Effects of oral contraceptives on diurnal profiles of insulin, insulin-like growth factor binding protein-1, growth hormone and cortisol in endurance athletes with menstrual disturbance

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BACKGROUND: Menstrual disturbances in female athletes are often explained as a consequence of energy deficiency. Oral contraceptive (OC) treatment may have favorable metabolic effects. We evaluated effects of OCs on diurnal secretions of insulin, insulin-like growth factor binding protein 1 (IGFBP-1), growth hormone (GH) and cortisol in relation to changes in body composition in athletes with menstrual disturbance compared with regularly menstruating athletes and controls.

METHODS: Age- and BMI-matched groups of endurance athletes with menstrual disturbance (OAM, n = 9) and regularly cycling athletes (RM, n = 8) and sedentary controls (CTRL, n = 8) were examined, and hormone levels measured, before and after 8 months of treatment with a low-dose combined OC (30 μg ethinyl estradiol + 150 μg levonorgestrel).

RESULTS: Before OC treatment, the diurnal profile of insulin was lower (P < 0.01) and levels of IGFBP-1 (P < 0.05) and cortisol (P < 0.05) were higher in OAM athletes than in CTRL, whereas GH secretion was higher than in RM athletes (P < 0.05). After treatment, diurnal secretions of these hormones were similar between groups with an increase of IGFBP-1 in the regularly menstruating subjects only (P < 0.001). OC treatment increased body fat mass in OAM athletes (P < 0.01 versus baseline). The change in total fat mass correlated positively with pretreatment diurnal levels of GH (rₛ = 0.67, P < 0.01) and cortisol (rₛ = 0.64, P < 0.01).

CONCLUSIONS: OC treatment in endurance athletes with menstrual disturbance increases body fat mass and results in diurnal levels of insulin, IGFBP-1, GH and cortisol that are comparable to those in regularly menstruating subjects. These results suggest that OCs improve metabolic balance in OAM athletes.

Key words: oral contraceptives / female athletes / menstrual disturbances / insulin-like growth factor binding protein 1 / body fat

Introduction

Menstrual disturbances in female athletes are often explained as a consequence of hypothalamic inhibition owing to energy deficiency. The characteristic hormonal consequences of energy deficiency include disruption of the growth hormone (GH)/insulin-like growth factor (IGF)-I axis with low levels of IGF-I and insulin, whereas the levels of IGF binding protein (IGFBP)-I, GH and cortisol are increased (Laughlin and Yen, 1996; Waters et al., 2001; Rickenlund et al., 2004a). These changes could be regarded as adaptations to a hypometabolic state and are also seen in patients with anorexia nervosa (Gianotti et al., 2002; Stoving et al., 2007). Low IGF-I activity, as well as elevated cortisol secretion, may lead to inhibition of the hypothalamic–pituitary–gonadal axis, which could explain the decreased LH pulsatility in amenorrheic athletes (Laughlin and Yen, 1996; De Souza et al., 2003; Loucks and Thuma, 2003; Rickenlund et al., 2004a).
We have previously demonstrated that oral contraceptive (OC) treatment results in gain in weight and fat mass in athletes with menstrual disturbance but not in regularly menstruating athletes and sedentary controls (Rickenlund et al., 2004b). The largest increase in fat mass was seen in athletes with the lowest amount of body fat before treatment (Rickenlund et al., 2004b). On the basis of these findings, we hypothesized that in irregularly menstruating athletes, OC treatment shifts the energy balance toward anabolism. In comparison, only small changes in body composition were found in regularly menstruating athletes and sedentary controls. The mechanisms by which OC treatment increases fat mass in athletes with menstrual disturbance are not fully established.

Combined estrogen/progestagen OC treatment results in inhibition of the hypothalamic–pituitary–gonadal axis. OCs also up-regulate the liver synthesis of several binding proteins (Song et al., 1989; Wiegratz et al., 2003a). Total levels of cortisol and thyroid hormones will increase owing to increased levels of their binding proteins, whereas the free fractions of these hormones remain essentially unchanged (Wiegratz et al., 2003a, b). Effects of OC treatment on glucoregulatory hormones are less explored, and there is little knowledge about the effects of OCs on IGFBPs (Karlsson et al., 1990; Westwood et al., 1999). However, both second generation and third generation OCs have been demonstrated to decrease levels of IGF-1, whereas IGFBP-3 remains unchanged (Balogh et al., 2000). When investigating the effects of short-term transdermal estradiol (E2) in weight-stable amenorrheic athletes, Waters et al. (2003) reported no change in the levels of GH, IGF-1 and IGFBP-1, whereas IGFBP-3 decreased. However, effects of OC treatment on diurnal hormone levels in athletes have not been studied. We hypothesized that the shift in energy balance by OCs is reflected by changes in diurnal glucoregulatory hormones.

The aim of the present study was to evaluate the effects of OCs on the diurnal profiles of insulin, IGFBP-1, GH and cortisol in relation to changes in body composition in endurance athletes with and without menstrual disturbance and sedentary controls.

Materials and Methods

Subjects

This study included subjects randomly selected from a larger cohort of athletes and sedentary controls (Rickenlund et al., 2003). Female athletes in endurance sports, such as medium- and long-distance running, marathon, orienteering, cross-country skiing and triathlon, were recruited from universities and high schools specializing in sports and at public sports events and championships in Sweden. Inclusion criteria were healthy, non-smoking nulliparous women aged 16–35 years with BMI (kg/m2) 18–24. This study included randomly selected to participate.

Body composition [bone mineral areal density (g/cm2), lean body mass (LBM) and fat mass] was determined by dual energy X-ray absorptiometry.
using the Lunar Model DPX-L equipment (Lunar Radiation, Madison, WI, USA).

The eating disorder inventory-2 (EDI-2) test was used as screening for eating disorders (Gamer, 1991). This test measures 11 parameters: drive for thinness, bulimia, body dissatisfaction, ineffectiveness, perfectionism, interpersonal distrust, interoceptive awareness, amenorrhea, depressiveness, impulsive behavior and social insecurity. The defined EDI score at risk for eating disorders, i.e. a cut-off point of 14 on the drive for thinness subscale (EDI-DT), was used in the evaluation (Gamer, 1991). Furthermore, a 24 h recall of food intake was delivered by all subjects at baseline. The intakes of energy and nutrients were computed using a food database (Dietist XP 3.0).

**Assays**

Fasting serum levels of FSH, LH, E2, thyroid-stimulating hormone (TSH), free thyroid (FT4) and prolactin were determined by commercial time-resolved immunofluorometric assays (TR-IFMAs) from PerkinElmer LifeSciences, Turku, Finland (AutoDELFIA®). Serum concentrations of testosterone and sex hormone-binding globulin (SHBG) were measured by radioimmunoassay (RIA) in untreated serum, using commercial kits obtained from Diagnostic Products Corp., Los Angeles, CA, USA (Coat-a-Count® Testosterone) and Eurodiagnostics AB, MALMO, Sweden (SHBG).

Fasting levels of total IGF-I were determined by RIA after acid ethanol extraction (Nichols Products Corp.). The levels were expressed in μg/l of the World Health Organization (WHO) first International Reference Reagent IGF-I 87/518. Free IGF-I was determined using ultrafiltration by centrifugation as described previously (Frystyk et al., 1994). The dimeric complex of IGF-I and IGFBP-1 (binary complex) and IGFBP-2 were determined by specific TR-IFMAs as described previously (Frystyk et al., 1995, 2002; Krassas et al., 2003). Fasting levels of corticosteroid-binding globulin (CBG) were determined using a commercial RIA (Medgenix Diagnostics SA, Fleurus, Belgium).

Diurnal serum levels of insulin were determined by RIA, using a commercial kit obtained from Pharmacia Diagnostics, Uppsala, Sweden, and expressed as mU/l of the WHO International Reference Preparation 66/304. Serum concentrations of IGFBP-1 were determined by RIA as described by Povoa et al. (1984). The IGFBP-2 and IGFBP-3 cross-reactivity was less than 0.5% and 0.05%, respectively. Diurnal serum concentrations of GH and cortisol were determined by commercial TR-IFMAs obtained from PerkinElmer LifeSciences (AutoDELFIA®). The concentrations of GH were expressed as μg/l of WHO first International GH Reference Preparation 80/505.

Detection limits and within and between assay coefficients of variation were for FSH 0.05 U/l, 2% and 3%; for LH 0.05 U/l, 2% and 2%; for E2 13.6 pg/ml, 5% and 8%; for TSH 0.005 mU/l, 3% and 5%; and for FT4 1.6 pg/ml, 5% and 4%; for prolactin 0.04 μg/l, 2% and 4%; for testosterone 2.8 ng/dl, 6% and 10%; for SHBG 0.005 mg/l, 4% and 8%; for total IGF-I 6 μg/l, 5% and 7%; for free IGF-I 0.050 μg/l, 15% and 20%; for IGFBP-2 10 μg/l, 5% and 12%; for IGFBP-3 20 μg/l, 5% and 15%; for CBG 0.3 μg/l, 4% and 6%; for insulin 2 mIU/l, 6% and 6%; for IGFBP-1 3 μg/l, 3.0% and 10.0%; for GH 0.012 μg/l, 2.0% and 3.3%; and for cortisol 0.6 μg/dl, 1.1% and 2.9%, respectively.

**Results**

**Baseline characteristics**

Baseline characteristics for the study groups are presented in Table I. Athletes and sedentary controls were comparable as regards age, menarcheal age, weight and height. There were no differences in the onset of training, amount of specific endurance training and maximal oxygen uptake between the athlete groups. Levels of FSH were lower in regularly menstruating athletes compared with controls. The OAM group had significantly lower levels of E2 and FT4 than controls and lower levels of prolactin than both regularly menstruating groups. There were no significant differences in hormone values between the three oligomenorrheic and six amenorrheic athletes in the OAM group (data not shown).

None of the subjects reported any eating disorder. Furthermore, no one displayed an EDI-score at risk for eating disorders and the mean EDI-DT score was comparable between groups (OAM 2.1 ± 3.0, RM 2.3 ± 3.7, CTR 0.4 ± 1.1). The 24 h recall showed no significant differences in total caloric intake at baseline between the three groups (OAM 2232 ± 414, RM 2543 ± 573, CTR 2155 ± 450 kcal). However, protein intake was significantly lower in the OAM group compared with the regularly menstruating athletes (84.3 ± 14.5 versus 103.1 ± 17.9, P < 0.05) and fat intake tended to be lower in the OAM athletes compared with the menstruating groups (53.7 ± 25.0 versus 76.2 ± 22.6 g, P = 0.057).

**Effects of OCs on body composition**

Data pertaining to body composition are presented in Table II. At baseline, there was no significant difference in BMI between groups. However, percentage of fat mass was significantly lower, whereas LBM in legs and the ratio of total LBM/fat mass was significantly higher in the OAM group compared with controls. OC treatment resulted in overall increases in BMI and body weight [both F(1,22) = 19.0, P < 0.001] but without significant differences between groups. However, there was a significant interaction regarding change in fat mass. Thus, oligo-/amenorrheic athletes displayed an increase in percentage of fat mass with OC, whereas this variable
remained unchanged in the regularly menstruating groups. There was no significant change in LBM in any group, whereas the ratio of LBM/fat mass ratio was normalized in the OAM group.

### Effects of OCs on fasting levels of IGF-I, IGFBP-2 and CBG

Fasting levels of IGF-I and its binding proteins are shown in Table III. There were no significant differences between groups in fasting levels of total and free IGF-I, IGFBP-2 and binary complex (IGF-I + IGFBP-1) before or during OC treatment. However, there was an overall decrease in levels of free IGF-I and IGFBP-2 by OC treatment. There was also a tendency to an overall increase in binary complex in the pooled cohort ($F(1,22) = 3.5$, $P = 0.07$).

Fasting levels of CBG before treatment were slightly higher in the OAM group compared with controls (OAM 52.7 ± 7.3, RM 50.2 ± 7.9, CTR 44.6 ± 6.5 μg/l, OAM versus CTR, $P < 0.05$). After treatment, there was a general increase in fasting CBG and mean levels were similar in the three groups [OAM 107.2 ± 24.5, RM 111.6 ± 16.7, CTR 110.1 ± 21.3 μg/l, $F(1,22) = 248$, $P < 0.001$].

### Effects of OCs on diurnal secretion of insulin, IGFBP-1, GH and cortisol

Diurnal levels of hormones and IGFBP-1 in OAM, RM and CTR are shown in Table IV. Before OC treatment, OAM displayed significantly lower insulin (AUC and 24 h baseline mean) and higher IGFBP-1 mean
Table III
Fasting levels of total and free IGF-I and IGFBP before and during treatment with OC in OAM athletes, RM athletes and CTRs

| Groups       | Before | During OC | Pretreatment | After OC |
|--------------|--------|-----------|--------------|---------|
| OAM (n=9)    |        |           |              |         |
| Total IGF-I  | 356 ± 104 | 144 ± 43 | 193 ± 43 | 129 ± 38 |
| Free IGF-I   | 139 ± 42  | 129 ± 38  | 193 ± 43 | 129 ± 38 |
| IGFBP-2      | 70 (2.2–15.0) | 18.7 (8.6–28.2) | 18.7 (8.6–28.2) | 18.7 (8.6–28.2) |
| Binary complex | 70 (2.2–15.0) | 18.7 (8.6–28.2) | 18.7 (8.6–28.2) | 18.7 (8.6–28.2) |

Values are expressed as mean ± SD or median (P25–P75). There were no significant differences within and between groups (one-way and two-way ANOVA). Significant overall treatment effects are described in the text. Binary complex is IGF-I + IGFBP-1.

Discussion
We have demonstrated that OC treatment in OAM endurance athletes increases body fat mass and results in diurnal levels of insulin, IGFBP-1, cortisol and GH that are comparable to those in regularly menstruating athletes and controls. The change in fat mass correlated with pretreatment diurnal levels of GH and cortisol, which together with insulin and IGFBP-1 differed significantly between oligo-/amenorrheic athletes and regularly menstruating subjects at baseline.

Before treatment, OAM athletes had lower diurnal levels of insulin and higher levels of IGFBP-1 (mean peak amplitude) and cortisol (AUC and 24 h baseline mean) than regularly menstruating subjects, as well as lower amount of body fat than controls. The production of IGFBP-1 is negatively regulated by insulin (Fernqvist-Forbes et al., 1999) and the low insulin levels in the athletes with menstrual disturbance most likely explain the increased IGFBP-1 secretion. However, free and total IGF-I was not significantly different between OAM athletes and subjects with regular menstruations. Both short-term fasting (Chen et al., 2005) and anorexia nervosa (Gianotti et al., 2002) have...
| Groups          | OAM (n = 9) | RM (n = 8) | CTR (n = 8) |
|-----------------|-------------|------------|-------------|
|                 | Before      | During OC  | Before      | During OC  | Before      | During OC  |
| Insulin (mIU/l) |             |            |             |            |             |            |
| AUC (mIU/l x 24 h) | 312 (209–390) b* | 401 (372–462) | 329 (289–374) | 435 (365–490) | 449 (381–494) | 527 (425–571) |
| 24 h baseline mean | 7.0 ± 2.3 b** | 8.7 ± 3.2 | 8.5 ± 2.0 | 9.0 ± 2.6 | 11.4 ± 3.0 | 12.6 ± 2.4 |
| Peaks/24 h      | 10 (9–12)   | 9 (8–11)   | 10.5 (10–13) | 9 (8.5–10) | 10 (8–11.5) | 10.5 (9–11) |
| Mean peak amplitude | 15.4 (12.1–25.3) | 22.7 (19.7–24.5) | 11.6 (11.1–14.1) | 20.6 (17.1–27.6) | 17.0 (14.6–26.5) | 22.2 (15.6–25.9) |
| IGFBP-1 (mg/l)  |             |            |             |            |             |            |
| AUC (mg/l x 24 h) | 520 (230–808) | 722 (500–844) | 259 (214–387) | 654 (454–1250)*** | 201 (147–358) | 568 (377–702)*** |
| 24 h baseline mean | 10.4 (4.2–14.0) | 12.9 (7.1–22.4) | 4.7 (4.0–5.3) | 9.4 (7.2–29.4) | 3.6 (2.5–6.2) | 12.8 (6.8–18.5) |
| Peaks/24 h      | 5.8 ± 1.9   | 5.3 ± 2.1   | 6.4 ± 1.1   | 5.6 ± 2.5   | 8.2 ± 1.8   | 4.0 ± 1.5 *** |
| Mean peak amplitude | 23.6 ± 13.6 b* | 28.4 ± 11.5 | 16.3 ± 9.2 | 37.2 ± 22.5** | 8.6 ± 3.9 | 29.3 ± 16.7 *** |
| GH (mg/l)       |             |            |             |            |             |            |
| AUC (mg/l x 24 h) | 50.9 (40.7–60.2) | 66.0 (35.2–76.7) | 56.9 (39.0–71.3) | 56.1 (41.9–71.9) | 33.2 (27.0–58.2) | 54.2 (34.7–62.3) |
| 24 h baseline mean | 0.35 (0.29–0.60) a* | 0.72 (0.36–1.07) | 0.16 (0.13–0.24) | 0.23 (0.18–0.85) | 0.15 (0.11–0.22) | 0.22 (0.17–0.35) |
| Peaks/24 h      | 10.0 (9.0–11.0) | 10.0 (9.0–11.0) | 9.0 (8.5–10.0) | 9.0 (8.5–10.0) | 8.0 (7.5–8.5) | 9.0 (8.0–12.0) |
| Mean peak amplitude | 3.6 (3.1–4.3) | 3.2 (2.8–4.8) | 5.4 (3.5–7.1) | 4.8 (4.4–5.7) | 3.5 (2.9–5.0) | 3.9 (3.0–5.4) |
| Cortisol (µg/dl) |             |            |             |            |             |            |
| AUC (µg/dl x 24 h) | 211 ± 41 b* | 353 ± 74 | 173 ± 33 | 305 ± 56 | 161 ± 34 | 293 ± 72 |
| 24 h baseline mean | 5.2 ± 1.1 b* | 9.7 ± 2.4 | 3.8 ± 1.0 | 7.8 ± 2.0 | 3.8 ± 1.1 | 7.8 ± 2.9 |
| Peaks/24 h      | 4.8 ± 1.0   | 3.1 ± 0.6   | 4.2 ± 0.5   | 3.5 ± 1.2   | 5.0 ± 1.5   | 3.9 ± 2.3   |
| Mean peak amplitude | 7.8 (7.2–9.5) | 14.6 (12.9–16.6) | 8.0 (7.1–9.0) | 13.8 (11.7–16.7) | 7.1 (5.9–9.0) | 14.9 (9.1–17.7) |

Values are expressed as mean ± SD or median (P 25–P 75). Significant differences between groups before OC treatment are indicated in the first OAM column as: aOAM versus RM and bOAM versus CTR (one-way ANOVA followed by Fisher's post hoc analysis). Significant differences within groups are indicated in the right column, respectively (two-way ANOVA followed by paired t-test in the case of significant interaction), whereas significant overall treatment effects are described in the text. AUC, area under curve. Significance levels are *P < 0.05, **P < 0.01 and ***P < 0.001.
been shown to be associated with significantly decreased levels of free and total IGF-I. In contrast, more modest reduction in caloric intake appears to have minor or no impact on IGF-I levels (Fontana et al., 2008). This is in agreement with the findings in our OAM athletes who had numerically lower caloric intake and significantly lower protein intake (on average 18%) than the regularly menstruating athletes. Although free IGF-I was lowest in the OAM group, the difference did not reach significance with the limited sample size. The higher GH secretion in OAM athletes may reflect a relative GH resistance as a result of nutritional deficits. This could be explained by the lower insulin secretion, as insulin is an important regulator of the hepatic GH receptor density (Leung et al., 2000).

The women in the present study were treated with an OC containing 30 μg ethinyl estradiol and 150 μg of the androgenic progestagen, levonorgestrel, for a mean period of 7 months. It has been shown from studies of normal subjects of different ages that oral administration of estrogens and androgens have partly opposite effects on the GH–IGF–IGFBP axis (Heald et al., 2005; Rooman et al., 2005; Veldhuis et al., 2005). Oral estrogens impair the metabolic actions of GH in the liver causing a fall in circulating-free IGF-I, which via

**Figure 1** Diurnal profiles of IGFBP-1 before and during treatment with OC (30 μg ethinyl estradiol + 150 μg levonorgestrel) in three representative study individuals: one athlete with OAM, one athlete with RM, and one regularly menstruating CTR.
negative feedback regulation may increase GH secretion (Rooman et al., 2005; Veldhuis et al., 2005). This fall of IGF-I appears to be caused both by depression of post-receptor GH signaling in the hepatocytes and by increase in circulating GH-binding protein, reducing the availability of GH to the receptor (Leung et al., 2004). Furthermore, IGFBP-1 is stimulated and IGFBP-2 is suppressed by oral estrogens. Androgens on the other hand have been reported to stimulate free IGF-I and have no effect on IGFBP-1 and -2 (Rooman et al., 2005).

It has been shown that the decrease in IGF-I during administration of combined OCs containing the androgenic progesterone levonorgestrel is lower than with the anti-androgenic dienogest (Balogh et al., 2000). In the present study, we found no change in fasting levels of total IGF-I but a general decrease in free IGF-I with a non-significant increase in the IGF-I–IGFBP-1 binary complex as well as a decrease in IGFBP-2. Thus, the effects of ethinyl estradiol may have been partly obviated by levonorgestrel.

Diurnal levels of insulin (AUC) increased during OC treatment in all groups. This is most likely a result of decreased insulin sensitivity known to occur during OC treatment (Crook and Godsland, 1998). Regularly menstruating athletes and sedentary controls had a substantial increase in IGFBP-1 (AUC and mean peak amplitude) and a decrease in the ratio of insulin/IGFBP-1. In contrast, this ratio was unchanged in athletes with menstrual disturbance and levels of IGFBP-1 displayed unchanged diurnal variations. Furthermore, there were general increases of GH (AUC), probably attributed to the decrease in free IGF-I. Diurnal levels of cortisol (AUC) were also increased in the three groups, which was most likely the result of a concomitant increase in CBG since free cortisol does not increase during OC treatment (Simunkova et al., 2008). The significant differences between groups before OC treatment in insulin (AUC), IGFBP-1 (mean peak amplitude) and cortisol (AUC and 24 h baseline mean) were abolished after treatment. OCs significantly increased fat mass in athletes with oligo-/amenorrhea but not in regularly menstruating athletes and sedentary controls. The increase in body fat was positively related to diurnal levels of cortisol and GH before treatment. Thus, high pretreatment levels of GH and cortisol indicate reduced energy stores, which can be reversed by OC treatment.

The precise mechanisms for the OC-associated increase in weight and fat mass in the athletes with menstrual disturbance but not in regularly menstruating subject are unknown. Sex steroids may interfere with appetite and metabolic functions. E2 is known to inhibit feeding in animals and to increase the activity of the cholecystokinin (CCK) satiation signaling pathway (Geary, 2001), whereas high-dose progestagens are appetite stimulating (Maltoni et al., 2001). We have previously demonstrated a suppressed secretion of the satiety peptide CCK during OC treatment related to an increase in body fat in young women (Hirschberg et al., 1996). Thus, some women may experience changes in appetite and weight by OC treatment, although studies so far in general have failed to show any effect on body weight and body composition (Franchini et al., 1995; Reubinoff et al., 1995; Lloyd et al., 2002; De Melo et al., 2004). Despite extensive clinical experience of OC treatment, effects on appetite and metabolism still remain to be explored.

In anorexia nervosa and other conditions with severe undernutrition, OC treatment has not been shown to have significant effect on weight recovery (Miller et al., 2006). However, in the present study, none of the subjects suffered from any eating disorder that would restrain food intake. Moreover, similar physical activity was reported during the study period. It is therefore possible that the OC treatment might have brought about a change in appetite and subsequently increased food intake. However, an alternative explanation is that OC treatment induces metabolic changes, such as decreased fat oxidation, resulting in increased fat mass as a source for energy utilization. Subjects with reduced energy stores may be more prone to gain weight than those with adequate nutrition.

A limitation with the present study was the relatively small sample size. However, the study comprised a well-defined cohort of female endurance athletes. The strength of the study was the prospective design by which the subjects were rigorously studied during 8 months of OC treatment.

In summary, this study demonstrates that OC treatment in endurance athletes with menstrual disturbance increases body fat mass and results in diurnal levels of insulin, IGFBP-1, GH and cortisol that are comparable to those in regularly menstruating subjects. These results suggest that OCs improve metabolic balance in OAM athletes. The treatment could therefore be beneficial for athletes with oligo-/amenorrhea resulting from hypothalamic inhibition. However, adequate nutrition should be encouraged as the first line of strategy.

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Oral contraceptives and hormone secretion in athletes

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