Journal of the American Association for Laboratory Animal Science
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Vol 50, No 6
November 2011
Pages 921–925

# Glucoregulatory Function in Adult Rhesus Macaques (*Macaca mulatta*) Undergoing Treatment with Medroxyprogesterone Acetate for Endometriosis

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**Endometriosis affects a large percentage of the rhesus macaques (*Macaca mulatta*) at our institution. When the disease is diagnosed in macaques on long-term research protocols, the treatment of choice in our facility is monthly administration of medroxyprogesterone acetate (MPA) to decrease estrogen release and subsequently diminish clinical signs associated with the disease. Because hormonal fluctuations associated with the normal menstrual cycle are known to affect parameters of glucoregulatory function in rhesus macaques, we evaluated the effect of MPA treatment on glucoregulatory function cross-sectionally in 6 animals and longitudinally in 4 animals with endometriosis. Our hypothesis was that monthly administration of MPA for the treatment of endometriosis would negatively affect glucoregulatory function in rhesus macaques. We found that adult female rhesus macaques on MPA therapy for 1.4 to 36.1 mo had lower insulin sensitivity than did age- and weight-matched healthy control animals. In addition, glucoregulatory function was reduced after MPA treatment as compared with pretreatment levels in a group of 4 macaques. These data suggest that glucoregulatory function should be considered when endometriosis treatment is planned for rhesus macaques.**

**Abbreviations:** FSIGTT, frequently sampled intravenous glucose tolerance testing; MPA, medroxyprogesterone acetate.

Endometriosis is a condition in which the endometrial stroma and glands disseminate to areas of the body other than the uterus. Endometriosis affects several species of nonhuman primates, including macaques and baboons.[12,13,20] The disease in nonhuman primates is similar to the human disease and its effects on appetite and behavior suggest that it might be painful.[13] At our facility, the prevalence of endometriosis was greater than 30% among adult female macaques undergoing necropsy.[20] In our macaque colony, evaluation for endometriosis initially is performed when signs of pain during menstruation or abnormal palpation (for example, uteromegaly, cystic structures, or masses) during physical exam are noted or when the menstrual cycle is abnormally long or irregular. After initial evaluation, the diagnosis of endometriosis typically is made through ultrasound-guided aspiration of endometrial cysts or by visualization at surgery and confirmation by histopathology. In some cases, endometriosis is diagnosed through incidental findings during an unrelated procedure. In all cases, treatment is initiated immediately after diagnosis to alleviate pain and discomfort.

One option for treatment of endometriosis in nonhuman primates is ovariectomy or ovariohysterectomy, sometimes combined with cauterization or removal of the disseminated endometrial tissue.[13] This procedure removes the primary source of estrogen for these animals and alleviates discomfort by eliminating the cyclical growth of the disseminated ectopic tissue. Surgical treatment can be challenging due to widespread adhesions and the likelihood of hemorrhage. In advanced endometriosis, pathologic lesions may make it difficult to recognize specific structures in the caudal abdomen, and incomplete ovariectomy can occur. Any ovarian remnants likely will result in continued proliferation of disseminated endometrial tissue and persistent discomfort. In one study, one third of rhesus macaques undergoing surgery for treatment of endometriosis continued to have symptomatic disease after surgery.[12] Even in healthy macaques undergoing bilateral ovariectomy, more than 40% continued to demonstrate cyclical serum hormonal changes after surgery.[8]

Due to the difficulties associated with surgical treatment of endometriosis, hormonal treatment to suppress estrogen secretion or to stop the endometrium from responding to the presence of estrogen often is preferred. Options for hormonal treatment in humans include progesterones (such as medroxyprogesterone acetate [MPA]), gonadotrophin-releasing hormone antagonists, and an ethisterone derivative (danazol).[19] Of these, progesterone-based therapies have been the most effective and have the fewest side effects.[19] MPA is a synthetic progesterone derivative that is used as a contraceptive in women and to treat endometrial and some renal cancers. Exogenous progesterone therapy is currently the most commonly used medical treatment for endometriosis in nonhuman primates.[12,13] At our facility, the standard treatment after diagnosis is 150 mg MPA given intramuscularly once monthly. Our clinical experience has found this dosage regimen to be the most efficacious in inducing cycle suppression. Treated macaques cease to cycle normally (based on absence of menstruation and lack of changes in sex skin), physical evidence of the disease subsides (based on ultrasound images of the uterus and endometrial cysts), and clinical signs of the disease are generally absent.

*Received: 04 Nov 2010. Revision requested: 18 Jan 2011. Accepted: 23 May 2011.*
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The primary risk of long-term MPA treatment in humans is an increased risk of osteoporosis.[14] In 2004, the US Food and Drug Administration released a health alert[18] stating that the use of MPA as a contraceptive has been associated with "the loss of significant bone mineral density" and that this risk increases with duration of use and may not be reversible.[15] This risk may be due to a loss of stored calcium[15] or a delay in peak bone mineralization.[5] Both can lead to osteoporosis and osteoporotic fractures later in life, even if MPA treatment is discontinued.[5] The alteration of glucose levels is listed as an unreferenced side effect in the package insert for MPA.[15] Multiple studies in women being treated with MPA have noted various alterations in glucoregulatory function but have been inconclusive due to sample size or population variation.[7,9,14] In addition, these findings suggest that patients with diabetes mellitus may require more intensive monitoring when on MPA and that even a single dose may affect glucose control in confirmed diabetics.[7,19]Given all these findings, we assessed the effects of MPA administration on glucoregulatory function in a cohort of female rhesus monkeys housed at our facility.

## Materials and Methods

**Study design.** To evaluate the effects of MPA treatment on glucoregulatory function in adult Indian-origin female rhesus monkeys with endometriosis, we first assessed the effects of MPA on 6 animals in a cross-sectional study design. Endometriosis had been diagnosed in all of these animals through routine screening by the veterinary staff at our facility (Wisconsin National Primate Research Center, Madison, WI). They were not involved in any research known to affect glucoregulatory function. Animals ranged in age from 12.3 to 22.2 y (mean ± SEM, 17.6 ± 1.7 y) and ranged in body weight from 6.2 to 12.7 kg (mean ± SEM, 9.6 ± 1.1 kg). Macaques had been on MPA (150 mg IM once monthly) for an average of 15.9 ± 5.8 mo (range, 1.4 to 36.1 mo). Glucoregulatory function at a single time point was evaluated by frequently sampled intravenous glucose tolerance testing (FSIGTT) according to the modified minimal model.[2] Basal levels of glucose and insulin were determined in anesthetized macaques immediately prior to administration of a glucose bolus. Glucose and insulin values were obtained at specific time points, and insulin sensitivity was calculated as previously described.[2] Data prior to MPA treatment was not available because these animals were treated due to a clinical condition. Instead, data from the study population were compared with those of age- and weight-matched female macaques not undergoing MPA treatment.

We then longitudinally evaluated the glucoregulatory response of 4 Indian-origin female rhesus macaques to MPA treatment. These animals are part of an ongoing study evaluating the effects of long-term, adult-onset caloric restriction on health and lifespan[3,11,17] and have had multiple evaluations of glucoregulatory function before and after initiation of clinical treatment with MPA (for endometriosis). One female macaque (L1; age at study onset, 10.7 y) was a member of an ad-libitum–fed control group, whereas the remaining 3 macaques (L2, 11.3 y at study onset; L3, 9.8 y; and L4, 13.7 y) have undergone moderate (30%) caloric restriction since 1994. Glucoregulatory function data at the time point immediately prior to initiation of MPA treatment (150 mg IM once monthly) and at a single point within 2 y after treatment initiation were assessed. In addition, glycosylated hemoglobin was measured within 6 wk of each FSIGTT. In the longitudinal study, animals effectively served as their own controls. Therefore, the difference in diet (restricted compared with ad libitum) likely did not affect the study results.

**Animal husbandry.** All animal protocols were completed at our facility with the approval of the Institutional Animal Care and Use Committee of the Graduate School of the University of Wisconsin, Madison. All 10 study macaques were negative for simian retrovirus. One macaque (C4) was positive for SIV; one animal (C5) was positive for HBV; and one animal (L1) was positive for both herpes B virus and simian T-lymphotrophic virus type 1. These retroviral infections have not been documented to affect glucoregulatory function, and the variable viral status of the monkeys studied is unlikely to have affected the results obtained.

All animals had 24-h access to water. Macaques in the cross-sectional study had ad libitum access to standard laboratory chow (Monkey Chow no. 2050, Teklad, Madison, WI), whereas those in the longitudinal study had access to food for 6 to 8 h daily. During the 6- to 8-h food access period, the control animal (L1) in the longitudinal study had ad libitum access to a semipurified diet (no. 85387, Teklad) containing 15% lactalbumin, 10% corn oil, and approximately 65% carbohydrate in the form of sucrose and corn starch, whereas the 3 macaques on moderate caloric restriction had access to 70% of their own individualized ad libitum intake amounts of a similar semipurified diet that was enriched by 30% in vitamins and minerals (no. 93131, Teklad).[17] Macaques were housed indoors either individually or in pairs in standard nonhuman primate caging. Temperature in the animal rooms was maintained at approximately 21 °C with an average relative humidity of 50% to 60%. Room lighting was controlled automatically to provide alternating 12-h periods of light and darkness. All monkeys had extensive visual and auditory contact with other animals in the room and were supplied with objects to enrich their environment.

**Glucoregulatory testing.** Glucoregulatory function was determined by FSIGTT according to the modified minimal model protocol as adapted for rhesus monkeys.[2] Immediately after measurement of body weight, monkeys were anesthetized with ketamine (maximum, 15 mg/kg IM) and diazepam (maximum, 1.25 mg/kg IM) with ketamine maintenance (5 to 15 mg/kg IM or IV) to prevent gross limb movement and attempts to roll over or sit up. A catheter was inserted through the saphenous or femoral vein. Pretreatment 2-mL blood samples were taken at −15, −10, −5, and −1 min relative to glucose administration; a 300-mg/kg glucose bolus administered over 1 min; and 2-mL blood samples were drawn at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 min after glucose administration. Tolbutamide (maximum, 5 mg/kg IV) was infused 20 min after glucose administration to induce a second incremental increase in circulating insulin levels. Plasma glucose was measured by the glucose-oxidase method (Yellow Springs Instruments, Yellow Springs, OH). Plasma insulin concentration was measured by using a double-antibody radioimmunoassay (Millipore Corporation, Billerica, MA). Glucose and insulin concentrations were analyzed by using the minimal-model method that describes the dynamics of insulin and glucose during a 3-h FSIGTT.[2] Total glycated hemoglobin was measured by using an affinity column (GlycoTeck, Helena Labs, Beaumont, TX).

**Statistics.** All statistical analyses were performed by using JMP statistical software (SAS Institute, Cary, NC) with significance defined as a $P$ value less than 0.05. For the cross-sectional study, paired $t$ tests were used to analyze data between MPA-treated macaques and age- and weight-matched control animals. For each MPA-treated animal, a group of age- and weight-matched controls (4 to 8 control macaques per MPA-treated animal; Table 1) was identified. The mean for each parameter

**Table 1.** Cross-sectional study results for MPA-treated and matched control macaques

| Macaque | Duration of MPA (mo) | No. of control macaques[a] | Age (y) | | Weight (kg) | | Basal glucose (mg/dL) | | Basal insulin (μU/mL) | | Insulin sensitivity ($\times 10^{-4}$) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | MPA | control | MPA | control | MPA | control | MPA | control | MPA | control |
| C1 | 1.4 | 6 | 22.2 | 22.4 | 7.05 | 8.11 | 73 | 62 | 15 | 36 | 2.40 | 3.90 |
| C2 | 8.0 | 4 | 12.3 | 12.5 | 11.85 | 11.25 | 58 | 60 | 80 | 53 | 0.61 | 2.86 |
| C3 | 8.1 | 5 | 15.6 | 15.3 | 12.71 | 11.00 | 60 | 65 | 93 | 67 | 0.73 | 3.59 |
| C4 | 10.5 | 5 | 14.3 | 14.1 | 6.18 | 6.49 | 56 | 60 | 28 | 24 | 2.20 | 9.30 |
| C5 | 31.1 | 8 | 20.3 | 20.2 | 10.21 | 10.31 | 50 | 62 | 86 | 79 | 2.53 | 3.95 |
| C6 | 36.1 | 6 | 21.3 | 21.3 | 9.66 | 10.19 | 43 | 79 | 45 | 92 | 0.25 | 3.94 |
| *P*[b] | | | 0.57 | | 0.89 | | 0.28 | | 0.96 | | 0.02 | |

[a]Number of healthy age- and weight-matched macaques that were used to calculate means for comparison.
[b]*P* value from paired *t* test of each study subject compared with age- and weight-matched healthy macaque ($n = 4$ to 8 animals per study subject). Statistical significance was defined as $P < 0.05$.

from the matched controls was used for the statistical analyses. In addition, percentage differences in insulin sensitivity between macaques in the cross-sectional study and their matched controls were correlated with time according to MPA treatment, age, and body weight. For the longitudinal study, paired *t* tests were used to compare body weight and glucoregulatory function before and after initiating treatment with MPA.

## Results

**Cross-sectional study.** The 6 macaque subjects did not differ from their matched controls in age, body weight, sex, or basal glucose or insulin levels (Table 1). However insulin sensitivity was significantly lower ($P = 0.02$) in macaques receiving MPA compared with their age- and weight-matched control groups. Specifically, the insulin sensitivity of macaques on MPA was 63% to 1477% (average, 447%; SEM, 215%) lower than values from animals not on MPA. Correlation analyses showed that the greatest predictor of the difference in insulin sensitivity was length of time on MPA, which explained 35% of the variation. Far less of this variation (3% and 2%, respectively) could be explained by the animal's age or body weight.

**Longitudinal study.** Body weight and basal glucose and insulin levels in the 4 macaques followed longitudinally were not significantly different after than before MPA treatment. However insulin sensitivity and glycosylated hemoglobin levels differed significantly ($P = 0.02$ and 0.01, respectively) after compared with before MPA treatment, representing significant declines in glucoregulatory function (Table 2).

## Discussion

Endometriosis is a common finding in laboratory-housed rhesus monkeys. Because of the pain associated with this condition, effective treatment is essential. Although surgery is potentially curative, this approach engenders many difficulties, including incomplete cycle suppression[8] and widespread intraoperative hemorrhage.[12,13] Therefore, medical suppression of estrogen secretion with exogenous progesterone (such as MPA) is often the best option for relief of clinical signs associated with endometriosis. However, the current cross-sectional and longitudinal studies show treatment of endometriosis with MPA, even for a short period of time, in adult female rhesus monkeys leads to deterioration in glucoregulatory function. Specifically, all female macaques from our facility's general colony that were currently being treated with MPA had significantly worse insulin sensitivity than did healthy age- and weight-matched controls. Furthermore, our longitudinal examination revealed that both insulin sensitivity and glycosylated hemoglobin levels were worse after MPA treatment. This finding is particularly notable for the 3 calorically restricted macaques on the current study, given that we have previously shown that caloric restriction prevents diabetes mellitus in rhesus monkeys, and no other calorically restricted animals at our facility ($n = 38$) have developed glucoregulatory impairments.[3]

A positive correlation between physiologic changes in progesterone levels (with estrous cycle) and serum glucose has been described in rodents.[16] Furthermore, the administration of a high dose of exogenous progesterone to obese mice prone to develop diabetes mellitus (db/db mice) led to early onset of the disease. Progesterone-receptor–knockout mice had lower fasting glucose levels and enhanced glucose clearance after glucose administration than did wildtype mice.[9] This difference was believed to be due to higher numbers of β cells in the pancreas in mice that did not have progesterone receptors. Prior work in rhesus macaques has shown that although basal insulin and glucose levels were not altered depending on phase of the menstrual cycle, insulin sensitivity was reduced during the luteal phase, a time of elevated progesterone and relatively low estradiol levels.[10] These influences of phase of the cycle on glucoregulatory endpoints suggest that physiologic levels of estrogen improve glucose regulation, whereas luteal levels of progesterone produce a mild insulin resistance. However, to date, the long-term effects of very high synthetic progesterone levels have not been evaluated in rhesus macaques.

MPA is effective for the treatment of endometriosis due to its progestin effects on the reproductive cycle, specifically the suppression of estrogen secretion and subsequent suppression of endometrial proliferation.[19] However, multiple studies have shown that MPA has a high affinity not only for progesterone receptors but also glucocorticoid and androgen receptors in vivo.[1] The affinity of MPA for glucocorticoid receptors likely explains many of the known side effects of MPA administration (such as weight gain) in humans. Insulin resistance is known to be linked to activation of glucocorticoid receptors, elevated cortisol levels, and inflammation in general.[6]

The specific pathogenesis of diabetes mellitus in humans, monkeys, and other animals is still debated, but it is agreed that at least a subset of persons or animals diagnosed with type 2 diabetes mellitus initially are characterized as insulin-resistant or as having metabolic syndrome.[7] This stage of the disease is characterized by elevations in insulin levels while the patient retains the ability to maintain normal glucose values. Some diabeticians argue that persons and animals at this point in the disease may be the most susceptible to clinical interventions.[6]

**Table 2.** Longitudinal study results.

| Macaque | Duration of MPA (mo) | Age (y) | | Weight (kg) | | Basal glucose (mg/dL) | | Basal insulin (μU/mL) | | Insulin sensitivity ($\times 10^{-4}$) | | Glycosylated hemoglobin | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| L1 | 19.9 | 62 | 79 | 20 | 575 | 62 | 79 | 20 | 575 | 7.00 | 0.72 | 8.8 | 12.3 |
| L2 | 6.0 | 56 | 45 | 14 | 115 | 56 | 45 | 14 | 115 | 4.66 | 1.50 | 7.8 | 10.7 |
| L3 | 9.8 | 60 | 65 | 27 | 39 | 60 | 65 | 27 | 39 | 8.99 | 2.51 | 9.5 | 10.9 |
| L4 | 18.4 | 66 | 67 | 10 | 61 | 66 | 67 | 10 | 61 | 5.03 | 2.77 | 8.1 | 10.6 |
| $P^a$ | | | | | | 0.63 | | 0.25 | | 0.02 | | 0.01 | |

Data represent values for individual macaques before (Pre) and after (Post) treatment with MPA.
[a]Results from paired *t* test of data before and after MPA treatment. Statistical significance was defined as $P < 0.05$.

Weight gain is a known side effect of MPA use in humans, and weight gain can predispose persons to the development of diabetes mellitus. In our experience, significant weight gains have not been noted in rhesus monkeys treated with MPA. Occasionally, the symptoms of endometriosis may have induced weight loss prior to treatment, and a return to predisease weight may occur once MPA is initiated, but MPA-treated monkeys do not appear to show a tendency toward obesity based on body condition assessments. In addition, due to the nature of the research assignment, 4 of the affected macaques (in the longitudinal study) are maintained at a target weight and receive a measured portion of food for weight maintenance. Therefore, weight gain cannot be linked to the development of diabetes mellitus in these animals.

In our experience, the use of long-term MPA appears to be highly correlated with glucoregulatory dysfunction in rhesus monkeys. However, because of ethical concerns regarding the effective treatment of endometriosis, the continued use of progesterone-based therapies such as MPA in rhesus macaques may be warranted until alternative treatments are proven effective. Other progesterone-based therapies likely can result in similar alterations in glucose metabolism as have been noted with the use of MPA, but this outcome has not been studied in nonhuman primates. Alternative hormonal therapies such as danazol or gonadotrophin releasing hormone agonists may be less likely to have the same effect on glucoregulatory function but may result in other undesirable side effects. Danazol effectively induces cycle suppression in macaques,[4] but its side effects have not been fully investigated in nonhuman primates. Danazol is used only infrequently in human cases of endometriosis because of an increased risk of ovarian cancer.[4] In addition, luprolidine, a gonadotrophin releasing hormone agonist, has been used to control endometriosis in macaques. This drug has not been used widely because of its high cost but may be a possible alternative if the effect of MPA on glucoregulatory function is too great.

Surgical treatment should be considered when possible. Short-term use of MPA prior to surgery may reduce the size and severity of lesions and increase the success of surgical treatment for endometriosis in rhesus macaques. The positive correlation between length of time on MPA and severity of glucoregulatory dysfunction suggests that short-term presurgical use may limit the likelihood of developing clinical diabetes. If surgical treatment (ovariectomy) is elected, animals should be monitored closely for recurrence of the disease. Monitoring should include hormone analysis to evaluate reproductive cycling, periodic ultrasonography to evaluate the presence of endometrial cysts, and assessing clinical parameters such as food intake and body weight. Our results emphasize that monitoring basal blood glucose and insulin levels may not be the most effective way to evaluate glucoregulatory function in these animals and that effects on insulin sensitivity and glycosylated hemoglobin are far more revealing.

The reversibility of MPA-induced diabetes mellitus is unknown. Currently, we have discontinued the use of MPA treatment in 2 female rhesus macaques at our facility that are presumed to be in menopause. We will monitor them closely for changes in glucoregulatory function after discontinuation of MPA. Currently, our treatment of choice for endometriosis in rhesus macaques at our facility continues to be MPA, due to the lack of an equally effective alternative therapy. However, all animals undergo extensive pretreatment measurements of glucoregulatory function and will be monitored for decline of glucoregulatory function throughout treatment. Treatment with insulin sensitizers will be considered when warranted, and in some cases, we may elect surgical treatment for endometriosis in lieu of hormonal therapy. We currently are evaluating possible alternative hormonal therapies that may offer effective treatment for endometriosis without altering glucoregulatory function. Future research should continue to explore the effects of MPA on glucoregulatory function to elucidate the mechanism of action of this phenomenon and determine whether these observed effects are reversible after treatment. Additional work should assess whether similar effects on glucoregulatory function occur when other types of progesterone-based therapies are used.

## Acknowledgments

We thank the animal care and veterinary staff of the Wisconsin National Primate Research Center for their ongoing daily care of this colony. We also thank the scientists who allowed this health assessment to be performed coincident with their ongoing research studies. We extend special thanks to Deb Werner Kelln, CVT, and Wendy Newton for their assistance with the performance of glucose tolerance testing and Saverio Capuano 3rd for editing and manuscript preparation assistance.

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