Objective: To determine factors associated with resumption of menses (ROM) in adolescents with anorexia nervosa.

Design: Cohort study with 2-year follow-up.

Setting: Tertiary care referral center.

Patients: Consecutive sample of 100 adolescent girls with anorexia nervosa.

Interventions: Body weight, percent body fat, and luteinizing hormone, follicle-stimulating hormone, and estradiol levels were measured at baseline and every 3 months until ROM (defined as 2 or more consecutive spontaneous menstrual cycles). Treatment consisted of a combination of medical, nutritional, and psychiatric intervention aimed at weight gain and resolution of psychological conflicts.

Main Outcome Measures: Body weight, body composition, and hormonal status at ROM.

Results: Menses resumed at a mean (±SD) of 9.4±8.2 months after patients were initially seen and required a weight of 2.05 kg more than the weight at which menses were lost. Mean (±SD) percent of standard body weight at ROM was 91.6±9.1%, and 86% of patients resumed menses within 6 months of achieving this weight. At 1-year follow-up, 47 (68%) of 69 patients had resumed menses and 22 (32%) remained amenorrheic. No significant differences were seen in body weight, body mass index, or percent body fat at follow-up in those who resumed menses by 1 year compared with those who had not. Subjects who remained amenorrheic at 1 year had lower levels of luteinizing hormone (P<.001) and follicle-stimulating hormone (P<.05) at baseline and lower levels of luteinizing hormone (P<.01) and estradiol (P<.001) at follow-up. At follow-up, a serum estradiol level of more than 110 pmol/L (30 pg/mL) was associated with ROM (relative risk, 4.6; 95% confidence interval, 1.9-11.2).

Conclusions: A weight approximately 90% of standard body weight was the average weight at which ROM occurred and is a reasonable treatment goal weight, because 86% of patients who achieved this goal resumed menses within 6 months. Resumption of menses required restoration of hypothalamic-pituitary-ovarian function, which did not depend on the amount of body fat. Serum estradiol levels at follow-up best assess ROM.

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Prolonged amenorrhea in anorexia nervosa has clinical implications for future health and is a source of concern for patients and their families. Early onset and long duration of amenorrhea predispose to osteopenia, which may be irreversible. Most bone acquisition occurs during early childhood and late adolescence. The adolescent years are especially critical because during these years, 60% of peak bone mass is acquired. The development of anorexia nervosa during adolescence may therefore result in morbidity many years after the adolescent has recovered from her eating disorder. The cause of amenorrhea and factors associated with resumption of menses (ROM) have not been elucidated clearly. Frisch and McArthur hypothesized that a critical body weight, representing a critical amount of body fat, was necessary for ROM in states of malnutrition. Loss of body fat was thought to result in decreased levels of circulating estrogens, because aromatization of androgens to estrogens occurs in adipose tissue. In those studies, however, body fat was not measured but was simply calcu-

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PATIENTS AND METHODS

PATIENTS

The study group consisted of 100 adolescent girls with anorexia nervosa (mean age, 16.9 years; range, 12-24 years), who were treated at the Eating Disorders Center of Schneider Children's Hospital, New Hyde Park, NY, between January 1, 1992, and September 30, 1995. All subjects met Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition criteria for anorexia nervosa and had been amenorrheic for at least 3 months before they were seen. Patients with primary amenorrhea, those receiving hormonal treatment, and those who did not return after their initial evaluation were excluded from the study.

The study was approved by the Long Island Jewish Medical Center Institutional Review Board, and written informed consent was obtained from each subject and from a parent when the subject was a minor.

SAMPLE SIZE DETERMINATION

A power analysis was performed to determine the number of subjects required to detect a 15% difference in percent body fat at follow-up between those resuming menses and those remaining amenorrheic. A sample size of 34 subjects in each group was required to detect a 15% difference in body fat with 80% power and an α set at .05. Assuming that one third of subjects would be unavailable for follow-up or would not have completed 1 year of treatment at the time of data analysis, we elected to enroll 100 subjects.

BASELINE ASSESSMENT

At the initial assessment, all patients underwent a baseline structured interview and physical examination. The structured interview assessed eligibility criteria and obtained details about age of menarche, amount of weight lost, duration of illness, and menstrual history, including date of last menstrual period, weight at which menses were lost, sexual activity, and use of contraception. The amount of exercise performed in the preceding month was quantified and recorded. Standing height was measured using a stadiometer. Body weight was measured using a digital scale with subjects wearing underwear and a hospital gown. Patients who were sexually active underwent a pelvic examination. Tri¬cpeps, biceps, subscapular, and suprailiac skinfold measurements were obtained by a nutritionist (J.S.) using Lange skinfold calipers. A single baseline blood sample was drawn for assay of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and prolactin levels. Body weight and hormone levels were measured at about the same time of the day (between 1 and 5 PM) during outpatient office visits.

At the initial visit, subjects were given a series of standardized questionnaires that formally assessed eating attitudes, behaviors, and coexistent depression. These self-administered questionnaires were completed at home and returned at the second visit.

INSTRUMENTS AND DEFINITIONS

Subjects were classified as "excessive exercisers," "moderate exercisers," or "nonexercisers" based on the criteria of De Cove¬rley and Nudelman et al. Excessive exercisers were defined as those women who reported exercising for 6 or more hours per week in the following activities: running, dancing, skiing, swimming, bicycling, aerobics classes, home exercises, or weight training. Exercise was quantified by multiplying the number of minutes (in 30-minute increments) by the frequency per week. Moderate exercisers exercised between 30 minutes and 5⅓ hours per week, and nonexercisers exercised for less than 30 minutes per week.

The Eating Attitudes Test (EAT-26) is a 26-item self-report questionnaire that assesses attitudes toward food, eating, and resulting behaviors. Each item is rated on a 6-point, forced-choice Likert scale ranging from "always" to "never." The responses to each question are weighted with a score of 3, representing the most abnormal response; 2, the next-most abnormal response; and 1, the third-most abnormal response. The final score is the sum of the weighted responses.

RESULTS

One hundred patients were enrolled in the study. Mean age was 16.9±2.8 years (range, 12-24 years). Subjects had lost an average of 13.0±6.7 kg during 17.1±16.6 months. They had been amenorrheic for an average of 11.3±11.6 months. Twenty patients experienced amen¬orrhea before the onset of weight loss. As expected, subjects were markedly underweight (77.3% of SBW for age and height; mean body mass index, 16.3±2.1).

Of the 100 patients enrolled, 69 were followed up for 1 year and 59 of these were followed up for 2 years. Nineteen were unavailable for follow-up and 12 have been in treatment for less than a year (Figure 1). The 69 study subjects did not differ from the 31 subjects who were unavailable for follow-up or who had been in treatment for less than a year with respect to age, height, body weight, or duration of illness. At the 1-year follow-up, 47 (68%) of 69 patients in the study group had resumed menses

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The objective of the present study was to determine the factors associated with ROM in adolescents with anorexia nervosa and, in particular, to clarify the roles of body weight, body fat, exercise, psychological functioning, and hypothalamic-pituitary-ovarian function in ROM. We hypothesized that ROM depended on restoration of hypothalamic-pituitary-ovarian function, which required nutritional rehabilitation and weight gain but could occur independently of percent body fat.
The Eating Disorders Inventory (EDI) is a 91-item self-report measure that assesses drive for thinness, body dissatisfaction, and bulimia and other dimensions associated with eating disorders, including ineffectiveness, perfectionism, interpersonal distrust, interoceptive awareness, and maturity fears. Scores reflect percentiles for normal populations.

The Beck Depression Inventory (BDI) is a 21-item inventory that assesses the emotional and vegetative symptoms of depression. Statements are ranked to reflect the range of severity of depression. Numerical weighted values from 0 (representing absence of depression) to 3 (representing severe depression) are assigned to each statement. The final score is the sum of the weighted scores and can vary from 0 to 63. A score of 16 and above indicates moderate to severe depression. The EAT-26, EDI, and BDI have been shown to be reliable and valid for use in adolescents.

Standard body weight (SBW) was defined as the median weight for height and age using National Center for Health Statistics tables. Percent body fat was calculated from the sum of the 4 skinfold measurements using the method of Durnin. This method has been validated for use in adolescent girls with anorexia nervosa. Body mass index was calculated as the weight in kilograms divided by the square of the height in meters.

Resumption of menses was defined as "the first month of resumed menses in those subjects who went on to have 2 or more consecutive spontaneous menstrual cycles," thereby reducing the possibility of confusing an irregular withdrawal bleed from hypothalamic-pituitary-mediated menstruation.

Hormone Measurements

Luteinizing hormone, FSH, and estradiol levels were measured by double-antibody radioimmunoassay in the pediatric endocrine laboratory using commercially available kits obtained from Diagnostic Products Corp, Los Angeles, Calif. Expected values for the follicular phase of the menstrual cycle are: LH (Second International Reference Population of Human Menopausal Gonadotropin), less than 38 IU/L; FSH (Second International Reference Population of Human Menopausal Gonadotropin), less than 20 IU/L; and estradiol, 37 to 734 pmol/L (10-200 pg/mL). The lower limits of detection for these hormones in our laboratory are: LH, 2 IU/L; FSH, 2 IU/L; and estradiol, 37 pmol/L (10 pg/mL). Values below the lower limit of detection were assigned the value of the lower limit of detection. Interassay and intrasay coefficients of variation for all 3 hormones were less than 8%.

Procedure

Treatment, which was primarily on an outpatient basis, consisted of a combination of medical, nutritional, and psychiatric intervention, as recommended by the Society for Adolescent Medicine, and was aimed at nutritional rehabilitation, weight restoration, and resolution of the underlying psychological conflicts. Exercise was limited in all patients until ROM. Body weight, height, skinfolds, and LH, FSH, and estradiol levels were measured every 3 months until ROM. In those who had resumed menses, hormone levels were measured during the early follicular phase of the menstrual cycle.

Statistical Analysis

The Kruskal-Wallis test was used to compare measures of weight, body mass index, percent body fat, questionnaire scores, exercise ratings, and hormone values in those who had resumed menses with those who remained amenorrheic after 1 year of follow-up. Analysis of covariance (ANCOVA) was used to analyze differences in follow-up measurements after adjusting for baseline values. The chi² test was used for nominal data. Baseline and follow-up measurements were compared using the paired t test. Logistic regression analysis was performed to identify characteristics associated with ROM within 1 year. All variables associated with ROM within 1 year at a probability of P<.10 were considered eligible for inclusion in the logistic regression analysis, which was performed in a forward stepwise manner. All data are expressed as mean±SD.

and 22 (32%) remained amenorrheic. Of those remaining in treatment, 56 (95%) of 59 patients resumed menses by year 2.

In those who resumed menses within 2 years of follow-up, total duration of amenorrhea was 21.8±15.8 months. Resumption of menses occurred at a mean of 9.4±8.2 months after the patients were initially seen, at a weight that on average was 2.05 kg greater than the weight at which menses were lost. Mean percent SBW at ROM was 91.6%±9.1%, and mean percent body fat was 20.5%±3.8%. Although 91.6% of SBW represented the average weight at which menses resumed, considerable variation was seen in individual patients (range, 75%-115%). Twenty-seven (48%) subjects resumed menses at a weight less than 90% of SBW, and 17 (36%) began menstruating within 3 months of attaining this weight. Overall, 48 (86%) subjects resumed menses within 6 months of achieving a weight at or above 90% of SBW (Figure 2).

Subjects who resumed menses and those who remained amenorrheic increased their weight, body mass index, and percent body fat (P<.001 for all) from baseline to follow-up. At the 1-year follow-up, no significant differences were observed in weight, percent SBW, body mass index, or percent body fat in those who had resumed menses compared with those who had not (Table 1). Similarly, no significant differences were observed in percent changes in these variables from baseline to follow-up when the group who resumed menses was compared with the amenorrheic group. Thirty-nine (83%) of 47 patients who resumed menses weighed more than the critical weight for return of menses suggested by Frisch, but so did 16 (73%) of 22 patients who remained amenorrheic (P=.32). Luteinizing hormone (P<.01) and estradiol (P<.001) levels were significantly lower in those who remained amenorrheic (Table 1). Using ANCOVA with baseline values as covariates, LH levels were no longer significantly different between...
the 2 groups, but estradiol levels at follow-up remained lower in the amenorrheic group ($r^2=0.33, F=14.3, P<.001$). In those who resumed menses, estradiol levels increased significantly from baseline to follow-up, 112.7±75.3 pmol/L (30.7±20.5 pg/mL) to 204.8±106.8 pmol/L (55.8±29.1 pg/mL) ($P=.001$), but no change was observed in estradiol levels from baseline to follow-up in those who remained amenorrheic. Ninety percent (36/40) of those who resumed menses, but only 19% (4/21) of those who remained amenorrheic, had a follow-up serum estradiol level above 110 mmol/L (30 pg/mL) (relative risk of resuming menses if serum estradiol ≥110 mmol/L [30 pg/mL], 4.6; 95% confidence interval, 1.9-11.2). Logistic regression analysis was conducted on body weight and LH and estradiol levels, the 3 variables at follow-up that were associated with ROM within 1 year at a probability of less than 0.10. Serum estradiol levels at follow-up were significantly associated with ROM with a model χ² of 28.8 (1 df, $P<.001$), indicating that the β coefficient was significantly different from zero. Addition of body weight and LH did not add to the model. The goodness of fit of this model was 56.208, indicating that the model did not differ significantly from a "perfect" predictive model.

At the initial assessment, compared with those who resumed menses, those who remained amenorrheic 1 year later were similar in age, age of menarche, duration of amenorrhea, duration of illness, and amount of weight lost (Table 2). No differences were observed in the EAT-26, EDI, or BDI scores or in the amount of exercise performed between the 2 groups. Eleven (50%) of 22 subjects in the amenorrheic group were excessive exercisers, but so were 17 (42%) of 41 of those who resumed menses. Six (27%) of 22 subjects who remained amenorrheic at year 1 had experienced amenorrhea before the onset of weight loss, compared with 10 (21%) of 47 of those who resumed menses ($P=.38$). At the initial assessment, those who remained amenorrheic 1 year later were of slightly lower weight ($P=.05$) and lower percent body fat ($P<.05$). Patients who remained amenorrheic had lower FSH levels ($P<.05$) at the initial visit, and all had undetectable LH levels ($P<.001$) (Table 1). The relative risk of remaining amenorrheic at 1 year if the initial LH was undetectable (<2.0 IU/L) was 10 times greater than if the initial LH level was measurable (95% confidence interval, 1.4-69.5).

Body weight, body fat, and LH, FSH, and estradiol levels at the first visit were considered for entry into the stepwise forward logistic regression analysis as predictors of ROM at 1 year. Serum LH levels were entered first and yielded a model χ² of 17.9 (1 df, $P<.001$). Addition of the 4 remaining variables did not increase the predictive value of the model. When the best predictor at the initial assessment (LH level) and the best predictor at follow-up (estradiol level) were entered together into a further regression analysis, only estradiol levels at follow-up were significantly associated with ROM. Serum LH level at the first visit did not increase the predictive power of the follow-up estradiol level.

![Figure 1. Model showing outcome of the 100 subjects enrolled.](image1)

![Figure 2. Time necessary for resumption of menses after achieving goal weight (90% of standard body weight). Study population included 59 adolescent girls treated for anorexia nervosa who were followed up for at least 2 years.](image2)

The patients in our study had been amenorrheic for an average of 21.8 months before ROM, and were therefore at high risk for developing osteopenia. Once treatment was initiated, two thirds of our patients resumed menses within 1 year. Our results show that a weight about 90% of SBW for age and height is the average weight at which ROM occurred and is therefore a reasonable treatment goal weight. This weight was, on average, 2.05 kg above the weight at which menses were lost.

Shomento and Kreipe, using data obtained from 83 patients an average of 74 months after they had been hospitalized for anorexia nervosa, found that the mean weight at ROM was 92.1±7.4% of SBW (determined using the National Center for Health Statistics percentiles). Their data were collected retrospectively by self-report many years after the patients had resumed men-
Table 1. Anthropometric and Hormone Values at Baseline and 1-Year Follow-up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>P</th>
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<tbody>
<tr>
<td>Weight, kg</td>
<td>44.4±5.5</td>
<td>50.4±5.2†</td>
<td>41.2±7.4</td>
<td>47.5±6.5†</td>
<td>.22</td>
</tr>
<tr>
<td>% Standard body weight</td>
<td>80.3±7.7</td>
<td>90.5±8.5†</td>
<td>76.9±12.6</td>
<td>87.8±12.3</td>
<td>.46</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>16.9±1.6</td>
<td>19.2±1.8†</td>
<td>16.2±2.5</td>
<td>18.7±2.5</td>
<td>.45</td>
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<td>Luteinizing hormone, IU/L</td>
<td>4.7±3.9</td>
<td>6.7±4.7†</td>
<td>≤2.0</td>
<td>4.2±3.2†</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Follicle-stimulating hormone, IU/L</td>
<td>7.3±5.9</td>
<td>8.2±3.2</td>
<td>4.2±3.2</td>
<td>8.5±4.9†</td>
<td>.40</td>
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<tr>
<td>Estradiol, pmol/L (pg/mL)</td>
<td>112.7±75.3</td>
<td>204.8±106.8</td>
<td>86.3±42.6</td>
<td>87.7±43.7</td>
<td>&lt;.01</td>
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Table 2. Menstrual History, Exercise, and Psychological Functioning at Initial Assessment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Resumption of Menses (n=47)</th>
<th>Amenorrhea (n=22)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>17.4±3.0</td>
<td>16.4±2.4</td>
<td>.17</td>
</tr>
<tr>
<td>At menarche, y</td>
<td>12.7±1.1</td>
<td>12.7±1.5</td>
<td>.80</td>
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<td>Duration of amenorrhea, mo</td>
<td>12.3±13.6</td>
<td>14.1±12.8</td>
<td>.37</td>
</tr>
<tr>
<td>Duration of illness, mo</td>
<td>20.6±19.0</td>
<td>15.5±17.9</td>
<td>.17</td>
</tr>
<tr>
<td>Weight loss, kg</td>
<td>11.0±5.9</td>
<td>13.7±6.7</td>
<td>.07</td>
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<tr>
<td>EAT-26 score</td>
<td>35.0±17.2</td>
<td>40.5±19.5</td>
<td>.20</td>
</tr>
<tr>
<td>Eating Disorders Inventory</td>
<td>Drive for thinness</td>
<td>77.0±28.9</td>
<td>.58</td>
</tr>
<tr>
<td>Body dissatisfaction</td>
<td>64.9±26.7</td>
<td>55.8±28.6</td>
<td>.25</td>
</tr>
<tr>
<td>Maturity fears</td>
<td>63.0±31.8</td>
<td>55.1±32.7</td>
<td>.54</td>
</tr>
<tr>
<td>BDI score</td>
<td>17.3±8.5</td>
<td>17.7±10.7</td>
<td>.79</td>
</tr>
<tr>
<td>Exercise, h/wk</td>
<td>5.8±6.7</td>
<td>7.3±7.0</td>
<td>.23</td>
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</tbody>
</table>

*Values are given as mean±SD. EAT-26 indicates 26-item Eating Attitudes Test; BDI, Beck Depression Inventory.
†Percentiles for normal populations.

We did not rely on self-report but prospectively followed our patients and actually measured height, weight, and skinfolds at ROM. Despite the more rigorous methods we used, our results are in agreement with those of Shomento and Kreipe and we recommend a treatment goal weight at or above 90% of median weight for height and age.

Our results further indicate that 86% of patients who achieved this goal weight resumed menses within 6 months. In a small percentage of patients, menstrual return occurred a year or more after reaching the treatment goal weight. Resumption of menses requires restoration of hypothalamic-pituitary-ovarian function. In anorexia nervosa, serum estradiol levels are low because of decreased ovarian production secondary to hypothalamic-pituitary suppression, not because of reduced body fat. Our findings do not support the Frisch hypothesis that a critical amount of body fat is necessary for ROM in anorexia nervosa. Others have challenged this hypothesis about the role of body fat in the regulation of onset of menarche or the development of amenorrhea in athletes.

The serum estradiol level at follow-up was closely associated with ROM. In the group of patients who remained amenorrheic, serum estradiol levels did not increase from baseline to follow-up, but in those who resumed menses, estradiol levels increased significantly. A cutoff estradiol level of 110 pmol/L (30 pg/mL) correctly identified 90% of those who resumed menses and 81% of those who remained amenorrheic.

Serum estradiol levels provide a convenient quantitive measure of ovarian function, but there are other ways of assessing reproductive recovery. Treasure et al studied ovarian morphologic characteristics in anorexia nervosa using pelvic ultrasonography and found that the emergence of a dominant follicle on ultrasonography was associated with increased levels of LH and estradiol and the onset of menstruation within a month in 50% of patients. Lai et al studied 26 girls with anorexia nervosa (mean age, 13.5 years) and found that mean ovarian volume on pelvic ultrasonography was low in those who remained amenorrheic a year later, consistent with regression of the ovaries. Ovarian volume in the 50% of patients who resumed menses within a year was normal. Interestingly, these investigators found a weight-for-height ratio necessary for ROM of 96.5% of the mean Tanner-Whitehouse British standards. This weight-for-height ratio is consistent with our findings, because they were using a different reference population, and US youth are slightly larger than their British counterparts.

At their first visit to our center, it was possible to predict which patients were likely to remain amenorrheic after 1 year of treatment. This group of patients is at highest risk for developing osteopenia. This group was more malnourished (lower body weight and lower percent body fat) and had lower gonadotropin levels at the initial visit. In fact, all patients who later remained amenorrheic had undetectable LH levels on their first visit, and subjects with an undetectable LH level at the first visit had a 10 times increased risk of remaining amenorrheic 1 year later.

It is well recognized that in anorexia nervosa, amenorrhea may precede notable weight loss, suggesting a possible biological predisposition to amenorrhea, presumably based on hypothalamic dysfunction. If this hypothalamic dysfunction were primary, we might anticipate that this subgroup of patients who experience amenorrhea before weight loss would be more likely to remain amenorrheic for a longer period. We found that one fifth of our patients experienced amenorrhea before weight loss but that these subjects were no more likely to remain amenorrheic after 1 year of follow-up. Our find-
ings do not support the hypothesis that the hypothalamic dysfunction in anorexia nervosa is primary, and we believe that it is secondary to malnutrition.

Our study has several limitations. First, we were able to follow up only those patients who remained in treatment, and about 20% of our subjects were unavailable for follow-up. It is likely that many of these patients have remained amenorrheic. Second, the questionnaires that assessed eating-related psychopathologic characteristics and depression were performed only at baseline, and it is possible that those who resumed menses were functioning better psychologically than the amenorrheic group after 1 year of treatment. In addition, exercise was curtailed in all patients, but exercise was assessed only at baseline, and those who remained amenorrheic at 1 year could have been exercising more at that time. Furthermore, the amount of exercise was determined by self-report, and patients with anorexia nervosa tend to underreport the amount of exercise performed.

In summary, we found that a weight about 90% of SBW for age and height was the average weight at which ROM occurred, and 86% of patients who achieved this weight resumed menses within 6 months. Resumption of menses did not depend on the amount of body fat, but did require restoration of hypothalamic-pituitary-ovarian function, which was best assessed during follow-up by measuring serum estradiol levels.

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