Wild, R.A., Zhang, R.J. and Medders, D. (1994) Whole endometrial fragments form characteristics of *in vivo* endometriosis in a mesothelial co-culture system. *J. Soc. Gynecol. Invest.*, **1**, 65–68.

Zhang, R., Wild, R.A. and Ojago, M. (1993) Effect of tumor necrosis factor-alpha on adhesion of human endometrial stromal cells to peritoneal mesothelial cells: an *in vitro* system. *Fertil. Steril.*, **59**, 1196–1201.

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