The effect of oral contraceptive agents on the basal metabolic rate of young women

BY BRONWYN DIFFEY¹, LEONARD S. PIERS²*, MARIO J. SOARES¹,² AND KERIN O’DEA²

¹The School of Nutrition and Public Health and ²Deakin Institute of Human Nutrition, Deakin University, 336 Glenferrie Road, Malvern VIC 3144, Australia

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The use of oral contraceptive agents by women may be a factor that contributes to the observed inter-individual variability in the BMR. We, therefore, measured the BMR, body build and composition in two groups of young women and also assessed their self-reported level of physical activity. One group had been using oral contraceptive agents for a period of 6 months or more (OCA, n 24), while the other group had never used oral contraceptives (NOCA, n 22). There were no significant differences in age, body build or composition. The absolute BMR in the two groups were not significantly different when compared using an unpaired t test (OCA: 5841 (SD 471) kJ/d. NOCA: 5633 (SD 615) kJ/d). However, using an analysis of covariance, with either body weight or a combination of fat and fat free mass as covariates, the OCA group had a BMR almost 5% higher than that of the NOCA group (OCA: 5871 v. NOCA: 5601 kJ/d; P = 0.002). When those subjects with high self-reported levels of physical activity were excluded, the difference in BMR between the two groups persisted (P = 0.001). An ANOVA of oral contraceptives use and phase of menstrual cycle showed significant differences in BMR with use of oral contraceptives (P = 0.004) but no difference in BMR between phases of the menstrual cycle. In conclusion, the use of oral contraceptive agents deserves consideration when conducting and analysing data from studies on energy metabolism in young women, as it results in a significantly higher BMR.

Basal metabolic rate: Body composition: Oral contraceptive agents

Many studies over the years have demonstrated that the intra-individual variability in the BMR is remarkably small, with a CV of about 3% (Benedict & Cathcart, 1913; Lusk & DuBois, 1924; Benedict, 1935; Berkson & Boothby, 1938; Soares & Shetty, 1987; Henry et al. 1989; Soares et al. 1989a). On the other hand, the inter-individual variability in the BMR is large with a CV of 8% (Henry et al. 1989; Soares et al. 1989a). This factor probably has more importance in the present context of assessing energy requirements in populations from the BMR, either measured or predicted by formulas based on body weight, age and sex. Durnin (1996) attributes most of the inter-individual variability to varying body mass and to some extent body composition. Factors such as hormonal influences and body temperature may modify energy metabolism as well (Durnin, 1996). This is especially true of women where the hormonal changes associated with the menstrual cycle could contribute to the inter-individual variability of the BMR.

The effect of the phase of the menstrual cycle on energy expenditure has been the subject of several studies. Numerous studies have reported a higher BMR (Solomon et al. 1982; Yamashita & Hayashi, 1989; Ferraro et al. 1992; Meijer et al. 1992) or sleeping metabolic rate (Bisdee et al. 1989), or total energy expenditure (Webb, 1986) in the luteal

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(post-ovulatory) phase of the menstrual cycle; while other studies have not (Weststrate, 1993; Piers et al. 1995). The higher BMR in the luteal phase of the menstrual cycle has been ascribed to the thermogenic effect of progesterone. Clearly the contribution of the phase of the menstrual cycle to inter-individual variability of the BMR is still to be resolved.

Another associated hormonal factor that is rarely addressed is the use of oral contraceptive agents by women. If physiological variations in the secretion of oestrogen and progesterone affect the BMR, exogenous administration of these hormones is also likely to have an effect. Despite the fact that over 70 million women worldwide are currently taking the oral contraceptive pill (Guillebaud, 1991), there are no studies that clearly demonstrate what effect, if any, oral contraceptive agents have on the inter-individual variability of the BMR. A recent study by Curtis et al. (1996) demonstrated that the intra-individual variability of the BMR of women using oral contraceptives was small, ranging from 2.4 to 4.9 %, and that the BMR did not exhibit a cyclical variation. However, the study did not attempt to determine if oral contraceptive agents had a stimulatory effect on the BMR. In the present study we compared the BMR of a group of young women who had been taking oral contraceptives for a period of 6 months or more, with the BMR of a group of young women who were not using, and had never used, oral contraceptive agents.

SUBJECTS AND METHODS

Subjects

Forty-six females participated in the study. Subjects were recruited from staff and students of Deakin University, or by personal approach. All were residents of Melbourne, Australia. Subjects were aged between 18 and 31 years, of Caucasian origin, in good health, weight-stable, and had no signs or symptoms of systemic illness.

Study design

BMR, anthropometry and body composition were compared in two groups of women. The first group consisted of women not taking oral contraceptive agents (n = 22; NOCA) of any kind, while the other group consisted of subjects who had been taking oral contraceptive agents (n = 24; OCA) for a period of 6 months, or more.

Anthropometry

Standing height was measured using a SECA stadiometer (model 708, 220; Germany) and recorded to the nearest 1 mm. Body weight was measured with subjects wearing light indoor clothing, without shoes, immediately after voiding, using a digital weighing scale (SECA, model 708, Germany), and recorded to the nearest 100 g. Regional fat distribution was estimated from the waist : hip circumferences ratio, as described by Callaway et al. (1988). Circumference measurements were all made to the nearest mm, without compressing the skin or tissues, using an inflexible fibreglass measuring tape (Callaway et al. 1988).

Skinfold thicknesses at four sites (biceps, triceps, subscapular and supra-iliac) were measured on the right side of the body and recorded to the nearest 0.2 mm (Harrison et al. 1988). Each skinfold was measured in triplicate and the mean of the three measurements...
used for further analyses. The sum of the four skinfold thicknesses was then used in the sex- and age-specific equations of Durnin & Womersley (1974) for the prediction of body density. Percentage body fat was calculated from body density. Fat mass (FM) was then calculated and fat-free mass (FFM) was estimated from the difference between body weight and FM.

Measurements of resistance and reactance for the estimation of FFM were made using a four-terminal impedance plethysmograph (RJL Systems, model 101, Detroit, USA) as described by Lukaski (1987). The lowest resistance and reactance values were recorded and used in the equation of Lukaski et al. (1986) to estimate FFM. FM was determined from the difference between FFM and body weight.

**BMR**

The BMR was measured by indirect calorimetry using a Deltatrac II metabolic monitor (Datex, Division of Instrumentation Corp., Helsinki, Finland), an open-circuit ventilated canopy measurement system. The measurement was conducted under standardized conditions (Schutz, 1984): subjects were lying (1) at complete physical rest; (2) in a thermoneutral environment; (3) 12–14 h after their last meal and a minimum of 8 h of sleep; (4) awake and emotionally undisturbed; and (5) without disease and fever.

The Deltatrac was calibrated using a calibration gas mixture of O$_2$–CO$_2$ (95:5, v/v) (Datex) each morning before the BMR measurements were made. Air-flow rates through the canopy (46.5 litres/min) were checked by means of ethanol-burning tests as described by the manufacturer (Datex), conducted once monthly, during the months of data collection. Performance of the Deltatrac monitor was also checked by monitoring the ratio CO$_2$ produced: O$_2$ consumed, during the ethanol burns. The mean ratio for the last 15 min of the tests was 0.66 (sd 0.04), which was within the manufacturer's recommended range of 0.64–0.69.

In a sub-group of subjects (n 7), BMR and body weight were measured under similar conditions on three separate occasions, 2–4 weeks apart, to establish intra-individual variability.

**Blood pressure and pulse rate**

Systolic and diastolic pressures and pulse rate were measured during the BMR measurement, using a Dinamap portable adult vital signs monitor 8100 (Critikon Inc., Tampa, FL, USA).

**Measurement protocol**

Subjects were required to follow the following instructions: (1) on the evening before the BMR measurement to complete their evening meal at a pre-specified time (at least 12 h before their measurement), after which they were to refrain from eating or drinking anything except water; (2) to abstain from any strenuous exercise for 36 h before the BMR measurement; (3) to get a minimum of 8 h sleep; (4) to refrain from eating or drinking anything on the morning of the BMR measurement, to keep all physical activity to a minimum, not bathe or shower.

On arriving at the laboratory subjects were asked to empty their bladder, then lie down and rest for a minimum of 30 min. During this time the Deltatrac was calibrated. After the
rest period the canopy of the Deltatrac was placed over the head of the subject who was instructed to remain awake and motionless, as far as possible, for the following 35 min. We have previously shown that this protocol yields a BMR not significantly different from a BMR measured immediately on waking, after an overnight stay in the laboratory (Soares et al. 1989a). All subjects listened to the radio station of their choice during the measurement, on a portable transistor radio with earphones. Pulse rate and blood pressure were recorded every 10 min, during the BMR measurement. On completion of the BMR measurement, subjects were asked to empty their bladder again. Their body weight and height were measured. They were then instructed to remove all jewellery and metal, and lie supine. Bioelectrical impedance analysis (BIA) measurements were then made, followed by the other anthropometric measurements (skinfold thicknesses, waist and hip circumferences etc.). All measurements were made at the Toorak campus of Deakin University.

Following the metabolic and anthropometric measurements each subject was interviewed to establish physical activity levels and general health. Questions included current occupation, leisure-time physical activities, personal health history, the use of medications, the day of their menstrual cycle (day 1 being the day of onset of their last menses) and about the use of oral contraceptive agents (brand, duration, regularity). To assess the effect of physical activity on BMR, subjects were retrospectively assigned to one of three groups depending on their self-reported level of physical activity. The groups were: (1) regular vigorous physical activity; (2) regular moderate physical activity and (3) sedentary. 'Regular' was defined as participation in physical activity, for the last 6–8 weeks, at least three times weekly, and for at least 20 min per session. Vigorous or strenuous physical activities included sports, such as football, netball, basketball, squash, athletics, tennis (fast pace or singles); jogging or running, moderate to racing pace; swimming, moderate to racing pace; cycling, moderate to racing pace; weight training; aerobics and or gymnastics; rowing, moderate to racing pace. Moderate physical activity included: cycling slowly, walking fast, volleyball, badminton, tennis moderate pace, swimming slowly, aerobics stretching, cricket, horse-riding, sailing, dancing. Sedentary was defined as performing the activities of daily living, but not participating in any regular physical activity (National Heart Foundation, 1990).

Statistical analysis

Statistical analyses were performed using SPSS for Windows (1994, version 6.1) statistical software package (SPSS Inc., Chicago, IL, USA). Data are expressed as means and standard deviations unless otherwise indicated. Differences were considered significant at the 5 % level (P < 0.05). Comparisons between groups were made using independent t tests and analysis of covariance (ANCOVA). Within-subject comparisons were made using a paired t test or ANOVA for repeated measures.

Ethical approval

Ethical approval for the study was obtained from the Deakin University Ethics Committee. Written informed consent was obtained from all subjects before the start of the measurements.
RESULTS

Oral contraceptive agents

All subjects taking oral contraceptives used either phasic or constant-dose combined pills. The most common phasic-dose pill used was a combination of levonorgestrel (50–125 μg) and ethinylestradiol (30–50 μg). The most common constant dose pill was levonorgestrel (125 μg) and ethinylestradiol (50 μg); other combinations included desogestrel (150 μg) and ethinylestradiol (30 μg); levonorgestrel (150 μg) and ethinylestradiol (30 μg); and norethisterone (500 μg) and ethinylestradiol (35 μg). None of the subjects was on progesterone-only pills.

Subject characteristics

Both groups of subjects were of similar age and build, i.e. height, weight, and BMI were similar. Four subjects from each group were involved in regular vigorous exercise and/or activities and therefore classified as being highly active. Of the remaining subjects there was a greater proportion of sedentary individuals in the OCA group compared with the NOCA group (Table 1). Mean pulse rates and diastolic blood pressure were similar in the two groups; however, systolic blood pressure was significantly (P < 0.01) higher in the OCA group (Table 1).

Table 1. Subject characteristics, body composition, blood pressure (BP), pulse, BMR, and activity levels of women in the study

<table>
<thead>
<tr>
<th></th>
<th>Not using oral contraceptive agent (NOCA) (n 22)</th>
<th>Using oral contraceptive agent (OCA) (n 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age (years)</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.660</td>
<td>0.068</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.6</td>
<td>8.1</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Pulse (beats/min)</td>
<td>58</td>
<td>10</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>108</td>
<td>5</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>57</td>
<td>7</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>68.4</td>
<td>5.7</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>95.6</td>
<td>5.7</td>
</tr>
<tr>
<td>Waist : hip ratio</td>
<td>0.72</td>
<td>0.04</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>43.2</td>
<td>5.7</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>18.4</td>
<td>4.5</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>29.7</td>
<td>5.2</td>
</tr>
<tr>
<td>Absolute BMR (kJ/d)</td>
<td>5633</td>
<td>614</td>
</tr>
<tr>
<td>Sedentary subjects (n)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Moderately active subjects (n)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Highly active subjects (n)</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

*Mean value was significantly different from that for the NOCA group, P < 0.01 (unpaired t test).
†Using bioelectrical impedance analysis and the equation of Lukaski et al. (1986).
Body composition

FFM and FM derived from BIA were similar between groups, when compared using an unpaired *t* test (Table 1). Estimates, based on the sum of four skinfold thicknesses (SFT), of FFM (NOCA: 43·8 (SD 4·7) kg; OCA: 43·2 (SD 3·4) kg) and FM (NOCA: 17·7 (SD 4·2) kg; OCA: 17·3 (SD 4·4) kg) were not significantly different from those estimated by BIA when tested using a paired *t* test (BIA-FFM: 43·1 (SD 4·7) kg; v. SFT-FFM: 43·5 (SD 4·0) kg; *n* 46; *t* 1·42; *df* 45; *P* = 0·161 and BIA-FM: 17·9 (SD 4·7) kg v. SFT-FM: 17·5 (SD 4·3) kg; *n* 46; *t* 1·42; *df* 45; *P* = 0·161). We have, therefore, used the data obtained from BIA measurements for subsequent analyses, unless otherwise indicated.

BMR

In seven subjects (five OCA, two NOCA) measured on three separate occasions, the within-individual CV of the BMR was less than 3 %, while the CV of body-weight change was less than 1 %.

The BMR during the initial 15 min (5756 (SD 525) kJ/d) was highly correlated with (*r* 0·97, *P* = 0·0005), and not significantly different (−0·5 %) from that measured during the final 15 min (5725 (SD 577) kJ/d) of the measurement (paired *t* test; NS).

The BMR in absolute terms was not significantly different between the two groups when tested using an unpaired *t* test (Table 1). However, on an ANCOVA with either body weight (NOCA: 5597 kJ/d v. OCA: 5874 kJ/d; df 1, 43; *F* 11·6; *P* = 0·001) or a combination of FFM and FM as covariates (Table 2), the BMR of the OCA group was significantly higher by 4·9 or 4·8 % respectively, when compared with the NOCA group (Fig. 1). The BMR of the OCA group was also significantly higher than that of the NOCA group, by approximately 5 %, using ANCOVA, with estimates of FFM and FM obtained from either skinfold thicknesses (NOCA: 5596 kJ/d v. OCA: 5875 kJ/d; df 1, 42; *F* 11·9; *P* = 0·001), or the mean of the BIA and skinfold thicknesses (NOCA: 5599 kJ/d v. OCA: 5873 kJ/d; df 1, 42; *F* 11·6; *P* = 0·001).

When highly active subjects were excluded, the BMR, adjusted for FFM and FM, using ANCOVA was still significantly different between the two groups (NOCA: 5548 kJ/d v. OCA: 5849 kJ/d; df 1, 34; *F* 12·0; *P* = 0·001), that of the OCA group being 5·4 % higher than that of the NOCA group.

Of the forty-six subjects studied eight were unsure of the exact day of their menstrual cycle at the time of their BMR measurement and were, therefore, excluded from the following analyses. A two-factor ANCOVA of the BMR, with FFM and FM as covariates, revealed no significant difference in the BMR between the two phases of the menstrual cycle (follicular: *n* 18; 5733 kJ/d v. luteal: *n* 20; 5767 kJ/d), nor was there a significant interaction between the phase of the menstrual cycle and the use of oral contraceptives. However, the difference in BMR between the subjects not taking oral contraceptives (*n* 15; 5568 kJ/d), as compared with those taking them (*n* 23; 5870 kJ/d), was still significant (df 1, 32; *F* 9·7, *P* = 0·004).

DISCUSSION

The International Dietary Energy Consultative Group, in their latest report, suggest a critical re-assessment of factors that explain the degree of variability in the BMR, both intra- and inter-individual (Durnin, 1996). The present study has clearly demonstrated that women who use oral contraceptives have a significantly higher BMR, by almost 5 %, compared with those who do not. This inter-individual factor needs to be accounted for in...
Table 2. Analysis of covariance of the BMR between those taking and those not taking oral contraceptive agents (OCA) with fat mass (FM) and fat-free mass (FFM) as covariates

<table>
<thead>
<tr>
<th>Source of variation</th>
<th>Sum of squares</th>
<th>df</th>
<th>Mean square</th>
<th>F</th>
<th>Significance of F (P &lt; )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covariates</td>
<td>9610864</td>
<td>2</td>
<td>4805431.8</td>
<td>65.4</td>
<td>0.000</td>
</tr>
<tr>
<td>Fat-free mass</td>
<td>6894462</td>
<td>1</td>
<td>6894461.9</td>
<td>93.8</td>
<td>0.000</td>
</tr>
<tr>
<td>Fat mass</td>
<td>2716402</td>
<td>1</td>
<td>2716401.8</td>
<td>37.0</td>
<td>0.000</td>
</tr>
<tr>
<td>OCA</td>
<td>828406</td>
<td>1</td>
<td>828405.8</td>
<td>11.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Residual</td>
<td>3087124</td>
<td>42</td>
<td>73503.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>13526393</td>
<td>45</td>
<td>300586.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Multiple classification analysis: BMR by OCA with FFM and FM as covariates

<table>
<thead>
<tr>
<th>Variable and category</th>
<th>n</th>
<th>Dev’n</th>
<th>Eta*</th>
<th>Unadjusted</th>
<th>Adjusted for independents and covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not taking OCA</td>
<td>22</td>
<td>-108.34</td>
<td>-140.81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taking OCA</td>
<td>24</td>
<td>99.31</td>
<td>129.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple R²</td>
<td></td>
<td>0.19</td>
<td></td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Multiple R</td>
<td></td>
<td>0.772</td>
<td></td>
<td>0.879</td>
<td></td>
</tr>
</tbody>
</table>

* Square root of the proportion of the variance in the dependent variable explained by differences between groups.
† Coefficient of the independent variables (OCA usage) when all independent variables are expressed in standardized (z score) form.

future studies on the BMR. Intra-individual variability, in a smaller group of seven subjects, was less than 3%, and is consistent with other reports (Benedict & Cathcart, 1913; Lusk & DuBois, 1924; Benedict, 1935; Berkson & Boothby, 1938; Soares & Shetty, 1987; Henry et al. 1989; Soares et al. 1989a).

Bisdee et al. (1989) proposed that oral contraceptive agents inhibit the slight increase in the BMR observed in the luteal phase of the menstrual cycle and may hence produce a decline in BMR. A preliminary study investigating the effect of 'progesterone-only' oral contraceptives, in five women, supported these observations and reported a significant decline in the BMR when women were taking the pill (McNeill et al. 1988). This, however, contradicts the well-documented thermogenic effect of progesterone when administered either to normal or ovariectomized women (Barton & Wiesner, 1945; Landau et al. 1955; Kappas & Palmer, 1965). Progesterone has been shown to increase significantly urinary excretion of N, suggesting an increase in protein catabolism (Landau et al. 1955). The subjects in the present study were weight-stable and it is possible that protein turnover in the OCA group was stimulated, resulting in a significantly higher BMR.

It has been documented that individuals engaged in high levels of physical activity have higher BMR, compared with their sedentary counterparts, even when adjusted for FFM (Poehlman et al. 1989). This has been attributed to a fitness effect per se (Poehlman et al. 1989) or a higher energy flux in these individuals (Soares et al. 1989b). The higher BMR observed in the group taking oral contraceptive agents persisted even when those subjects with high levels of physical activity were excluded from the analysis, the adjusted difference in BMR between the two groups being 5.4%. This difference was observed
Fig. 1. Regression of the BMR v. body weight, of women not taking oral contraceptive agents (NOCA, n 22, □ —) and those taking oral contraceptive agents (OCA, n 24, ■ —).

despite the higher proportion of sedentary individuals in the group of women taking oral contraceptive agents.

The females taking oral contraceptives in the present study were found to be taking a variety of different combination oral contraceptives. All contained a mix of synthetically derived progesterone and oestradiol. It has been suggested that the higher oestradiol levels in the luteal phase of the menstrual cycle lead to an elevation in catecholamine levels, possibly due to competitive inhibition of catechol-O-methyl transferase (Davidson et al. 1985); this may similarly occur in response to exogenous oestradiol. The stimulatory effect of catecholamines on energy expenditure is well documented (Sims & Danforth, 1987), and this may be responsible, in part, for the observed difference in BMR between the two groups.

Meijer et al. (1992) observed that three subjects using oral contraceptives had similar increases in their sleeping metabolic rate during the luteal phase of the menstrual cycle, compared with women not using oral contraceptives. They ascribed the lack of any effect on the BMR to the low oestrogen content of the most commonly used oral contraceptive agent used in that country (The Netherlands). They inferred that oral contraceptives with a low oestrogen content do not affect the metabolic rate. However, the majority of the women in the present study were using an oral contraceptive with a low dose of oestrogen (30–50 µg). It is more likely that the small sample size in the study of Meijer et al. (1992) (n 3) led them to this different conclusion.

The pressor effect of oral contraceptive agents has been well documented in the literature. Women taking oral contraceptive agents have been shown to have significantly higher systolic and diastolic blood pressures, compared with those using intra-uterine devices for contraceptive purposes (Task Force on Oral Contraceptives, 1989a; Godsland
et al. 1995). However, it is not clear if this effect is due to the oestrogen (Woods, 1988) or progestogen content of oral contraceptives (Task Force on Oral Contraceptives, 1989b; Whitworth et al. 1992).

The effect of the phase of the menstrual cycle on the BMR in the present study could not be determined, as there were only a few subjects who were not taking oral contraceptives and were aware of the exact day of their menstrual cycle, on the day of the BMR measurement. However, a significantly higher BMR was still observed in those subjects taking oral contraceptive agents, even after the phase of the menstrual cycle was taken into account.

In summary, the present study clearly demonstrated a stimulatory effect of oral contraceptive agents on the BMR. This was accompanied by a small, but significant, pressor effect. The use of oral contraceptive agents deserves consideration when conducting, and analysing data from, studies on energy metabolism in females.

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