Fertility control

Combined oral contraceptives and body weight: do oral contraceptives cause weight gain? A primate model

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BACKGROUND: The aim of this study was to determine if oral contraceptive (OC) use affects body weight, body composition and metabolism in primates.

METHODS: Reproductive-age female rhesus monkeys of normal and obese BMI were studied to document baseline weight stability, then treated continuously with an OC (dosed to achieve equivalent human serum levels for a 30 μg ethinyl estradiol/150 μg levonorgestrel preparation) for 237 days. Monkeys were monitored for changes in body weight, levels of physical activity (measured by a triaxial Actical accelerometer), food/caloric intake, percent body fat (dual energy X-ray absorptiometry, DEXA) and metabolism (24 h metabolic rate and serum metabolic substrate and hormone concentrations).

RESULTS: All 10 monkeys completed the study protocol with no adverse events. While body weight (−0.73% change) and percent body fat (−1.78% change) of the normal BMI group did not significantly decrease from baseline, obese monkeys showed a significant decrease in body weight (−8.58% change, P < 0.01) and percent body fat (−12.13% change P = 0.02) with OC treatment. In both the obese (P = 0.03) and the normal BMI (P = 0.01) groups, there was a significant increase in basal metabolic rate with OC use. No changes were seen in food intake, activity level or % lean muscle mass with OC use for either BMI-based group.

CONCLUSIONS: Overall, OC use appears to cause a slight increase in basal metabolic rate in female monkeys, leading to a decrease in body weight and percent body fat in obese individuals.

Key words: oral contraceptives / weight gain / BMI / metabolism

Introduction

The USA has the highest unintended pregnancy rate of any developed country (Darroch et al., 2001), with 49% of all pregnancies unintended (Henshaw 1998). Oral contraceptives (OCs) are the most popular form of birth control and discontinuation due to perceived side effects, such as weight gain, plays an important role in contributing to this high unplanned pregnancy rate.

Weight regulation is a major health concern for many women. Weight gain is a common complaint (30–75%) among OC users and has been found to be the leading reason cited for discontinuation of OCs among U.S. women (Oddens et al., 1994; Rosenberg, 1998; Fletcher et al., 2001; Picardo et al., 2003). Many women who stop taking an OC out of concern for weight gain, substitute a less effective method or no method, and increase their risk of unintended pregnancy. Despite the popular notion that OCs lead to weight gain, a recent Cochrane review (2004) of 42 randomized trials found that the available evidence is insufficient to determine if OCs have any effect on weight (Gallo et al., 2004). However, none of the studies in this meta analysis included obese women.

In general, adults tend to gain weight with age (Hedley et al., 2004). This is especially true in the USA where obesity is at epidemic proportions, currently at 30% and rising (WHO, 2006). It is not surprising that women often blame OCs for their weight gain, as OCs may be the only medication women take consistently throughout their reproductive lifetime. Theoretically, the biological mechanism for contraceptive-induced weight gain could be due to fluid retention secondary to mineralocorticoid and/or renin–angiotensin–aldosterone activation and/or an increase in subcutaneous fat secondary to a hormonally induced increase in appetite and food intake (Flegal and Troiano, 2000; Gallo et al., 2004). However, the most likely reason for the growing girth of women in our population is a combination...
of genetic, environmental and lifestyle factors that have nothing to do with OC use (Speroff et al., 1999). This is further supported by a wealth of data in rodent models showing that steroid hormones, in particular estradiol, suppress food intake (Wade and Zucker, 1970; Shinoda et al., 2002).

Detailed studies of the effect of combined hormonal contraceptives on weight gain have not been completed as it is difficult to control for factors such as caloric intake and activity level in women during long-term trials. Non-human primates are ideal subjects in which to examine the role of OCs on body weight since the control of reproductive function, metabolism and food intake are similar in humans and non-human primates (Hotchkiss and Knobil, 1994; Grove et al., 2005; Wagner et al., 2006), and factors such as caloric intake and activity level can be closely controlled and monitored. In this study, we sought to investigate whether OCs influence body weight in normal weight and obese non-human primates while measuring caloric intake, basal metabolic rate, activity level, total energy expenditure, thermic effect of food and serum biomarkers and hormones.

Materials and Methods

All aspects of the study were reviewed and approved by the Oregon National Primate Research Center (ONPRC) Animal Care and Use Committee and were performed according to federal guidelines.

Experimental design

The overall goal of this study was to determine if the use of OCs has an effect on body weight. Two groups of adult female monkeys were selected for the study based on their BMI: a normal BMI group (BMI: range 22.5–27.3 kg/m²; weight: mean 5.76 ± SD 0.58 kg; n = 5) and an obese group (BMI: range 32.5–33.1 kg/m²; weight: mean 8.11 ± SD 0.58 kg; n = 5; Fig. 1). Of note, the obese group was inherently obese and not made so for the purposes of this study. This was a longitudinal study design with 3-month baseline period, an 8-month OC treatment period and a 3-month post-treatment period. Experimental measures were performed before, during, and after treatment.

Figure 1 Examples of the study participants: a normal weight (left panel) and an obese (right panel) rhesus monkey.

A combination OC with 30 μg ethinyl estradiol (EE)/150 μg levonorgestrel (LNG) (Seasonale, Pomona, NY, USA) was dosed in a continuous fashion (no placebo days) for a treatment period of ~8 months (237 days). Dosing studies prior to study initiation were performed for each monkey in order to ensure a comparable human equivalent dose for this OC (EE 145 ± 45 pg/ml, LNG 5.6 ± 1.5 ng/ml) (Kunz et al., 1994; Duramed, 2010). Each monkey had a set dose to achieve this plasma level, which ranged from 1/8 to 1/2 tablet daily. EE and LNG levels were stable over the course of the study, exhibiting a 7.5% and a 10.1% variation, respectively.

Animals

Ten adult reproductive age (8–16 years of age) female rhesus monkeys (Macaca mulatta) living in individual stainless steel cages in a temperature-controlled room (24 ± 2°C) with lights on for 12 h per day (07:00–19:00 h) were studied. Animals were fed two meals a day of Purina LabDiet fiber-balanced monkey chow (No. 5000, Purina Mills, St. Louis, MO, USA) at ~09:30 and 15:30 h. Each animal’s allotment of monkey chow was individualized, based on caloric levels previously determined to provide weight stability. Monkeys were fed 539 ± 25 calories of monkey chow per day, with a range from 473 to 663 calories/day. Monkeys were also provided with portions of fresh fruits, vegetables and other small food items daily as part of the environmental enrichment program at the ONPRC.

Experimental measures

Body weight and length

Body length was measured once at the beginning of the study. Body weight was measured every other day for the entire study, before the morning meal.

Dual energy X-ray absorptiometry scans

Percent body fat and percent lean body mass were determined using dual energy X-ray absorptiometry (DEXA). DEXA’s were performed under Ketaset (ketamine hydrochloride 10 mg/kg IM, Vedco, St. Joseph, MO, USA) sedation and then scanned with a Hologic Dena scanner (Discovery scanner, Hologic Inc., Bedford, MA, USA) in the whole body mode. Animals were scanned at the end of the baseline period (pretreatment) and at the end of the OC treatment period. During the post-treatment period, 5 of 10 animals were scanned, but for technical reasons accurate scans could not be obtained on the remaining five animals.

Food/caloric intake

At the beginning of the initial baseline period the number of calories required to keep each animal’s weight stable was determined by assessing what level of calorie intake was needed to maintain a stable body weight in each animal over a 3-month period. Animals were then maintained on this diet throughout the rest of the study. Food intake was monitored at each meal throughout the study.

Physical activity

Naturally occurring levels of physical activity for each animal were assessed continuously using triaxial Actical accelerometers (Phillips, Phoenix, AZ, USA) using previously published methods (Sullivan et al., 2006). Animals wore a loose-fitting metal collar with an attached metal casing that housed the activity monitor. The monitor was programmed to record total activity counts per minute. Animals were sedated with Ketaset (keta- mine hydrochloride 10 mg/kg IM) and the monitors were downloaded and reprogrammed at least every 45 days.
Metabolic rate
For each monkey, 24-h metabolic rate was measured at the end of the baseline control period, at the end of OC treatment, and again at the end of the post-treatment period (Sullivan et al., 2006). For metabolic rate measurement, each monkey was housed for a 24-h period in a sealed Lexan and stainless steel metabolic chamber (Columbus Instruments, Columbus, OH, USA) and the amount of carbon dioxide produced and oxygen consumed was measured using a computer-controlled indirect open circuit calorimeter (Oxymax system, Columbus Instruments). During metabolic rate measurements, a familiar monkey was housed across from the test animal to ensure that they were in an accustomed social setting. Animals were placed in the chamber at 10:00 h on the testing day and removed at the same time the next day. Prior to testing, each monkey was fed their standard morning meal. A 110 g banana was fed at 15:00 h during metabolic testing, by placing the banana into the metabolic chamber through a small sealed window at the top of the chamber.

Blood samples
Fasting (overnight) blood samples (plasma and serum) were collected every 2–3 weeks throughout the study for measurements of circulating levels of metabolic substrates and hormones, including glucose, insulin and leptin.

Serum assays
Serum glucose concentrations were measured on an YSI 2300 Stat Plus glucose analyzer (Yellow Spring Instruments, Yellow Sprigs OH), with automatic calibration and linear detection to 900 mg/dl. Insulin, leptin and testosterone were measured by the Endocrine Technology and Support Lab, ONPRC (Beaverton, OR, USA) using double-antibody radio-immunoassay (RIA) kits (Millipore-Linco, Bellerica, MA, USA; Insulin: Cat. #HI-14K; Leptin: Cat. #HL-84K; testosterone: DSL-4100, Diagnostic Systems Laboratories, Inc., Webster, TX, USA). The human insulin assay has a range of detection between 2 and 200 mU/mL. The detection limit of the assay at 100 μl sample volume is 2 μU/mL. The leptin assay has a range of detection between 0.5 and 100 ng/ml. The sensitivity of this assay for a 100 μl sample is 0.5 ng/ml. For both hormones, all samples in this study were included in one assay, and the intra-assay variation was 6.51% for the insulin assay and 1.3% for the leptin assay. The sensitivity of the Testosterone assay was 0.05 ng/ml and the intra-coefficient of variation for the assays was 2.23%.

EE and LNG levels were measured by the Endocrine Technology and Support Lab, ONPRC (Beaverton, OR) using RIA kits (Immunometric Ltd, London, UK; EE2: Cat. # IM-1182; LNG: Cat. # IM-115). The EE assay has a range of detection between 78 and 5000 pg/ml, and a detection limit of 100 pg/ml. The LNG assay has a range of detection between 23 and 750 fmol/tube, and a sensitivity of 36 pg/ml. The intra-assay and inter-assay variations for the EE and LNG assays were 6.0 and 7.1% and 6.7 and 9.6%, respectively.

Data analysis
Mean body weight measures for a 1-month period during the baseline period were calculated for each monkey and used as the baseline body weight. For all analyses, normality and homoscedasticity were initially tested and all data met the criteria for using parametric analyses. Repeated-measures ANOVA was used to evaluate differences across time, with specific post hoc analyses performed using Least Significant Difference tests. Data are presented as means ± SE. Alpha values were considered significant if P ≤ 0.05. Statistical analyses were performed with SPSS software, version 16.0 (SPSS, Chicago, IL, USA).

Results

Body weight and length
There was a significant but small decrease in body weight in all monkeys (n = 10) when comparing the baseline period to the end of OC treatment (4.65% change from baseline; from 6.93 ± 0.41 to 6.56 ± 0.32 kg; P = 0.04). Body weight returned to baseline after OC cessation (P = 0.20). Analyzing weight change for each BMI group, the obese group showed a significant decrease in body weight with OC use (−8.58% change from baseline; from 8.11 ± 0.58 to 7.41 ± 0.45 kg; P < 0.01; Fig. 2A), whereas the normal BMI group had a smaller decline that was not statistically significant (−0.73% change from baseline; from 5.76 ± 0.58 to 5.72 ± 0.45 kg; P = 0.80; Fig. 2A).

Dual energy X-ray absorptiometry
There was a significant decrease in percent body fat with OC use when compared with baseline for the entire group (22.8 ± 3.65–15.84 ± 1.53%, P = 0.02). As with body weight, the decrease in body fat was significant in the obese monkeys (32.17 ± 5.15–20.04 ± 2.17%, P = 0.02; Fig. 2B) but not in the normal weight monkeys (13.42 ± 5.15–11.64 ± 2.17%, P = 0.22; Fig. 2B). At the end of the post-treatment period, percent body fat had increased such that there was no difference from baseline percent body fat.
There was no change across the study in lean body mass for the entire group or for either BMI group.

**Food intake**

There was no change in food intake across the study for the entire group or for either BMI group.

**Metabolic rate**

In both the obese (pre-OC 0.85 ± 0.06 Kcal/h/kg, OC use 1.0 ± 0.107 Kcal/h/kg, \( P = 0.03 \)) and the normal BMI (pre-OC 0.83 ± 0.07 Kcal/h/kg, OC use 1.27 ± 0.06 Kcal/h/kg, \( P = 0.01 \)) groups, there was a significant increase in metabolic rate at night (basal metabolic rate) with OC use, that returned to baseline in the post-treatment period (Fig. 3A and B). There were no significant changes in metabolic rate during the day for either group (Fig. 3A and B).

**Physical activity**

At baseline, mean physical activity levels for the entire group were 295 601 ± 141 166 activity counts/day. Although obese animals demonstrated lower activity levels (154 244 ± 47 954 activity counts/day) at baseline than normal BMI animals (436 957 ± 180 750 activity counts/day), the difference was not statistically significant (\( P = 0.11 \)). With OC use, there were no significant changes in activity for the obese monkeys (133 248 ± 45 872 activity counts/day; \( P = 0.33 \)) or normal weight animals (281 806 ± 100 524 activity counts/day; \( P = 0.07 \)). Post-treatment, there continued to be no significant changes in activity levels in either of the groups.

**Serum hormones**

At baseline, no statistical differences in fasting glucose concentrations were found between groups but serum insulin and leptin levels were significantly higher in the obese versus the normal BMI animals (Table I). The obese group had a significant decrease in glucose levels with OC use whereas the normal BMI group had no change. Insulin increased with OC use in both groups but only reached statistical significance for the entire group and the normal BMI group. Leptin levels were similar at all time points in the normal weight group but declined with OC use in the obese BMI group and this trend continued post-OC use as well. Testosterone levels were not different between or within groups at any time point.

**Discussion**

The use of OCs in rhesus monkeys caused a decrease in body weight and percent body fat, resulting from an increase in basal metabolic rate, without an impact on percent lean body mass, food intake or activity levels. Both obese and normal weight monkeys showed increases in basal metabolic rate during OC use; however,
accompanied significant decreases in body weight and percent body fat were found only in the obese group. The decrease in body weight in the obese group was significant (−8.58%) and was accompanied by a decrease in percent body fat and fasting glucose levels, and a trend toward a decrease in plasma leptin concentrations that became significant in the post-treatment period. With OC cessation, the changes in metabolic rate and body weight resolved and returned to baseline levels.

Human studies have not conclusively determined if OCs have a significant impact on body weight in reproductive aged women, but few studies have included obese subjects (Gallo et al., 2004). However, there are a number of human studies with similar findings to our study demonstrating mild to moderate weight loss with OC use (Rosenberg, 1998; Risser et al., 1999; Coney et al., 2001), or at least no weight gain (Berenson and Rahman, 2009; Uras et al., 2009). The use of steroid hormones during menopause has also been reported to cause mild weight loss (Ongphiphadhanakul et al., 1998; Chmouilovsky et al., 1999), a decrease in weight gain (Espeland et al., 1997; Gambacciani et al., 2001) or no effects on body weight (Reubinoff et al., 1995; Salbach et al., 2000; Sumino et al., 2003). Since detailed, controlled long-term metabolic studies are difficult to complete in women, the non-human primate offers the closest model to study this elusive outcome as certain factors such as caloric intake and energy expenditure can be more closely monitored. Non-human primates are particularly good for these complex integrative studies as the regulation of reproductive function, food intake and body weight is very similar to the regulation of these processes in humans (Hotchkiss and Knobil, 1994; Grove et al., 2005).

Our findings in ovary-intact monkeys treated with OCs conclusively show weight loss in obese individuals. Previous studies in ovariectomized monkeys have also shown that estradiol treatment leads to decreased food intake and body weight (Czaja and Goy, 1975; Kemnitz et al., 1986). It is likely that the estrogen content of the OC is responsible for the slight increase in basal metabolic rate and loss of body weight in obese monkeys occurring with OC use. Estrogen is a known modulator of energy homeostasis and in rodents, plays a similar role to leptin by increasing activity and basal metabolic rate and decreasing appetite, body weight and adipose tissue (Gao and Horvath, 2008; Roepeke, 2009). These effects result in weight loss in animals when calories are not increased to compensate. Our study design limited our ability to fully determine if OCs would increase appetite, as we set the maximum food intake available at an amount that provided weight stability at baseline. Not allowing ad libitum food access may provide less of a “real world” human experience, but this design allowed for the examination of OC effects on metabolism and subsequent weight changes due to changes in metabolic rate. It is possible that an increase in appetite could offset the increase in metabolic rate and result in weight gain in some women with a susceptible phenotype. However, the randomized trials that have been performed represent a natural exposure with unrestricted calories, and do not clearly demonstrate a differential effect of OC exposure as a risk factor for weight gain (Gallo et al., 2004). Progestins provided as Injectable contraceptives have been reported to lead to an increase in body weight (Clark et al., 2005; Bonny et al., 2006), but progestins delivered in OCs do not appear to lead to an overall increase in weight in clinical trials in women (Davidsen et al., 2007) and we found no evidence in this study of weight gain with combined OC administration to either the normal weight or obese monkeys. Testosterone levels did not appear to play a role in the weight and metabolic changes observed in the monkeys on OCs as no changes in testosterone levels were found throughout the study in either group. We questioned whether the loss of body fat, but not muscle mass, may have stemmed from androgenic capacity of the OC we chose; however, we did not find evidence for this conclusion.

It is possible that the reason we found a greater decrease in percent body fat in the obese group was that they had more fat stores available for fuel mobilization. It is also possible that weight loss was slower to occur in the normal weight group, but would have occurred eventually if OC treatment had been extended beyond 8 months. There are a number of physiological systems that regulate body weight so body weight loss can be slow because when one system is altered other systems change activity to counteract weight loss (Sullivan and Cameron, 2010). Alternatively, obese animals may have a different endocrine response to OCs compared with normal weight animals, leading to differences in weight loss. We did find differences in serum insulin and leptin between the obese and normal BMI animals, as well as significant changes in these hormones with OC treatment in the obese group. However, the changes in body weight may have led to these hormonal differences rather than the reverse.

Theoretically, our use of continuous OC dosing (no hormone-free interval) may have affected our results. The use of continuous OCs is becoming a common practice in humans to suppress menstruation for both medical and social reasons (Edelman et al., 2009). In humans, continuous OCs have been found to maintain hypothalamic–pituitary–ovarian axis suppression better than cyclic OCs (Birch et al., 2006) and thus also decrease menstrual-associated symptoms (Edelman et al., 2009) but otherwise are seen to be fairly similar to cyclic dosing. We chose to use continuous dosing to better maintain drug exposure in animals during the study. It is possible that our use of continuous OCs may have enhanced the effect of OCs to cause weight and percent body fat loss in obese females.

Along with a significant decrease in body weight and percent body fat, the obese monkeys showed an improvement in metabolic regulation with a trend toward a decrease in circulating leptin with OC use, paralleling the decrease in percent body fat that occurred in these animals during this time. This is not surprising as leptin plays a key role in regulating the size of body fat stores to central nervous system pathways regulating body weight (Porte et al., 2002). Similarly, as the normal weight monkeys had no significant change in weight, circulating leptin levels were stable over the course of the study. The changes in fasting glucose and insulin with OC treatment appear consistent with steroid hormone exposure and, in the obese group, weight loss, but overall do not appear clinically relevant (Ropero et al., 2008; Lopez et al., 2009).

Our results demonstrate that combined OCs increase basal metabolic rate and result in weight loss due to a reduction of body fat but not lean body mass in obese female macaques maintained on a stable diet. None of the animals on OCs showed weight gain. This argues against OC discontinuation for weight loss purposes, as discontinuation places a woman at risk for an unplanned pregnancy, a known cause for significant and rapid weight gain! Further studies need to be performed to demonstrate whether an ad libitum diet affects these findings in obese and normal weight individuals, and to
determine whether progestin-only contraceptives affect weight and metabolism differently.

**Authors’ roles**

Drs A.E., J.T.J. and J.C. significantly contributed to the study design, execution, analysis, manuscript drafting and discussion. Ms M.B. played a key role in study execution, database maintenance, analysis and manuscript drafting.

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