Commentary

Induced Endometriosis in Nonhuman Primates

Ov D. Slayden

Division of Reproductive & Developmental Sciences, Oregon National Primate Research Center, Oregon Health & Sciences University, Beaverton, Oregon

In this month’s issue of Biology of Reproduction, Afshar et al. [1] report on the effects of endometriosis on gene expression in the baboon endometrium. This work underscores the value of an appropriate animal model for conducting research relating to human disorders. To determine if the development of endometriosis directly alters endometrial physiology within the uterus, the authors made use of a research protocol where endometriosis was induced in the baboon by intraperitoneal inoculation of autologous menstrual endometrium [2–6]. The menstrual inoculate developed into endometriotic lesions, and the uterine endometrium was analyzed at defined time points following induction of the disease. The analysis revealed altered endometrial gene expression, providing supportive evidence that it is the presence of endometriosis, rather than an inherent defective endometrium, that causes an aberrant endometrial phenotype in subjects with the disease.

Endometriosis is a gynecological disorder defined by the presence of endometrium-like tissues at “ectopic” sites outside the uterus [7]. The predominant theory, the Sampson Hypothesis [8, 9], proposes that endometriosis arises from retrograde menstruation of endometrial fragments through the fallopian tubes. While this theory has not been unequivocally proven, it appears logical [9], and there is substantial evidence that endometriosis-like lesions can be created in animal models through endometrial transplantation [10–14].

Endometriosis affects approximately 10% of reproductive aged women, and infertility is a common outcome in 30%–50% of these patients [15, 16]. The underlying cause of endometriosis-associated infertility remains controversial because of multiple disease-related factors, including defective ovarian function, altered hormonal milieu, failed fertilization, menstrual irregularity, and embryo implantation failure [16]. While it has been recognized for more than a decade that patients with endometriosis display altered endometrial physiology [17], it has been difficult to prove a causal relationship between presence of ectopic lesions and endometrial abnormalities [16]. This gap in our understanding arises from the fact that women are rarely diagnosed in the early stages of the disease [18] and that controlled clinical experiments are hindered because patients with endometriosis cannot be readily compared with both disease-free patients (negative controls) and patients suffering from other disorders that result in a similar symptomatology (positive controls) [19].

Spontaneous endometriosis occurs only in women and menstruating Old World nonhuman primates, including baboons and macaques [10, 20], and, like endometriosis in women, nonhuman primates are rarely diagnosed with early stage disease. The limitations on clinical studies and those using naturally occurring endometriosis in nonhuman primates have resulted in the development of strategies to create endometriosis-like lesions in nonprimate animal models [10]. Autologous transplantation of rodent endometrium [10] has been used extensively as a model and has definite advantages, including low cost and the possibility of genetic manipulation using transgenic animals [20–23]. Rodent models have the additional advantage of providing a valuable tool for the design of therapeutic interventions [24]. An alternate approach is to engrat human endometrium or fragments of endometriotic lesions into immunodeficient mice, including nude mice, SCID mice, and RAG-2 null mice, which have a compromised immune system and are less capable of rejecting xenografted tissues. Although the grafted tissue displays endometriosis-like morphology, relevance to the human disease is confounded by the immunologic deficiency of the animals [19, 22]. The peritoneal environment in these mice is not identical to the human, and lesions formed in this way are not truly comparable to lesion formation in women. Moreover, the wide phylogenetic gap between nonprimate species and humans makes translational interpretation of uterine physiology difficult. Nonprimate rodent species display a short estrous cycle with an abbreviated luteal phase; they do not menstruate or develop spontaneous endometriosis, and the nonpregnant endometrium does not undergo decidualization without artificial manipulations that include exposure to exogenous progesterone [25]. Thus, none of the currently available rodent models succeed in reproducing the effects of the disease on the human endometrium.

Nonhuman primates, including baboons and macaques, have endometrial morphology, physiology, and menstrual cycles that are similar to those of women; they develop spontaneous endometriosis and constitute the most physiologically suitable models for the disease in women [19, 26]. Spontaneous endometriosis is rare in most primate colonies [20], and there are no reliable noninvasive screening technologies to identify animals with the disease [26]. Induction of endometriosis in the baboon was initially described by D’Hooghe [13, 26, 27], and although the efficiency of the baboon model was recently challenged [28], it has been utilized extensively by Fazleabas and coworkers over the last decade at the University of Illinois at Chicago and

---

1Supported by NIH P51 OD011092.
2Correspondence: Ov D. Slayden, Division of Reproductive & Developmental Sciences, Oregon National Primate Research Center; Oregon Health & Sciences University, Beaverton, Oregon
E-mail: slaydeno@ohsu.edu

© 2013 by the Society for the Study of Reproduction, Inc.
eISSN: 1529-7268 http://www.biolreprod.org
ISSN: 0006-3363