Baboon model for the study of endometriosis

Cleophas M Kyama[1,2], Atilla Mihalyi[2], Daniel Chai[2], Peter Simsa[2], Jason M Mwenda[2] & Thomas M D'Hooghe[1,2†]

†Author for correspondence
[1]Leuven University Fertility Centre, Department of Obstetrics & Gynaecology, University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium
Tel.: +32 1634 3624; Fax: +32 1634 3607; E-mail: thomas.dhooghe@uz.kuleuven.ac.be
[2]Institute of Primate Research, Division of Reproductive Biology, Karen, Nairobi, Kenya

Endometriosis is a benign, estrogen-dependent disease and is now recognized as an enigmatic disease owing to its various clinical manifestations and locations. The lack of a reliable and specific method for the early detection of endometriosis often results in delayed diagnosis. So far, research has born inadequate findings regarding understanding the basic etiology or pathophysiology of endometriosis. Animal models that accurately represent the cellular and molecular changes associated with the initiation and progression of human endometriosis have significant potential to facilitate the development of better methods for the early detection and treatment of endometriosis. A number of animal model systems have been developed for the study of this disease. These models replicate many of the known salient features of human endometriosis. This review provides an insight into the use of the baboon model for studies focused on understanding human endometriosis.

Keywords: animal models, baboon, cynomolgus, endometriosis, nonhuman primate models, nonprimate models, rhesus

Endometriosis is an important gynecological disease classically defined as the presence of ectopic endometrial-like stroma and glands. The disease is associated with pelvic pain and infertility [1,2]. It is estimated that endometriosis affects at least 10% of women during childbearing age. According to the retrograde menstruation theory [3], the reflux of endometrial cells through the fallopian tubes leads to development of endometriosis. Nonetheless, it remains unresolved why only a limited number of women develop the disease even though retrograde menstruation seems to be a universal phenomenon among women of reproductive age [4].

Women with endometriosis aberrantly express certain cytokines and growth factors, as has been reported previously [5]. These cytokines are said to modulate and spur production of other factors such as chemokines, and hence abrogate inflammation [5]. However, most cytokines/growth factors have multiple actions, and new genomic and proteomic approaches are needed to better understand the complex multifactorial etiology of endometriosis [6–8].

Endometriosis cannot always be treated successfully by current medical and surgical interventions, and attempts for early diagnosis have been overwhelmed by the lack of suitable methods to study and manage the disease. Currently, significant efforts have been made towards developing new intervention strategies as alternative treatment options for the condition [9–14]. This review provides an insight on the use of the baboon model for studies focused on understanding etiology, pathophysiology and preclinical testing of new target molecules in the management of human endometriosis.

Animal models: need for new approaches in endometriosis research

Even though endometriosis has been known for over a century, the current understanding on mechanisms that cause the disease remains obscure. Endometriosis is now recognized as an enigmatic disease owing to its various clinical manifestations and locations [15]. However, several decades devoted to biomedical research have yielded inadequate findings regarding understanding the basic etiology or pathophysiology of the disease. Still missing are the key indicators of the pathological aberrations of endometriosis that could provide insight into the early natural history of the disease process or offer relevant targets that may have therapeutic ramifications. Molecular epidemiology research techniques including not only genomics and proteomics, but also epigenetics (methylation of DNA, which influences transcription patterns), transcriptomics (study of RNA showing gene expression) and, in particular, metabonomics (study of small molecules) are all needed to better understand the multifactorial etiopathogenesis of endometriosis.

Factors that have hindered progress in the management of endometriosis

The following are factors that have obstructed progress in the management of endometriosis:

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- Knowledge of the molecular pathophysiology and cellular biology is still limited;
- The natural history and spontaneous evolution are not well understood [16];
- There is a lack of noninvasive methods to assess the true prevalence and incidence of this disease in the general population;
- Demands of specialized skills for adequate laparoscopic assessment of the pelvis, for recognition of the various types and appearances of the disease [17], and for surgical treatment;
- Treatment options for disease eradication are inadequate [18,19];
- Delayed diagnosis of the disease [20];
- Difficulties in performing randomized, multicenter-oriented research with adequately defined groups of patients and controls, including standardized surgical and medical approaches [21,22];
- Spontaneous endometriosis occurs only in human and nonhuman primates [23,24].

Owing to ethical reasons, properly controlled invasive studies cannot be carried out in humans.

For all these reasons, an appropriate animal model is of paramount importance in understanding the pathophysiology of endometriosis. A number of animal models have been utilized to investigate the pathophysiological mechanisms involved in endometriosis and to test new drugs as treatment options for endometriosis [9,12,25]. Although animal models are useful, some of them have inherent differences that lessen their applicability to human endometriosis studies. A suitable animal model is essential in endometriosis research and this model should ideally have a disease genotype and phenotype mimicking the pathological features observed in humans. This model should also provide a superb *in vivo* system to investigate the alterations in protein and gene expression that act as useful indicators of pathological abnormalities prior to or during disease development.

Nonprimate models

Nonprimate models such as rodent models have been used as experimental animals for the study of endometriosis. In rats, rabbits or hamsters, the disease is induced through autologous transplantation of the endometrium or the uterine horn [26–29], which can be stitched surgically onto the peritoneum. However, it appears that the endometriotic lesions consisting of clear vesicles in the rat, or the vascularized hemorrhagic solid masses observed in the rabbit, are quite different from the variety of pigmented and nonpigmented lesions exhibited in human endometriosis [17,30].

Rodent models offer some advantages due to their low cost and ease of manipulation. However, several fundamental drawbacks diminish their applicability to human disease, such as the lack of a menstrual cycle, lack of spontaneous endometriosis and the wide phylogenetic gap with humans.

The use of immunocompromized animals, such as athymic (nude) mouse and severe combined immunodeficient mouse as models for endometriosis [31,32] has been developed, since they do not reject human endometrial tissue xenografts [33], which can be introduced either subcutaneously or into the peritoneal cavity.

Recently, an improved mouse model of endometriosis was developed in nude mice, using green fluorescence protein as a reporter gene to allow optical *in vivo* imaging of endometrial tissue implantation [34–36]. In this new model, genetically modified and fluorescent endometrial tissue is transplanted into the peritoneal site, where it generates endometriotic-like lesions expressing green fluorescence protein [36,37]. The main advantage includes noninvasive monitoring via the skin for at least 3 weeks, allowing easier localization of the lesions when the animals are dissected [36,37]. Although powerful in terms of their ability to allow noninvasive assessment of disease development in a controlled *in vivo* environment, these models are prone to the perils of biological reductionism. It is questionable whether the data derived from such studies will be applicable to women in view of the wide phylogenetic differences between humans and rodents.

Relevance of nonhuman primate models in endometriosis

Endometriosis is difficult to eradicate because the disease etiology and pathogenesis are poorly understood. Endometriosis occurs exclusively in menstruating species, including nonhuman primates and humans. Some risk factors identified in women with endometriosis (e.g., long duration of uninterrupted menstruation) have also been identified in nonhuman primates with spontaneous endometriosis, including rhesus macaques [38] and baboons [39,40].

So far, the use of nonhuman primates in endometriosis research has been limited, mainly due to considerable experimentation and maintenance costs in captivity. However, nonhuman primates provide key advantages that make them relevant animal models in endometriosis research:

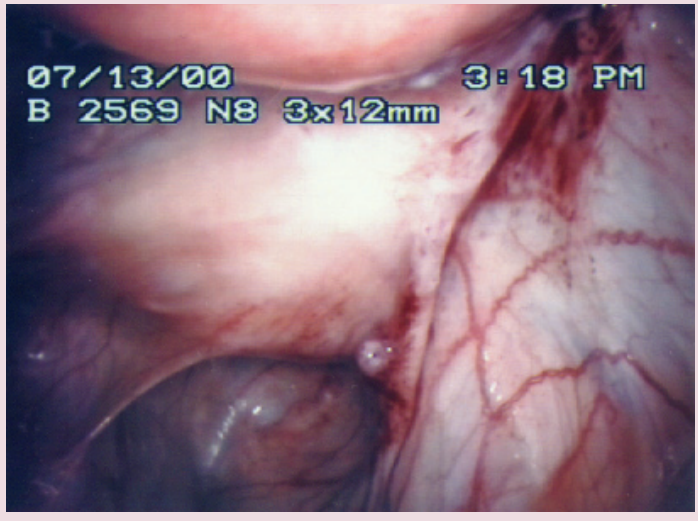
- Their close phylogenetic relatedness to humans [41];
- Their reproductive anatomical and physiological similarities to humans [42];
- Many nonhuman primate species develop spontaneous endometriosis that is macroscopically and histologically identical to the human disease [23,38,44];
- Induced endometriosis in nonhuman primates is macroscopically and microscopically similar to spontaneous endometriosis in women (**Figure 1**) [28,45,46];
- Owing to closely shared similarities in gene and protein expression between humans and baboons, human antibodies or PCR primers can be used in baboons to better understand the establishment and progression of endometriosis [24,47,48];
- Nonhuman primates are large animal models, while in capacity can allow repeated surgical study procedures in a controlled experimental environment [49].

Endometriosis studies on rhesus & cynomolgus monkeys

Most of the early endometriosis research has been done in rhesus and cynomolgus monkeys [50,51]; only limited studies are available in the de Brazza monkey [52], an endangered species. The prevalence of spontaneous endometriosis among rhesus macaques varies between 29–31% according to necropsy studies [38,53] and 43% according to laparoscopy assessment in a breeding colony [54].

Rhesus monkeys with spontaneous endometriosis have been used in the investigation of the genetic epidemiology of the disease [55]. A dose–effect relationship has been demonstrated between dioxin exposure and severity of endometriosis in rhesus monkeys [56]. Spontaneous endometriosis in rhesus monkeys has also been associated with irradiation, but only after at least 6 years of exposure [57]. Natural progression of experimental endometriosis in cynomolgus monkeys has been reported, but complete regression of macroscopic disease after pregnancy occurred in monkeys with minimal and mild disease [58], suggesting that pregnancy exerts a beneficial effect on endometriosis.

Figure 1. White vesicle as an illustration of peritoneal endometriosis in baboons.



Baboon model to investigate human endometriosis

Prevalence of endometriosis in baboons

Spontaneous minimal endometriosis occurs in baboons of proven fertility [59] with a prevalence of 25%, and with laparoscopic appearances, pelvic localization [44] and microscopic aspects [60] similar to the human disease. The prevalence of endometriosis in baboons without previous hysterotomy (8%) was comparable with the reported 7.5% prevalence of endometriosis in asymptomatic women undergoing sterilization [61]. An increased prevalence of endometriosis (27%) has been observed in baboons that had been maintained in captivity for more than 2 years [46].

Extensive research carried out at the Institute of Primate Research (IPR), Nairobi, Kenya has demonstrated that the baboon is an excellent model for the study of endometriosis [41,62–64].

Advantages of the baboon model in endometriosis research

There are several advantages to the use of the baboon model in endometriosis research:

- The baboon is an established model for studies in cardiovascular and endoscopic surgery, endocrinology, teratology and toxicology [66];
- Baboons are not an endangered species but are abundant in many African countries, where they represent an important threat to agriculture [67];
- Noninvasive follow-up of menstrual cycle. Baboons have a menstrual cycle of 33 days, which is comparable with humans [41]. Perineal

skin inflation and deflation, in the baboon, with relative precision, correspond to the follicular and luteal phases, respectively, enabling noninvasive follow-up of menstruation;

- Baboons have 42 chromosomes, a very close phylogenetic homology to the 46 chromosomes in humans [41,65];
- Uninterrupted continuous breeding. The baboon menstrual cycle continues throughout, even in captivity [67], as opposed to the seasonal breeding observed in rhesus monkeys during captivity [55];
- The large size of baboons (weight of adult female: 12–15 kg) allows repetitive blood sampling and performance of even complicated surgical procedures [68];
- The sufficiently large cervix of the baboons allows transvaginal accessibility of the baboon uterine cavity with the possibility to take biopsies from endometrium, to perform nonsurgical uterine flushing to recover preimplantation embryos without hysterotomy [69], and to carry out embryo transfer and hysteroscopy procedures;
- Baboons experience a high prevalence of spontaneous endometriosis [44];
- Endometriotic lesions in baboons undergo active remodeling, with some disappearing, while other new lesions are formed [70]. Some lesions develop more aggressively and progress to the typical or colored lesions found in women [17]. Laparoscopic appearances (**Figure 1**), pathological aspects and pelvic localization of the implants are similar to those of the human disease [44];
- Ovarian endometriotic cysts have been reported in baboons maintained in captivity [40].

Disadvantages of the baboon model in endometriosis research

Among the potential drawbacks of using baboon in endometriosis research are the difficulty of dealing with conscious baboons, and the maintenance and experimentation costs, since larger animals require larger cages and larger doses of medications. Therefore, it is important to do reproductive research in baboons as much as possible in or close to their natural environment in Africa. This is possible at the IPR, where the baboon model for endometriosis has been developed over the last 17 years.

The natural history & spontaneous evolution of endometriosis in baboons

The natural history of endometriosis is poorly understood. The disease seems to be dynamic, progressing in some women [71], while remaining static in some, and resolving in others [16]. In baboons, spontaneous endometriosis is a progressive disease [72]. Serial laparoscopies were performed in 13 baboons with spontaneous endometriosis within a period of up to and including 30 months. Periods of development and regression were observed, resulting in overall disease progression in all baboons [73], based on a significant increase in American Fertility Society (AFS) score and in both number and surface area of lesions [70,73]. Remodeling, defined by transition between typical, subtle and suspicious implants, was observed in 23% of lesions [73]. Endometriosis did not undergo regression during the first and second trimester of pregnancy [59].

Subsequently, the incidence of spontaneous endometriosis in baboons with an initially normal pelvis was determined over a period of 32 months [74]. The cumulative incidence of minimal endometriosis (proven by histology) was 64% up to 32 months of follow-up. The eight baboons that developed proven endometriosis were followed during a longer period of time and had undergone more serial laparoscopies than the animals that did not get the disease [74]. Remodeling of endometriotic implants was also observed in these baboons [70,74]. Collectively, these baboon data suggest that endometriosis is a dynamic and moderately progressive disease, with periods of development and regression and with active remodeling between different types of lesions [41]. This concept of remodeling was shown for the first time in baboons [70], and has afterwards been confirmed in women with endometriosis [75]. It cannot be excluded that subclinical laparoscopy-associated inflammation was a cofactor in the development of endometriosis [76]. Indeed, a transient increase in subclinical pelvic inflammation, characterized by a tenfold increase in peritoneal fluid (PF) volume, a threefold increase in white blood cell concentration, a tenfold increase in PF IL-6 concentration, and a twofold increase in PF TGFβ-1 concentration, was observed 3–4 days, but not 30 days after a diagnostic laparoscopy [76]. However, rhesus monkeys that had been exposed to at least one laparoscopy showed no increased risk for endometriosis compared with rhesus monkeys without any previous laparoscopies [53], questioning the importance of laparoscopies in the spontaneous evolution of endometriosis in primates.

Endometriosis & infertility

A causal relationship between endometriosis and infertility has not been definitively established. Cytokines, which impair fertilization, are present in the peritoneal secretions of most patients with endometriosis. TNF-α is cytotoxic to gametes [77] and sperm motility is inhibited in proportion to TNF-α concentration [78]. Peritoneal macrophages can phagocytose sperm *in vitro*, and these macrophages are more activated in women with endometriosis than in those without the disease [79]. Sperm function can be impaired after exposure to PF of patients with endometriosis [80].

In women with moderate-to-severe endometriosis [81], pelvic adhesions may cause impairment of tubo-ovarian function and infertility. An inverse relationship between pregnancy rates and the degree of endometriosis has often been proposed, but this has not been substantiated in prospectively controlled fertility trials [2]. Subfertility associated with minimal-to-mild endometriosis is even more controversial [2].

In baboons, two independent prospective controlled studies showed that animals with minimal endometriosis have a normal fertility [82,83]. Subfertility was found in baboons with spontaneous or induced endometriosis AFS stages II, III and IV. Ovarian endometriosis was not observed in baboons with either spontaneous or induced endometriosis participating in the fertility trials [82,83]. These results indicate that, in baboons, minimal endometriosis is not associated with infertility and is probably not a disease but a physiological phenomenon caused by cyclic retrograde menstruation [41,82,83]. By contrast, more extensive peritoneal endometriosis with (AFS stage III and AFS stage IV) or without (AFS stage II) adhesions is associated with subfertility, even in the absence of ovarian involvement [83]. These data, together with other data from women, strongly indicate that endometriosis is associated with subfertility, as reviewed recently [2].

In baboons, serial laparoscopies were carried out to investigate the re-epithelialization of the ovulation stigma by serial laparoscopies during the luteal phase in baboons [84]. If a fresh ovulation stigma was observed in baboons within 5 days after ovulation, it diminished in size but remained visible up to 8, 12 and 16 days after ovulation in 91, 75 and 50% of animals, respectively [84]. If the data obtained in baboons can be extrapolated to the clinical investigation of the infertile woman, it would appear that laparoscopies performed for the documentation of a fresh ovulation stigma preferably should be done as early after ovulation as possible, but can be safely performed up until 4–5 days after ovulation [84]. The results from the baboon study [84] suggest that re-epithelialization of the ovulation stigma takes time and explain why in clinical practice the ovulation stigma can be observed in the late luteal phase.

Etiopathogenesis of endometriosis

Factors favoring endometrial ectopic implantation

Retrograde menstruation

Retrograde menstruation has been reported in 83% of baboons [69], and in 70–90% of women with spontaneous endometriosis [4]. According to Sampson's hypothesis [3], menstrual debris, refluxed into the peritoneal cavity, contain viable endometrial cells that develop into endometriosis. Retrograde menstruation is agreed to be a universal phenomenon in women of reproductive age [4], but fails to account for all cases of the disease.

Peritoneal inflammation

Menstrual endometrial cells may invoke several mechanisms that provoke peritoneal inflammation, such as spur inflammatory mediators, which are postulated to be significantly involved in the development and pathogenesis of this disease. Women with endometriosis have also been demonstrated to aberrantly express immunological modulators and growth factors compared with controls [5,85]. Recently, we demonstrated increased endometrial and peritoneal gene expression of inflammatory cytokines during the menstrual phase in women with endometriosis [86].

The key question is whether endometriosis causes inflammation? Based on data obtained in baboons, peritoneal inflammation seems to be a consequence, not a cause, of the disease [47,85], owing to the following reasons:

- In baboons, inflammation due to spontaneous retrograde menstruation and experimental intrapelvic injection of endometrium is associated with increased PF volume and increased PF concentration of white blood cells and inflammatory cytokines [47,76]. This peritoneal inflammatory effect is observed within 1 month after intrapelvic injection of endometrium [47], but disappears after 2–3 months [24];
- An increased white blood cell concentration and an increased proportion of macrophages and cytotoxic T cells has been reported in the PF of baboons with spontaneous endometriosis [24,41];

- The percentage of $CD4^+$ and IL2R+ cells has been shown to be increased in the peripheral blood of baboons with stage II to IV endometriosis (both spontaneous long-term endometriosis and induced endometriosis) compared with those with recent spontaneous endometriosis (stage I) or a normal pelvis.

Impaired immunosurveillance

The survival and growth of implanted endometrial tissues are associated with angiogenesis and the potentially decreased natural killer (NK) cell cytotoxicity [87]. In an earlier study in baboons, a high dose of immunosuppression with azathioprin and methylprednisolone over 3 months did not affect the incidence of spontaneous endometriosis or the extent of induced endometriosis, and had a marginal stimulatory effect on the progression of spontaneous endometriosis [88], suggesting that overall immunosuppression does not have much effect on the incidence, prevalence or degree of endometriosis. Similarly, there is no evidence that the prevalence of endometriosis is higher in women using long-term immunosuppression. D'Hooghe and colleagues [88] reported no difference in lymphocyte-mediated cytotoxicity and NK cell activity between baboons with and without endometriosis. In baboons, studies have shown that MMP-7 is a dominant metalloproteinase during establishment of endometriosis and may regulate the invasive events of the endometriotic tissue [89].

Steroid receptor & aromatase aberrations

The molecular interplay between inflammation and endocrine factors represents complex pathophysiological events. The upregulation of endometrial aromatase expression in women with endometriosis, a rate-limiting-step enzyme in estradiol biosynthesis, has been associated with the pathogenesis of endometriosis [10]. Inflammatory cytokines such as IL-6, IL-11 and TNF-α have been shown to abrogate the aromatase activity in peripheral tissues such as adipocytes [10]. Studies in baboons have demonstrated that endometriotic lesions express aromatase and estrogen receptor at 8–10 months after disease induction [90], suggesting that increased estrogen supply is necessary for promoting endometrial cell proliferation in ectopic sites.

Baboon model for preclinical studies & development of new treatment options for endometriosis

Endometriosis is a debilitating condition associated with morbidity and a lot of suffering. Current treatment is limited to hormonal drugs that suppress the menstrual cycle and the activity of endometriotic lesions, but the adverse effects of these drugs decrease their compliance, and endometriosis usually recurs after cessation of hormonal treatment. Therefore, there is a renewed interest in developing new treatment options using nonhormonal and immune/inflammatory targets, as has been reviewed recently [11,18]. Even if peritoneal inflammation is a consequence rather than a cause of endometriosis, the coexistence of endometriosis and peritoneal inflammation may offer new anti-inflammatory therapeutic options in the treatment of endometriosis. Nevertheless, more specific anti-inflammatory agents may affect the development of endometriosis. For example, drugs suppressing macrophage activation, such as verapamil (calcium channel blocking agent) and pentoxifylline, have been tested in hamsters and mice, respectively [91,92]. Future potential targets in the management of endometriosis may include nonsurgical and nonhormonal methods to eliminate pain and improve fertility. These have been reviewed extensively [8,11,14,62,93]. Recently, it was demonstrated that neutralization of TNF-α activity with anti-TNF-α may reverse the chronic inflammatory state associated with spontaneous or induced endometriosis in baboons [9,12,13,94].

In the future, the baboon model for endometriosis should be used to test new drugs in the prevention or treatment of endometriosis and endometriosis-associated subfertility [8,22,64]. Since intrapelvic injection of menstrual endometrium causes moderate-to-severe endometriosis in most baboons, it is possible to perform either prevention studies (prevent attachment of menstrual endometrium on the uterine peritoneum) or treatment studies (reduce extent of induced endometriosis after medical or surgical therapy) [8,22]. Furthermore, placebo-controlled, randomized trials can be performed to evaluate the effect of new anti-endometriosis drugs on endometriosis-associated subfertility, with the possibility of complete standardization for the degree of endometriosis (after intrapelvic injection of menstrual endometrium), for the presence of ovulation (can be interpreted based on the perineal cycle), and for male factors (timed intercourse with male baboon of proven fertility, controlled by behavioral observation and postcoital test, as described previously [8,22]).

Intrapelvic injection of menstrual endometrium also allows the possibility to study early endometrial–peritoneal interaction at

Executive summary

Need for new approaches in endometriosis research

- Endometriosis is now recognized as an enigmatic disease owing to its various clinical manifestations and locations.
- Several decades devoted to biomedical research have yielded inadequate findings regarding understanding the basic etiology or pathophysiology of the disease.
- New molecular genetic approaches are needed to better understand the multifactorial etiopathogenesis of endometriosis.

Nonprimate models

- Nonprimate models, such as rodent models, have been used as experimental animals for the study of endometriosis.
- Disease is induced through autologous transplantation of the endometrium or the uterine horn, which can be stitched surgically onto the peritoneum.
- Rodent models have some advantages, such as low cost and ease of manipulation.
- Some fundamental drawbacks diminish their applicability to human disease, such as lack of a menstrual cycle, lack of spontaneous endometriosis and the fact that they exhibit a wider phylogenetic gap with humans.

Relevance of nonhuman primate models in endometriosis

- Endometriosis occurs exclusively in menstruating species, including nonhuman primates and humans.
- Nonhuman primates provide key advantages that make them relevant animal models in endometriosis research, such as close phylogenetic relatedness to humans and anatomical and physiological similarities to humans.
- Use of nonhuman primates is limited, owing to the limited availability and the maintenance and experimentation costs in captivity. Therefore, it is important to perform reproductive research in baboons as much as possible in or close to their natural environment in Africa. This is possible at the Institute of Primate Research, Nairobi, Kenya, where the baboon model for endometriosis has been developed over the last 17 years.

Baboon model to investigate human endometriosis

- Prevalence of spontaneous minimal endometriosis in baboons of proven fertility was 25%, with laparoscopic appearances, pelvic localization and microscopic aspects similar to the human disease.
- Extensive research has demonstrated that the baboon is an excellent model for the study of endometriosis and has several advantages in endometriosis research compared with rhesus or cynomolgus monkeys.
- In baboons, spontaneous endometriosis is a progressive disease and remodeling, defined by transition between typical, subtle and suspicious implants, occurs.

Etiopathogenesis of endometriosis

- Retrograde menstruation has been reported in 83% of baboons and in 70–90% of women with spontaneous endometriosis.
- Menstrual endometrial cells may invoke several mechanisms that provoke peritoneal inflammation, such as spur inflammatory mediators, which are postulated to be significantly involved in the development and pathogenesis of this disease.
- Impaired immunosurveillance has been associated with survival and growth of implanted endometrial tissues.
- Studies in baboons have demonstrated that endometriotic lesions express aromatase and estrogen receptor between 8 and 10 months after disease induction.

Baboon model for preclinical studies & development of new treatment options for endometriosis

- Current treatment is limited to hormonal drugs that suppress the menstrual cycle and the activity of endometriotic lesions, and endometriosis usually recurs after cessation of hormonal treatment.
- Future potential targets in the management of endometriosis may include nonsurgical and nonhormonal methods to eliminate pain and improve fertility.
- The baboon model for endometriosis should be used to test new drugs in the prevention or treatment of endometriosis and of endometriosis-associated subfertility.

short-term intervals during *in vivo* culture, and could provide very important insights into the early development of endometriotic lesions [8,22] and offer a better understanding of the role of endometrium, peritoneum and PF in the onset of endometriosis. This would be very important to assess the validity of the Sampson hypothesis.

Conclusion & future perspective

Endometriosis is an incapacitating condition among women of reproductive age and a major disease burden on healthcare systems worldwide. The extensive experimental studies performed on the baboon as a model of endometriosis underscore the critical role of the baboon as a better model for understanding human endometriosis.

Future research in endometriosis should focus on using baboons to study the early endometrial–peritoneal interaction at short-term intervals, which could result in novel biomarkers for endometriosis that could contribute to the noninvasive diagnosis of this

disease. Accurate diagnosis of endometriosis is critical and instrumental in understanding the disease etiology. A noninvasive diagnostic method will be useful in epidemiological studies on endometriosis. The current treatment options, both medical and surgical, are insufficient. Thus, new approaches such as genomics and proteomics are needed to find new target molecules and possibly develop disease biomarkers.

The baboon model for endometriosis should be used to test new drugs in the prevention or treatment of endometriosis and endometriosis-associated subfertility.

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