Abstract

Endometriosis is a common women’s health problem that is characterized by the presence of tissue resembling endometrium outside the uterus. The condition causes painful periods, chronic pelvic pain, and subfertility, which are potentially debilitating; and it affects millions of women worldwide. The diagnosis is made on visual inspection of the pelvis, usually at laparoscopy. The natural history is unknown, and well-controlled experiments are difficult to perform because of the need for repeated surgical procedures to assess endometriotic lesions over time. Thus, despite over 50 years’ research, the cause of endometriosis remains unclear, and treatment options are limited. Animal models provide an invaluable tool to study risk factors, prevalence, and the natural history of endometriosis especially in those menstruating nonhuman primates that develop the disease spontaneously. Many of the practical problems associated with studying the disease in humans can therefore be overcome. The pathophysiology of endometriosis can also be investigated and new treatments assessed in both nonprimates and nonhuman primates, with “disease” induced by placing autologous uterine tissue in ectopic sites, or human endometrium in the case of nude mice. However, although nonprimates have obvious advantages as a model, the extent to which the induced lesions are truly representative of the disease itself is debatable. This review explores the value of the experimental models that have been used to date.

Key Words: endometriosis; induced disease; nonprimate; primate; spontaneous disease

The Clinical Problem in Humans

Endometriosis is a common, benign gynecological condition that is characterized by the presence of endometrial tissue outside the uterine cavity. The most commonly affected site is the pelvis, particularly the ovaries, peritoneum, uterosacral ligaments, and pouch of Douglas. Occasionally the bowel and sites outside the pelvis (e.g., the lungs, umbilicus, and diaphragm) may also be affected.

Clinical manifestations include dysmenorrhea (painful menstrual periods), noncyclical pelvic pain, dyspareunia (pain on intercourse), and subfertility. On vaginal examination, pelvic tenderness and induration are common findings. An adnexal mass may be palpable if there are ovarian cysts, and the uterus may be in a fixed, retroverted position.

Direct visualization of endometriotic lesions is required for an unequivocal diagnosis of endometriosis. Biopsy is usually not performed unless there is doubt about the diagnosis. Laparoscopy is the favored technique because it is minimally invasive and allows magnification of the lesions. The lesions vary in appearance depending on their age, the stage of the menstrual cycle, and the extent of the disease. Active lesions are generally red or appear as clear vesicles, whereas less active lesions are black or brown patches or appear as white scars. More severe disease results in the formation of adhesions, and ovarian “chocolate” cysts (endometriomas), which are filled with old blood. Disease severity can be divided into four stages, from minimal (Stage I) to severe (Stage IV), using the revised American Fertility Society (AFS1) classification system (AFS 1985).

The exact prevalence of endometriosis in the population cannot be ascertained because of the need to perform an invasive procedure to determine who is affected. Nevertheless, estimates range from 2 to 22% in asymptomatic women, 40 to 60% in women with dysmenorrhea, and 20 to 30% in women being investigated for subfertility (Farquhar 2000).

Risk factors associated with endometriosis include the following: increasing age within the reproductive years, greater exposure to menstruation because of short cycle length, long duration of flow and reduced parity, and increased peripheral body fat associated with increased serum estrogen levels. Factors thought to decrease estrogen levels (e.g., exercise and smoking) show an inverse relation with the disease (Eskenazi and Warner 1997).

Treatment for endometriosis consists of medical and surgical approaches. The choice depends on factors such as the nature of the main symptom (pain or subfertility), the disease severity, and the woman’s age. Medical options in-
volve hormonal manipulation, which mimics pregnancy (combined oral contraceptive pill), menopause (gonadotropin-releasing hormone [GnRH\(^1\)] analogues), or a hyperandrogenic state (danazol). All of these treatments relieve pain effectively, but they are of no value in improving fertility. Side effects are relatively common and may prove to be unacceptable to the patient. Women taking danazol, for example, may experience androgenic side effects such as acne, weight gain, and excess hair growth; and women taking GnRH analogues may suffer hypoestrogenic symptoms such as hot flushes, vaginal dryness, and loss of libido.

Surgical techniques usually involve laparoscopic removal of endometriotic lesions and cysts, and clearance of adhesions to restore normal anatomy. Such procedures result in improved fertility and pain relief; however, surgery is not without risks and complications, such as damage to other pelvic structures and adhesion formation (Farquhar 2000). In women who have completed their families, hysterectomy and removal of both ovaries may be considered for disabling symptoms.

**Value of Animal Models**

Our current understanding of the pathophysiology and cause of endometriosis is limited. The most widely accepted theory was proposed by Sampson (1927), who suggested that endometriosis results from retrograde menstruation (i.e., the flow of menstrual debris from the uterus along the fallopian tubes into the pelvis). Sampson hypothesized that the shed endometrial cells, which are viable, implant onto the peritoneal surface and form ectopic (endometriotic) lesions. The theory is supported by several observations. For example, the incidence of endometriosis is higher in women with increased retrograde menstruation because they menstruate more frequently or have a congenitally absent cervix. However, it has been reported that up to 90% of women may experience some degree of retrograde menstruation (Halme et al. 1984) yet not all develop endometriosis, which has led to the hypothesis that women with endometriosis have decreased immunological clearance of shed endometrial cells within the peritoneal cavity (Oosterlynck et al. 1991).

This explanation still leaves many unanswered questions, such as how endometriosis can form outside the peritoneal cavity, how the disease arises in women who have no uterus, and why it has even occurred in men (although extremely rarely). Other hypotheses such as coelomic metaplasia and lymphatic/blood-borne dissemination have been proposed, but endometriosis has largely remained an enigma.

One of the main reasons for lack of progress is the difficulty of studying the disease in humans. Controlled experiments are limited because it is not possible to monitor the true disease prevalence/progression without performing repeated laparoscopies, which is difficult on many grounds. Therefore, animal models are an extremely important tool in elucidating the mechanisms underlying this disease.

Both nonprimate and primate models have been used to study endometriosis for many years. Nonprimates, including rodents, do not undergo spontaneous disease, but it can be induced using either autologous uterine tissue or human endometrium. Primates do develop endometriosis spontaneously, and the disease can also be induced for research purposes.

**Nonprimate Models**

**Induced Disease**

Autologous transplants have been performed in rabbits (Schenken and Asch 1980), rats (Vernon and Wilson 1985), and hamsters (Steinleitner et al. 1991b). The procedure involves removing one of the uterine horns at minilaparotomy. The uterine tissue is cut into small sections and sutured into the peritoneal cavity or reintroduced by inoculation. Syngenic mice have also been used similarly. Donor animals have both uterine horns removed; the tissue is then minced and reintroduced into the peritoneal cavity of the recipient animal by inoculation (Somigliana et al. 1999).

In this experiment, both recipient and donor animals were subjected to prior ovariectomy and given estrogen supplementation to abrogate any differences in the stage of the estrous cycle.

Human endometrium has been successfully implanted into the homozygous "nude" mouse. The endometrium can be collected from menstrual fluid at the time of surgery for benign conditions or from a biopsy taken at any point in the menstrual cycle. Endometrial biopsies can be performed on patients, with or without endometriosis, undergoing laparoscopy for pain and/or subfertility, or by taking samples directly from the uterus once it has been removed from patients undergoing hysterectomy. Samples of ectopic endometrium can also be obtained from ovarian endometriomas (Zamah et al. 1984). Transplantation of human tissue into the mouse is then performed at minilaparotomy (Nisolle et al. 2000a), subcutaneously (Zamah et al. 1984), or by inoculation into the peritoneal cavity (Somigliana et al. 1999).

Numerous factors must be optimal for both auto- and xenotransplants to succeed. First, both endometrial epithelium and stromal tissue are required, as demonstrated in rats by the failure of uterine lavage alone (which would have yielded only epithelial cells) to provide sufficient cells to establish ectopic growth within the peritoneal cavity (Vernon and Wilson 1985). Zamah and colleagues (1984) also found that single cell human endometrial suspensions could not induce ectopic endometrial growth in nude mice but that whole uterine fragments could. They also found that tissue from an endometrioma persisted for longer than proliferative eutopic endometrium, implying that eutopic endometrium is in some way structurally different.

Second, it appears that prior hormonal treatment of the transplanted cells can affect the lesions produced. Beliard
and colleagues (2002) reported that before injection into the peritoneum of nude mice, pretreatment of human endometrial cells with estrogen or estrogen plus a progestin—but not a progestin alone—resulted in a higher percentage of animals developing endometriotic-like lesions. Administration of hormones to the recipient animals had no effect.

The investigation of the mechanisms by which immune factors (Rock and Markham 1992). The rat model has enabled in vivo studies of the pathogenesis of endometriosis, with immune factors playing a role in the pathophysiology of endometriosis. For example, the stage of the menstrual cycle in which the grafts were harvested. These results imply that in the rodent model, the stage of the cycle of the donor endometrium is not an important factor influencing how well ectopic lesions are created.

Use of the Nonprimate Models to Investigate Pathological Mechanisms and Drug Effects

The creation of nonprimate models has facilitated research on the pathophysiology of endometriosis. For example, studying the in vivo mechanisms involved in the attachment of endometrial cells and the early evolution of lesions is now possible by examining the morphology of transplanted tissue at different time intervals.

Nisolle et al. (2000a) used nude mice to establish the progression of human menstrual endometrium transplanted into the peritoneal cavity at minilaparotomy by removing samples on days 1, 3, and 5 after the surgery. As early as day 1, stromal cells were seen to attach to the mesothelium, and by day 3 there was reorganization of epithelial and stromal cells into endometrial glands. By day 5, cystic endometrial lesions were seen that, compared with transplants removed on days 1 and 3, showed greater proliferative activity in glandular cells and a higher vascular endothelial growth factor score in stromal cells. These findings suggest that stromal cells are involved in the attachment process, and glandular cells, in the growth of the lesion. Uchiide and colleagues (2002) reported that the stromal component of the autotransplant in a rat model showed proliferation and infiltration of mast cells, eosinophils, macrophages, lymphocytes, and plasma cells. Lesions were initially found to increase as time elapsed after transplantation, but eventually proliferation declined and the infiltrating cells disappeared. This observation supports the theory that endometriosis may cause an inflammatory response.

It has long been hypothesized that immune factors play an important role in the pathogenesis of endometriosis (Rock and Markham 1992). The rat model has enabled investigation of the mechanisms by which immune factors may be involved by testing the effects of drugs that modulate the immune system. Thus, the immunomodulator loxoribine causes regression of both epithelial and stromal components of endometriotic lesions in the rat (Keenan et al. 1999). Intraperitoneal and subcutaneous treatment with interferon-α-2b in the rat reduced the size of induced lesions (Ingelmo et al. 1999), as did intraperitoneal injection of interleukin-12 in a syngenic mouse model (Somigliana et al. 1999). Finally, the antiproliferative properties of progesterone antagonists (e.g., onapristone and ZK 136 799) have been observed in rats with surgically induced endometriosis (Stöckemann et al. 1995).

Suggestions have also been made that peritoneal inflammatory cell hyperactivation may be part of the abnormality in patients with endometriosis-associated subfertility. Verapamil, a calcium channel blocking agent that inhibits macrophage activation, enhances reproductive performance in a hamster endometriosis model (Steinleitner et al. 1991b); and pentoxifylline, a drug that reverses the effect of macrophage hyperactivation, has been shown to abrogate macrophage-mediated subfertility in a mouse model (Steinleitner et al. 1991a).

Assessment of the Nonprimate Model

Although the use of nonprimates is advantageous with respect to their relative low cost and their ability to establish endometriotic-like lesions, the models have numerous disadvantages. The large number of experimental techniques differ even within these models, and the obviously wide phylogenetic gap between nonprimates and humans makes comparisons quite difficult. Most importantly, nonprimates lack a menstrual cycle and do not develop spontaneous endometriosis. The rat does ovulate spontaneously, but the luteal phase is shorter than in humans. The rabbit lacks a luteal phase altogether. The endometriotic lesions produced in nonprimates differ from those in humans. The rat forms cysts that contain clear serous fluid, with no evidence of neoangiogenesis. Hemorrhagic solid lesions are found in the rabbit, but they are very different from the lesions that occur in humans.

Nude mice that are athymic, lacking T lymphocytes, can act as recipients to human tissue; however, it is possible that thymus aplasia may indirectly influence growth factors and cytokines in the peritoneal fluid. Questions may also arise as to whether the rodent peritoneal environment contains all the paracrine stimuli necessary for neoangiogenesis. Detailed immunohistochemical analyses of these models have not been performed, therefore the degree to which nonprimate disease models are representative of human disease is still unknown.

Primate Models

Methods Used to Induce Disease

The first study to create endometriosis artificially in nonhuman primates was carried out in 1950 on rhesus monkeys. In an attempt to create a model for retrograde menstruation, Te Linde and Scott (1950) repositioned the cervix so that
menstrual tissue was found in 50% of the monkeys after 10 mo, but massive adhesions were also present. Subsequently, D’Hooghe and colleagues (1994) attempted to increase the amount of retrograde menstruation in a baboon model by occluding the cervix using three methods: insertion of silicone into the cervical canal (n = 1), electrocoagulation plus cervical suturing (n = 4), and supracervical ligation (n = 2). Supracervical ligation performed during laparotomy proved to be the only method that provided sufficient resistance to normal antegrade menstruation so as to increase the volume of retrograde menstruation. Endometriosis was found to develop within 3 mo in both of the animals that were subjected to this procedure.

Intraperitoneal injection of endometrium has also been used to induce endometriosis in the baboon (D’Hooghe et al. 1995b). Seventeen baboons were injected retroperitoneally with luteal (n = 6) or menstrual (n = 7) endometrium, and intraperitoneally with menstrual (n = 4) endometrium. Endometrium was obtained by transcervical biopsy with a curette or at laparotomy by creating an opening in the fundus before introducing a curette into the uterine cavity. The tissue was then either minced and reintroduced, or simply aspirated and directly reintroduced by intraperitoneal injection. All animals had laparoscopies after 2 mo; thereafter six animals that received injections of luteal, and five of menstrual endometrium had laparoscopies after 5 and 12 mo, respectively. The authors reported that the surface area of menstrual endometrium had laparoscopies after 5 and 12 mo, although disease has also been reported in other species (Table 1).

Numerous risk factors for the development of spontaneous endometriosis in primates have been examined and include experimental procedures such as laparoscopies, hysterotomies, and treatment with estradiol implants. In a case control study of rhesus monkeys at the Wisconsin National Primate Research Center, utilizing necropsy records to determine disease status, 61 affected animals were compared with an equal number of unaffected controls, matched for age at death and year of death (Hadfield et al. 1997). Exposure either to three or more estradiol implants or to one or more hysterotomies was a significant risk factor for the development of endometriosis, with estimated relative risks of 9.7 (95% confidence interval [CI]: 2.5-37.2) and 5.8 (95% CI: 1.6-20.2), respectively. Animals that had been exposed to one or more laparoscopies showed no increased risk for endometriosis.

The disease prevalence among animals necropsied between 1981 and 2001 in the same colony was 31.4% (95% CI: 26.9-35.9%); prevalence increased with advancing age at death and calendar period (Zondervan et al. 2004). Familial aggregation was strongly suggested by a significantly higher average kinship coefficient among affected animals compared with unaffected animals (p < 0.001), and a higher recurrence risk for full sibs (0.75, 95% CI: 0.45-1.0) compared with paternal (0.47, 95% CI: 0.42-0.52) and maternal half-sibs (0.26, 95% CI: 0.10-0.41). Subsequently, a large multigenerational pedigree and nine nuclear families consisting of 1,602 females has been assembled, which includes 142 animals with endometriosis identified in the colony over the 20-yr period. The pedigree provides a unique resource to investigate the interaction between genetic susceptibility and environmental factors in a species (MacKenzie and Casey 1975), and lesions are found at similar sites (D’Hooghe et al. 1991; Dick et al. 2003), although minimal disease is the most common finding in most species. Spontaneous endometriosis has been studied principally in rhesus macaques and baboons, although disease has been reported in other species (Table 1).

### Spontaneous Disease: Genetic Epidemiology and Risk Factors and Similarities with Human Disease

Primates develop endometriosis spontaneously. The tissue is morphologically identical to its human counterpart (MacKenzie and Casey 1975), and lesions are found at similar sites (D’Hooghe et al. 1991; Dick et al. 2003), although minimal disease is the most common finding in most species. Spontaneous endometriosis has been studied principally in rhesus macaques and baboons, although disease has also been reported in other species (Table 1).

Table 1 Species of nonhuman primates in which spontaneous endometriosis has been reported

<table>
<thead>
<tr>
<th>Common name</th>
<th>Species</th>
<th>Referencea</th>
</tr>
</thead>
<tbody>
<tr>
<td>African green</td>
<td>Ceropithecus aethiops</td>
<td>Cary et al. (1982)</td>
</tr>
<tr>
<td>Grey-cheeked mangaby</td>
<td>Cercocebus albigena</td>
<td>Schmidt and Hartfiel (1978)</td>
</tr>
<tr>
<td>De Brazza’s monkey</td>
<td>Ceropithecus neglectus</td>
<td>Binhazim et al. (1989)</td>
</tr>
<tr>
<td>Gorilla</td>
<td>Gorilla gorilla</td>
<td>Dore and Lagace (1985)</td>
</tr>
<tr>
<td>Taiwan rhesus</td>
<td>Macaca cyclopsis</td>
<td>Chin (1994)</td>
</tr>
<tr>
<td>Cynomolgus monkey</td>
<td>Macaca fascicularis</td>
<td>Fanton and Hubbard (1983)</td>
</tr>
<tr>
<td>Rhesus monkey</td>
<td>Macaca mulatta</td>
<td>Fraser (1929)</td>
</tr>
<tr>
<td>Olive baboon</td>
<td>Papio anubis</td>
<td>D’Hooghe et al. (1991)</td>
</tr>
<tr>
<td>Yellow baboon</td>
<td>Papio cynocephalus</td>
<td>Cornillie et al. (1992)</td>
</tr>
<tr>
<td>Kenya baboon</td>
<td>Papio doguera</td>
<td>Folse and Stout (1978)</td>
</tr>
<tr>
<td>Hamadryas baboon</td>
<td>Papio hamadryas</td>
<td>Shalev et al. (1992)</td>
</tr>
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aSee text. This reference list is not exhaustive.
affected by essentially the same disease that occurs in humans.

It is conceivable that captivity itself may influence the likelihood of disease developing. In a study comparing disease in baboons held for long periods in captivity with those just captured from the wild, increased duration of captivity appeared to be associated with a higher prevalence of spontaneous disease (D’Hooge et al. 1996a). Clinical endometriosis was found in 32% of the animals that had been in captivity for more than 2 yr, 17% of those baboons in captivity for 1 to 2 yr, and only 11% of baboons that had been in captivity for less than a year. It is unclear, however, whether these effects can truly be attributed to living in captivity (perhaps because captive animals are heavier than those in the wild, or because they menstruate more often, which would increase exposure to retrograde menstruation), or whether it is simply an age-related effect.

**Diagnostic Methods to Detect Disease in Primates**

The diagnosis of endometriosis in nonhuman primates, as in humans, has been made primarily at the time of surgery (i.e., laparoscopy or laparotomy), although radiological methods have also been used. Zondervan and coworkers (manuscript in preparation) conducted magnetic resonance imaging (MRI) scans on 113 rhesus monkeys who were the living descendants of the affected animals in the research group’s original necropsy study (Hadfield et al. 1997). Endometriosis was suspected radiologically in 22 (19%) monkeys. The disease appeared radiologically as peritoneal or ovarian lesions <gt3 cm diameter (n = 5); as peritoneal or ovarian lesions 1-3 cm diameter (n = 3), or as equivocal findings (n = 14; i.e., lesions <1 cm diameter).

**Use of the Primate Models to Investigate Pathological Mechanisms and Drug Effects**

The study of spontaneous endometriosis in primates has increased understanding of the natural progression of the disease. D’Hooge’s research group, in particular, has noted that endometriosis in baboons is a dynamic process that undergoes periods of development, regression, and remodeling, but that it is ultimately progressive. This process was characterized by following serial laparoscopies over a period of 30 mo on 12 baboons with spontaneous disease (D’Hooge et al. 1996b).

The primate model has also made it possible to study the effects of endometriosis on fertility. In a pivotal study, 71 baboons (normal pelvis = 34; spontaneous endometriosis = 16; induced disease = 21) were mated during 286 cycles (D’Hooge et al. 1996c). The disease severities of the 37 affected animals were staged using the revised AFS system: minimal = 9; mild = 14; moderate = 7; and severe = 7. The pregnancy rates were lower in the animals with moderate/severe disease (9%) and mild disease (10%) compared with animals with minimal disease (24%) or the control group (19%). These data suggest that mild to severe endometriosis, but not minimal disease, affects fertility in baboons. Schenken and colleagues (1984) also reported that chemical and term pregnancy rates were lower in monkeys (*Macaca fascicularis*) with moderate/severe endometriosis, which they attributed to the failure of follicular rupture and/or pelvic adhesions.

The role of the immune system, including the effects of immunosuppression on the development and progression of endometriosis, is another factor that has been investigated in primates. D’Hooge and colleagues (1995a) studied eight baboons with a normal pelvis and 24 with endometriosis (spontaneous = 10; induced by intraperitoneal seeding of menstrual endometrium = 14). Sixteen animals (normal pelvis = 4; spontaneous endometriosis = 5; induced disease = 7) were given daily intramuscular injections of 0.8 mg/kg of methylprednisolone and 2 mg/kg of azathioprine for 3 mo; the remaining 16 animals were not treated. Immunosuppressed baboons with spontaneous endometriosis had significantly more, and a larger surface area of, endometriotic lesions than untreated animals. However, immunosuppressed and untreated animals with induced disease had comparable findings. None of the immunosuppressed animals that initially had a normal pelvis developed endometriosis.

In women with endometriosis, changes in the white blood cell population have been noted (Halme et al. 1982). The primate model has allowed this phenomenon to be further explored to determine whether these findings are incidental or related to the disease process. D’Hooge and colleagues (1996d) analyzed the peripheral blood and peritoneal fluid of 60 baboons (normal pelvis = 23; spontaneous endometriosis = 19; induced disease = 18). The percentage of cluster designation (CD4)4+ and interleukin 2R+ cells detected in the blood of baboons with mild to moderate, spontaneous, and induced endometriosis increased, suggesting the disease activates the immune system. However, in peritoneal fluid, the percentage of leucine (Leu) M5+ macrophages and CD8+ lymphocytes increased only in spontaneous disease. The authors concluded therefore that alterations in peritoneal fluid in the white blood cell population are a potential cause of the disease.

More specifically, it had been hypothesized that endometriosis results from decreased clearance of endometrial cells because of reduced macrophage/natural killer (NK) cell activity (Oosterlynk et al. 1991). However, this hypothesis is not supported in the baboon model: NK cell activity was comparable in 31 baboons with endometriosis and 11 with a normal pelvis, as was antiendometrial lymphocyte-mediated cytotoxicity in 15 baboons with endometriosis and 13 with a normal pelvis (D’Hooge et al. 1995c).

The primate model is also extremely useful in evaluating the effects of new drug treatments for the disease. Substances such as tumor necrosis factor (TNF) binding protein 1, which neutralizes TNFα, a cytokine associated
with inflammation, have been evaluated in the induced primate model by comparing its effect with a GnRH analogue and a placebo. Anti-TNFα was reported to be successful in reducing the severity of disease (D’Hooghe et al. 2001).

Progesterone receptor modulators and antagonists that are antiproliferative and inhibit secretory activity may also have a role in the treatment of endometriosis. Monkeys with induced disease were treated for 1 yr with monthly depot injections of GnRH analogues, a progesterone receptor modulator, or a combination of the two. All treatment options decreased the size of implants compared with controls; but the progesterone receptor modulator, either alone or in combination with a GnRH analogue, maintained estradiol secretion, suggesting that long-term treatment may be possible without the consequences of hypoestrogenism (i.e., bone density loss associated with the GnRH analogues) (Grow et al. 1996). Since 1996, clinical trials have been under way in humans (Kettel et al. 1998).

Assessment of Primate Models

Although experimentally induced endometriosis is fundamentally different from spontaneous disease, it should be borne in mind that the primary purpose of some of the experiments (e.g., the cervical occlusion model [D’Hooghe et al. 1994]) was to test specific hypotheses. Induced disease also provides a unique opportunity to measure parameters such as the immune system before and after disease induction. When these data are contrasted with the findings from animals with spontaneous disease, a unique opportunity arises to differentiate between cause and effect. Yet in almost all other respects, spontaneous endometriosis is the best possible model, although it is important to note that moderate to severe disease with cystic ovarian lesions is not commonly found in nonhuman primates.

Conclusion

Animal models are invaluable in the study of endometriosis, the debilitating disease that affects millions of women worldwide. The models overcome the practical problems associated with studying the disease in women and enable testing of observational hypotheses derived from human disease. The resulting information has led to a greater understanding of disease prevalence, incidence, pathogenesis, and associated subfertility. Although many questions still remain, it is our hope that animal models will help to answer them. These answers should translate in the long term to better diagnostic and treatment strategies for humans.

References


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