Non-Human Primate Models of Endometriosis


Review

Primate Model Research for Endometriosis

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Endometriosis is defined as the existence of endometrial tissue outside the uterine cavity, and it includes a chronic, inflammatory reaction associated with female infertility and pelvic pain. Endometriosis occurs in 7 to 10% of women. Although it has been studied for more than 50 years, the pathogenesis and development of endometriosis are still poorly understood. There is no curative therapy for endometriosis, which often recurs after surgical or medical treatment. There is a consensus that the adverse current of menstrual blood plays a crucial role in the development of endometriosis. This places a major limitation on research using rodent models of endometriosis, although these are still widely employed, because rodents do not menstruate and endometriosis does not occur spontaneously in these animals. In fact, menstruation and spontaneous endometriosis only occur in women and some non-human primates, making models that employ non-human primates the best animal models for research into the pathogenesis, pathophysiology, spontaneous onset, and treatment of endometriosis. This review assesses the effectiveness and potential of the non-human primate models of endometriosis. It also describes the current findings and theories on the pathogenesis of endometriosis that have been obtained by research using non-human primates.

Keywords: animal model; endometriosis; menstruation; non-human primates; pathogenesis

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endometriosis.

Pathogenesis of Endometriosis

Despite extensive research on endometriosis, it is still not fully understood why women develop this condition, although there are several prominent hypotheses. First, the implantation theory of Sampson proposes that some of the endometrial lining shed during menstruation is transported through the fallopian tubes and implanted in the pelvic cavity (Sampson 1927). A second hypothesis is that endometrial tissue is disseminated through lymphatics and blood vessels (Sampson 1927). Third, the coelomic metaplasia theory proposes that undifferentiated coelomic cells are transformed into endometrium-like tissue (Ferguson et al. 1969).

Sampson’s theory is the leading hypothesis for the pathogenesis of endometriosis, but it does not explain why the condition only develops in certain women. Nearly all women have retrograde menstruation, but endometriosis only affects 7-10% of them, so some mechanism is needed that allows endometrial tissue to be implanted in pelvic structures. Thus, to explain Sampson’s theory, immunologic abnormalities have attracted attention worldwide. Deficient cellular immunity may result in the inability to recognize endometrial tissue in abnormal locations (Steele et al. 1984). A low level of natural killer cell activity may result in decreased cytotoxicity for autologous endometrium (Oosterlynck et al. 1991). It has been reported that there is an increase of leukocytes and macrophages in the peritoneal cavity and ectopic endometrium of women with endometriosis (Dmowski et al. 1994). These cells secrete cytokines, including interleukin-1, -6 and -8, tumor necrosis factors, and RANTES (regulated upon activation normal T-cell expressed and secreted), and growth factors into the peritoneal fluid. Sinaii et al. reported that women with endometriosis have higher rates of autoimmune diseases, hypothyroidism, fibromyalgia, chronic fatigue syndrome, allergies, and asthma compared with the general female population (Sinaii et al. 2002).

Problems with Rodent Models of Endometriosis

Rodent models have been widely used for research on endometriosis. These models can be classified into two types, which are homologous and heterologous models. Homologous models are based on the surgical transplantation of endometrial tissue of the same or syngeneic animals into immunocompromised animals (Cummings and Metcalf 1995; Becker et al. 2006). In contrast, heterologous models employ xenotransplantation of human endometrial tissue into the peritoneal cavity of immunocompromised mice (Somigliana et al. 1999; Nisolle et al. 2000). Rodent models have some advantages, including low cost, easy handling, and the possibility of genetic manipulation using knockout and transgenic mice (Dinulescu et al. 2005). However, these models also have some major disadvantages. One of the major differences between rodents and humans is that rodents do not menstruate and do not develop spontaneous endometriosis. Therefore, findings about endometriosis in rodent models will not necessarily correspond to human endometriosis. Also, these models are not suitable for
Non-Human Primate Models of Endometriosis

Use of non-human primates in research has the disadvantage of needing special infrastructure, as well as logistical problems and the need for training in the handling these animals. In addition, non-human primates are very costly, so few institutions can perform studies with these animals. However, non-human primates develop spontaneous endometriosis, with lesions that are histologically identical and occur at similar sites to those in humans (MacKenzie and Casey 1975; D’Hooghe et al. 1991; Dick et al. 2003). Therefore, non-human primate models are suitable for investigating both the pathogenesis and treatment of endometriosis.

Endometriosis is common in non-human primates, affecting 36% of female rhesus monkeys (DiGiacomo 1977), 27% of baboons (D’Hooghe et al. 2009), and 28.7% of cynomolgus monkeys (Ami et al. 1993). In fact, the incidence of endometriosis is higher in non-human primates than in humans, so it is comparatively easy to find non-human primates with this condition. However, spontaneous endometriosis develops over a period of several years in non-human primates, so many researchers have tried methods of producing endometriosis in non-human primates more rapidly.

It has been suggested that there is a relationship between the development of endometriosis and surgery on the uterus (DiGiacomo 1977; Bertens et al. 1982), irradiation (Wood et al. 1983; Fanton and Golden 1991), deficient cell-mediated immunity (Dmowski et al. 1981), vitamin D (Saegusa 1990), and exposure to 2,3,7,8-tetrachloro-dioxin (Rier et al. 1993) among other factors. Some non-human primate models of endometriosis are presented in Table 1.

The first non-human primate model of endometriosis was described by Te Linde and Scott (1950). It was based on autologous transplantation. In seven rhesus monkeys, surgically excised fragments of endometrium were transplanted to the anterior cul-de-sac, posterior cul-de-sac, ovary, broad ligament, rectal wall, cecal wall, and abdominal wall. One monkey died of tuberculosis, but one to four endometrial grafts were viable in each of the other six monkeys after 26 to 522 days (Te Linde and Scott 1950).

Scott et al. (1953) reported another non-human primate model. In a rhesus monkey, the descending uterine vessels were clamped, cut, and tied, the distal cervix was transected and the proximal cervix was moved to the anterior abdominal wall. The peritoneum was then stripped over an area 15 mm wide from the proximal cervix and the abdominal peritoneum was attached to the remaining intact peritoneum around the uterus. The cervix was placed into a pocket in the rectus abdominis muscle for one year, after which viable endometrial stroma and glands, smooth and striated muscle, and a fibrous tissue reaction were found in this area (Scott et al. 1953). Various other studies of endometriosis have since been performed in monkeys.

D’Hooghe et al. (1994) attempted to increase the volume of retrograde menstruation in baboons by occluding the cervix through insertion of silicone into the cervical canal (n = 1), electrocoagulation plus cervical suturing (n = 4), and supracervical ligation (n = 2). Endometriosis developed within three months in all 7 baboons (D’Hooghe et al. 1994). Rier et al. (1993) reported a high incidence of endometriosis in Rhesus monkeys exposed to high levels of 2,3,7,8-tetrachloro-p-dioxin, with 3 of 7 monkeys exposed at 5 ppt and 5 of 7 monkeys exposed at 25 ppt developing moderate to severe endometriosis. Sillem et al. (1996) placed minced endometrium into the cul-de-sac of the pelvis in cynomolgus monkeys, trying three different tissue treatment methods (minced endometrium alone, minced endometrium digested enzymatically, and minced endometrium incubated with a protease inhibitor) in 10 monkeys each. After three weeks, endometriosis was found in 23 of the 30 monkeys (Sillem et al. 1996). Yang et al. (2000) performed auto-transplantation of endometrial fragments into the pelvic cavity in 23 cynomolgus monkeys and fed the animals a diet containing 2,3,7,8-tetrachloro-p-dioxin.

Table 1. Non-human primate models of endometriosis.

<table>
<thead>
<tr>
<th>Methods</th>
<th>Animal</th>
<th>N</th>
<th>Rate of endometriosis (%)</th>
<th>Detection period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Te Linde and Scott 1950</td>
<td>Transplantation of endometrial tissue</td>
<td>Rhesus Monkey</td>
<td>6</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Scott et al. 1953</td>
<td>Cut and tie the uterine cervix</td>
<td>Rhesus Monkey</td>
<td>10</td>
<td>5 (50)</td>
</tr>
<tr>
<td>D’Hooghe et al. 1994</td>
<td>Occlusion of the uterine cervix</td>
<td>Rhesus Monkey</td>
<td>7</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Rier et al. 1993</td>
<td>TCDD*</td>
<td>Rhesus Monkey</td>
<td>14</td>
<td>8 (57)</td>
</tr>
<tr>
<td>Sillem et al. 1996</td>
<td>Transplantation of endometrial tissue</td>
<td>Cynomolgus Monkey</td>
<td>30</td>
<td>23 (76)</td>
</tr>
<tr>
<td>Yang et al. 2000</td>
<td>Transplantation of endometrial tissue + TCDD*</td>
<td>Cynomolgus Monkey</td>
<td>18</td>
<td>18 (100)</td>
</tr>
</tbody>
</table>

* 2,3,7,8-tetrachloro-p-dioxin
After one month, endometriosis was found in all of these monkeys. Thus, a number of non-human primate models of endometriosis have been created over the past decades. Although endometriosis has been confirmed to occur in these models, the pathogenesis has not been determined so far.

**New Directions for Research**

Non-human primate models of endometriosis, either induced or spontaneous, provide excellent tools for research into the pathogenesis and treatment of endometriosis. The inflammatory cytokine TNF-α potently stimulates inflammation and TNF-α levels are elevated in the peritoneal fluid of women with endometriosis (Halme 1989; Arici et al. 1998). Neutralization of TNF-α with TNF-binding protein-1 was reported to inhibit the development of endometriotic lesions (D’Hooghe et al. 2006). In addition, a decrease in the number and surface area of active red lesions was observed in female baboons with spontaneous peritoneal endometriosis after neutralization of TNF by treatment with etanercept (Barrier et al. 2004). However, some TNF-α inhibitors have been shown to be toxic in baboons (Falconer et al. 2006). To avoid harmful effects in humans, it is useful to employ such non-human primate models of endometriosis.

**Discussion**

Among the primates in which endometriosis occurs spontaneously, those chiefly used for research on endometriosis are baboons, rhesus monkeys, and cynomolgus monkeys. Baboons are larger, so it is easier to obtain blood and tissue samples and to perform complex surgery. However, being larger and stronger makes handling baboons more difficult and they require large cages. Rhesus monkeys and cynomolgus monkeys are smaller and easier to handle. Cynomolgus monkeys breed continuously in captivity, while rhesus monkeys show seasonal breeding. Although cynomolgus monkeys only weigh 3-7 kg, laparoscopy can be performed easily and repetitively, so these cynomolgus monkeys are suitable for large-scale research on endometriosis.

The pathogenesis of endometriosis has not been clarified despite active research, suggesting that there are multiple causes and various factors that interact for the disease to occur. It will be necessary to examine the huge volume of research from the past and the future to solve this difficult problem. For basic research on endometriosis, non-human primate models cannot be bettered. The causes of endometriosis may eventually be clarified by non-human primate research, and these models are also useful for research into the prevention and treatment of endometriosis.

**Conclusion**

Animal models remain indispensable for research into many diseases, but we do not have a well-established animal model of endometriosis. Although rodents do not menstruate or develop spontaneous endometriosis, various rodent models have been used by many researches. To investigate the pathogenesis of endometriosis, it seems more reasonable to use non-human primates, since these primates menstruate and develop spontaneous endometriosis like humans.

**Conflict of Interest**

All authors have no conflict of interest in this study.

**References**


DiGiacomo, R.F. (1977) Gynecologic pathology in the rhesus monkey (Macaca mulatta). II. Findings in laboratory and free-


