Inhibitory Effect of Obesity on Gonadotropin, Estradiol, and Inhibin B Levels in Fertile Women

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Abstract

DE PERGOLA, GIOVANNI, SIMONA MALDERA, MASSIMO TARTAGNI, NICOLA PANNACCIULLI, GIUSEPPE LOVERRO, AND RICCARDO GIORGINO. Inhibitory effect of obesity on gonadotropin, estradiol, and inhibin B levels in fertile women. *Obesity.* 2006;14: 1954–1960.

Objective: To examine whether obesity and insulin resistance have an independent effect on the gonadotropin, estradiol, and inhibin B serum levels and follicle count in the early follicular phase of fertile women with a wide range of BMI and without signs of hyperandrogenism.

Research Methods and Procedures: Twenty-two overweight and obese (BMI $\geq$25.0 kg/m^2) women and 10 normal-weight (BMI $<$25.0 kg/m^2) women, all having apparently normal fertility, were studied. Serum concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, inhibin B, and insulin, level of insulin resistance (estimated by homeostasis model assessment for insulin resistance), and follicle count were measured during the early follicular phase (Days 2 to 5 of the menstrual cycle).

Results: Overweight women showed lower FSH ($p < 0.001$), LH ($p < 0.001$), and inhibin B ($p < 0.05$) levels compared with normal-weight women, whereas estradiol concentrations and follicle count were not significantly different between the two groups. When normal-weight and overweight women were examined as a group and multiple regression analyses were performed, estradiol showed a negative association with BMI (or waist circumference) ($p < 0.05$) and a positive correlation with LH ($p < 0.05$) and FSH ($p < 0.05$); inhibin B maintained a positive association only with estradiol ($p < 0.05$); and FSH and LH showed a negative correlation with BMI (or waist circumference) ($p < 0.001$ and $p < 0.01$, respectively).

Discussion: Overweight and obese fertile women have lower FSH, LH, inhibin B, and estradiol levels in the early follicular phase, with a possible direct inhibitory effect of body mass on gonadotropin and estradiol production, independently of age, insulin (concentrations and sensitivity), and other hormones. By contrast, the number of ovary follicles does not seem to be influenced by insulin and body mass in these patients.

Key words: gonadotropins, inhibin B, estradiol, follicle count, menstrual dysfunction

Introduction

Obesity is an increasingly prevalent health hazard and causes many disorders of female reproduction (1,2). In fact, overweight women have a higher incidence of menstrual dysfunction, anovulation, and infertility than other women of reproductive age (1–5). Even though altered pulsatile gonadotropin secretion is a well-defined mechanism in obese patients (6), it is not known whether obesity and/or hyperinsulinemia may have independent effects on the ovary's hormone secretion (e.g., estradiol), mainly in women with normal menstrual cycles and normal ovary appearance, in the absence of hyperandrogenism. Moreover, no information is available about the possible effects of obesity and/or hyperinsulinemia on the ovary's follicle count in the early follicular phase of obese women with normal cycles.

Recently, inhibins have attracted the interest of many researchers. Inhibins are heterodimeric gonadal peptides

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containing an α subunit and βA subunit (inhibin A) or βB subunit (inhibin B) that have been suggested to negatively regulate follicle-stimulating hormone (FSH)[1] secretion, even though there is no direct evidence of this phenomenon (7,8). Locally, inhibins act by enhancing follicle development, thus reflecting the reserve of small antral follicle growth (7,9). Interestingly, in girls affected by anorexia nervosa, weight gain, with an increase in adipose tissue and leptin levels, is paralleled by an increase in inhibin B levels (10).

Inhibin A and inhibin B display different secretory patterns throughout the menstrual cycle. Serum and follicular fluid inhibin B levels are maximal in the early to midfollicular phases, most likely under the stimulation of FSH, whereas peak inhibin A levels are observed in the late follicular and luteal phases (11). In particular, βA subunit (inhibin A) is expressed mainly by the dominant follicle and the corpus luteum, whereas βB subunit (inhibin B) expression predominates in the granulosa cells of the preantral or small antral follicles (12). Little is known about factors regulating the shift in inhibin production when a follicle becomes dominant.

In polycystic ovary syndrome (PCOS), inhibin B levels are inversely correlated with BMI (13–16) and insulin levels (14), suggesting that 1) both body mass and hyperinsulinemia may inhibit inhibin B secretion, and 2) granulosa cell activity or follicular production of inhibin B, and possibly follicle health, are decreased in obesity. Remarkably, insulin suppression has been shown to result in increased inhibin B in the absence of changes in luteinizing hormone (LH), FSH, BMI, sex hormone-binding globulin, and leptin in PCOS women, thus confirming that insulin negatively regulates inhibin B in these patients (13). However, insulin has been demonstrated to have no direct effect on inhibin B secretion in in vitro studies using human granulosa cells from small antral follicles (17). This observation seems to argue against a direct effect of insulin on inhibin B production, making it possible that insulin suppresses inhibin B indirectly by inhibiting follicle and granulosa cell proliferation in women with PCOS (17).

No study has evaluated the independent effect of obesity and hyperinsulinemia on inhibin B levels in women without hyperandrogenism. The only study aimed at examining the effect of obesity and hyperinsulinemia on gonadotropin, estradiol, and inhibin B levels in women with normal menstrual cycles and without PCOS showed a negative effect of obesity on inhibin B levels (13) and no relationship between insulin and inhibin B. However, in that study, ovary follicle number was not evaluated in the early follicular phase, the level of insulin resistance was not estimated, and progesterone levels were not measured in the luteal phase.

In this cross-sectional study, we have tested the hypothesis of a possible independent relationship of obesity and insulin resistance to the serum levels of gonadotropin, estradiol, and inhibin B and to the number of the ovary follicles in the early follicular phase in a population of women with a wide range of BMIs, normal menstrual cycles, normal luteal phase progesterone levels, and no clinical or laboratory sign of hyperandrogenism.

Research Methods and Procedures

Subject Population

This study was approved by the Institutional Review Board of the Bari University Hospital, and informed consent was obtained from all obese patients and control subjects before entry into the study. The investigation was conducted according to the principles expressed in the Declaration of Helsinki.

Twenty-two overweight and obese (BMI $\geq$25.0 kg/m^2) women were recruited consecutively at the Outpatient Clinic for the Study of Obesity, Section of Internal Medicine, Endocrinology, and Metabolic Diseases, Department of Emergency and Organ Transplantation, University of Bari School of Medicine. The control population comprised 10 healthy never-obese women (BMI $\leq$25.0 kg/m^2) recruited among physicians and medical students.

All of the study subjects were normal glucose-tolerant, according to World Health Organization criteria (18), and were judged to be in good health on the basis of physical examination, medical history, routine blood work, urinalysis, and electrocardiogram. Thyroid-stimulating hormone and thyroid hormones were in the normal range in all of the study subjects.

Exclusion criteria were a history of menstrual disturbances (i.e., cycle length $<$25 days or $>$32 days), hirsutism, abnormal serum level of prolactin or androgens (androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulfate, 17-OH-progesterone), cysts at ultrasound, and any hormonal or drug treatments during the 3 months before the study. Moreover, women with luteal phase progesterone levels lower than 5 pg/mL were also excluded from the study.

Anthropometric Data

Weight was measured to the nearest kilogram. Height was determined to the nearest centimeter. BMI was calculated as the weight (kg) divided by the square of height (m). Waist circumference was measured at the narrowest part of the abdomen, i.e., at the natural indentation between the 10th rib and the iliac crest (minimum waist).

Hormonal Immunoassays and Metabolic Parameters

After an overnight fast, blood samples were drawn at 8 AM during the early follicular phase (cycle Day 2, 3, 4, or 5)

[1] Nonstandard abbreviations: FSH, follicle-stimulating hormone; PCOS, polycystic ovary syndrome; LH, luteinizing hormone; $HOMA_{IR}$, homeostasis model assessment for insulin resistance; FBG, fasting blood glucose.

Table 1. General, anthropometric, hormonal, and ovary ultrasound characteristics of NW and OW study subjects

	NW (n = 10)	OW (n = 22)	p
Age (years)	29.8 ± 5.61 (range: 21 to 42)	30.6 ± 8.19	NS
BMI (kg/m^2)	21.4 ± 1.43 (range: 19.7 to 24.0)	35.3 ± 5.61 (range: 26.0 to 47.4)	<0.001
Waist circumference (cm)	73.4 ± 4.86 (range: 63 to 80)	105.2 ± 15.6 (range: 75 to 137)	<0.001
FBG (mg/dL)	85.2 ± 9.99 (range: 70 to 103)	91.8 ± 14.4 (range: 68 to 125)	NS
Fasting insulin (μUI/mL)	13.6 ± 5.77 (range: 9.6 to 28.0)	26.6 ± 15.4 (range: 5.6 to 74.0)	<0.05
$HOMA_{IR}$	2.76 ± 0.94 (range: 1.9 to 4.8)	6.10 ± 3.82 (range: 1.2 to 16.0)	<0.05
FSH (mU/mL)	8.24 ± 1.57 (range: 5.5 to 15.0)	4.45 ± 1.57 (range: 0.25 to 6.8)	<0.001
LH (mU/mL)	6.67 ± 3.07 (range: 3.5 to 13.0)	2.7 ± 1.89 (range: 0.9 to 9.8)	<0.001
Inhibin B (pg/mL)	86.6 ± 43.3 (range: 40 to 181)	55.0 ± 35.2 (range: 9 to 127)	<0.05
Estradiol (pg/mL)	46.0 ± 56.1 (range: 10.6 to 199.0)	27.5 ± 17.5 (range: 5.6 to 67.6)	NS
Number of follicles per ovary	6.05 ± 1.77 (range: 2 to 7)	5.05 ± 2.04 (range: 3 to 10)	NS

NW, normal weight; OW, overweight; FBG, fasting blood glucose; $HOMA_{IR}$, homeostasis model assessment for insulin resistance; FSH, follicle-stimulating hormone; LH, luteinizing hormone; NS, not significant.

to measure FSH, LH, estradiol, inhibin B, and insulin serum levels and plasma glucose, and during the luteal phase (Day 20, 21, or 22 of the menstrual cycle) to measure serum progesterone levels. It is noteworthy that blood samples were collected on the third day of the menstrual cycle in 78% of the women under study, i.e., 17 of 22 obese women and 8 of 10 normal-weight women.

Serum inhibin B was measured by enzyme-linked immunosorbent assay (DSL, Padua, Italy). The detection limit of the inhibin B assay is 7.0 pg/mL. Estradiol, LH, FSH, and progesterone were measured by immunoenzymatic assay (Adaltis, Bologna, Italy). Intra- and inter-assay coefficients of variation were <4.7% and <7.0%, respectively, for all of these determinations. Plasma insulin concentrations were measured by radioimmunoassay (Behring, Scoppitto, Italy), and intra- and inter-assay coefficients of variation were 3.7% and 7.5%, respectively. Results are expressed in μIU/mL. Plasma glucose levels were determined by the glucose-oxidase method (Sclavo, Siena, Italy).

Insulin resistance was assessed by using the homeostasis model assessment for insulin resistance ($HOMA_{IR}$), based on a mathematical correlation between fasting plasma glucose and insulin levels (19).

Transvaginal Ultrasound of the Ovaries

In the morning, during the early follicular phase (cycle Day 2, 3, or 4), a transvaginal ultrasound was performed by means of a transvaginal ultrasound scanner (Toshiba Corp., Tokyo, Japan), with a 5.0-MHz probe. In each ovary, the total number of small follicles (2 to 10 mm) was counted. The total follicle count was the sum of the counts of the left ovary and the right ovary. This number was divided by two to obtain the follicle count per ovary.

Statistical Analysis

Results are presented as means ± standard deviation for all parameters. Variables with a skewed distribution (waist circumference, insulin, LH, estradiol) were logarithmically transformed before analyses to improve the approximation to a Gaussian distribution. Student's t test for independent samples was used to evaluate the differences between the groups for continuous variables. Significant relationships between study parameters were evaluated by Pearson's correlation coefficient. A multiple regression analysis was performed to test the joint effect of different variables on the investigated dependent variable. All statistical analyses were performed using Statistica 6.0 for Windows software (StatSoft, Inc., Tulsa, OK).

Results

Table 1 shows general, anthropometric, hormonal, and morphological ultrasound ovarian characteristics of the study subjects. As expected, overweight women had higher

Table 2. Simple correlations of inhibin B with the other study parameters in NW and OW women

	NW (n = 10)	OW (n = 22)
Age (years)	0.062	−0.196
BMI (kg/m^2)	0.592	−0.220
Waist circumference (cm)	0.000	−0.175
FBG (mg/dL)	−0.288	−0.244
Fasting insulin (μU/mL)	0.894*	−0.043
$HOMA_{IR}$	0.910*	−0.120
FSH (mU/mL)	0.619	−0.001
LH (mU/mL)	0.547	0.135
Estradiol (pg/mL)	0.863*	0.385
Number of follicles	0.373	0.001

NW, normal weight; OW, overweight; FBG, fasting blood glucose; $HOMA_{IR}$, homeostasis model assessment for insulin resistance; FSH, follicle-stimulating hormone; LH, luteinizing hormone.
* $p < 0.001$.

Table 3. Simple correlations of estradiol with the other study parameters in NW and OW women

	NW (n = 10)	OW (n = 22)
Age (years)	0.218	−0.447*
BMI (kg/m^2)	0.330	−0.213
Waist circumference (cm)	0.157	−0.339
FBG (mg/dL)	−0.553	0.014
Fasting insulin (μU/mL)	0.925†	0.188
$HOMA_{IR}$	0.817‡	−0.526*
FSH (mU/mL)	0.650*	0.151
LH (mU/mL)	0.827‡	0.460*
Number of follicles	0.171	0.170

NW, normal weight; OW, overweight; FBG, fasting blood glucose; $HOMA_{IR}$, homeostasis model assessment for insulin resistance; FSH, follicle-stimulating hormone; LH, luteinizing hormone.
* $p < 0.05$; † $p < 0.001$; ‡ $p < 0.01$.

waist circumference, $HOMA_{IR}$, and insulin levels and lower FSH, LH, and inhibin B levels compared with normal-weight controls. Age, fasting blood glucose (FBG), and estradiol levels and the follicle count per ovary were not significantly different between the groups.

Table 2 shows the associations between inhibin B and the other study parameters in the two groups separately. Inhibin B was positively correlated with insulin, $HOMA_{IR}$, and estradiol in normal-weight controls but not in overweight women.

Table 3 shows the associations between estradiol and the other study parameters in the two groups separately. Estradiol was positively correlated with insulin, $HOMA_{IR}$, FSH, LH, and inhibin B in normal-weight women. In overweight women, estradiol was positively associated with LH and negatively correlated with age and $HOMA_{IR}$.

Table 4 shows Pearson's correlation coefficients of inhibin B and estradiol with the other study parameters in the whole population. Inhibin B was correlated with estradiol levels. Both inhibin B and estradiol were positively associated with FSH and LH. Inhibin B was negatively correlated with BMI and waist circumference, and estradiol was negatively correlated with FBG. Both FSH and LH were negatively associated with BMI, waist circumference, and FBG, whereas only LH was negatively correlated with $HOMA_{IR}$. BMI showed a positive association with age, waist circumference, FBG, insulin, and $HOMA_{IR}$. Waist circumference was positively correlated with age, FBG, insulin, and $HOMA_{IR}$.

Multiple Regression Analyses

These analyses were performed by pooling together the data from normal-weight and overweight individuals. When inhibin B was considered as the dependent variable (fitted model: adjusted $R^2 = 0.351$, $p < 0.008$) with age, BMI, $HOMA_{IR}$, FSH, and logarithmically transformed LH and

Table 4. Correlations of inhibin B and estradiol with the other study parameters in the whole population (n = 32)

	Inhibin B (pg/mL)	Estradiol (pg/mL)
Age (years)	−0.179	−0.135
BMI (kg/m^2)	−0.360*	−0.228
Waist (cm)	−0.360*	−0.299
FBG (mg/dL)	−0.319	−0.446*
Fasting insulin (μU/mL)	−0.073	0.136
$HOMA_{IR}$	−0.165	−0.004
FSH (mU/mL)	0.448†	0.597‡
LH (mU/mL)	0.466†	0.580‡
Estradiol (pg/mL)	0.648‡	/

FBG, fasting blood glucose; $HOMA_{IR}$, homeostasis model assessment for insulin resistance; FSH, follicle-stimulating hormone; LH, luteinizing hormone.
* $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$.

Table 5. Multiple regression analysis for the entire population (NW + OW; $n = 32$) with inhibin B (pg/mL) as the dependent variable and age, BMI, $HOMA_{IR}$, and FSH, LH, and estradiol concentrations as independent variables

Variable	β	T(25)	p
Age (years)	0.014	0.084	NS
BMI (kg/m^2)	−0.352	−1.116	NS
$HOMA_{IR}$	0.020	0.093	NS
FSH (mU/mL)	−0.152	−0.590	NS
LH (mU/mL)	−0.046	−0.191	NS
Estradiol (pg/mL)	0.688	3.188	<0.005

NW, normal weight; OW, overweight; $HOMA_{IR}$, homeostasis model assessment for insulin resistance; FSH, follicle-stimulating hormone; LH, luteinizing hormone; NS, not significant.

Table 6. Multiple regression analysis for the entire population (NW + OV; $n = 32$) with estradiol (pg/mL) as the dependent variable and age, BMI, $HOMA_{IR}$, and FSH, LH, and inhibin B concentrations as independent variables

Variable	β	T(25)	p
Age (years)	−0.154	−1.230	NS
BMI (kg/m^2)	−0.403	−2.122	<0.05
$HOMA_{IR}$	0.054	0.316	NS
FSH (mU/mL)	0.467	2.591	<0.05
LH (mU/mL)	0.381	2.182	<0.05
Inhibin B (pg/mL)	0.420	3.182	<0.01

NW, normal weight; OW, overweight; $HOMA_{IR}$, homeostasis model assessment for insulin resistance; FSH, follicle-stimulating hormone; LH, luteinizing hormone; NS, not significant.

estradiol concentrations as independent variables, inhibin B maintained an independent association only with estradiol (Table 5). Similar results were obtained both when BMI was replaced by waist circumference and when $HOMA_{IR}$ was replaced by insulin and glucose (data not shown). On the other hand, the negative correlation between inhibin B levels and BMI (or waist circumference) was not retained when any other variable was introduced into the statistical model (age, insulin, FBG, $HOMA_{IR}$, FSH, LH, or estradiol) (data not shown).

When logarithmically transformed estradiol concentrations were considered as the dependent variable (fitted model: adjusted $R^2 = 0.604$, $p < 0.00{,}003$) with age, BMI, $HOMA_{IR}$, FSH, inhibin B, and logarithmically transformed LH concentrations as independent variables, estradiol maintained an independent negative association with BMI and an independent positive association with FSH, LH, and inhibin B (Table 6). Similar results were obtained both when BMI was replaced by waist circumference and when $HOMA_{IR}$ was replaced by insulin and glucose (data not shown).

When FSH was considered as the dependent variable (fitted model: adjusted $R^2 = 0.607$, $p < 0.00{,}006$) with age, BMI, $HOMA_{IR}$, FBG, insulin, inhibin B, and logarithmically transformed estradiol concentrations as independent variables, FSH maintained an independent negative association with BMI (Table 7). Similar results were obtained when BMI was replaced by waist circumference.

When logarithmically transformed LH concentrations were considered as the dependent variable (fitted model: adjusted $R^2 = 0.537$, $p < 0.00{,}035$) with age, BMI, $HOMA_{IR}$, FBG, insulin, inhibin B, and logarithmically transformed estradiol concentrations as independent variables, LH maintained its negative association with BMI and positive correlation with estradiol (Table 8). Similar results were obtained when BMI was replaced by waist circumference.

Discussion

This cross-sectional study, performed in 10 normal-weight and 22 overweight or obese women with normal menstrual cycles who were referred to our Obesity Center for weight loss, was aimed at examining the possible independent effects of body mass and insulin levels on the

Table 7. Multiple regression analysis for the entire population (NW + OV; $n = 32$) with FSH (mU/mL) as the dependent variable and age, BMI, $HOMA_{IR}$, and FBG, insulin, inhibin B, and estradiol concentrations as independent variables

Variable	β	T(25)	p
Age (years)	0.223	1.650	NS
BMI (kg/m^2)	−0.777	−4.146	<0.001
$HOMA_{IR}$	0.661	0.595	NS
FBG (mg/dL)	−0.231	−0.713	NS
Fasting insulin (μU/mL)	−0.399	−0.395	NS
Inhibin B (pg/mL)	−0.077	−0.490	NS
Estradiol (pg/mL)	0.453	2.600	NS

NW, normal weight; OW, overweight; FBG, fasting blood glucose; $HOMA_{IR}$, homeostasis model assessment for insulin resistance; FSH, follicle-stimulating hormone; LH, luteinizing hormone; NS, not significant.

Table 8. Multiple regression analysis for the entire population (NW + OV; $n = 32$) with LH (mU/mL) as the dependent variable and age, BMI, $HOMA_{IR}$, and FBG, insulin, inhibin B, and estradiol concentrations as independent variables

Variable	β	T(25)	p
Age (years)	0.138	0.950	NS
BMI (kg/m^2)	−0.595	−2.939	<0.01
$HOMA_{IR}$	−0.028	0.027	NS
FBG (mg/dL)	0.009	−0.713	NS
Fasting insulin (μU/mL)	0.009	0.008	NS
Inhibin B (pg/mL)	−0.045	−0.267	NS
Estradiol (pg/mL)	0.496	2.628	<0.01

NW, normal weight; OW, overweight; FBG, fasting blood glucose; $HOMA_{IR}$, homeostasis model assessment for insulin resistance; FSH, follicle-stimulating hormone; LH, luteinizing hormone; NS, not significant.

function of the pituitary-ovary axis, as investigated by measuring the FSH, LH, estradiol, and inhibin B plasma levels and the number of ovary follicles in the early follicular phase. To the best of our knowledge, this is the first study evaluating these parameters in the early follicular phase in normally ovulating overweight women with regular menstrual cycles and neither clinical nor hormonal signs of hyperandrogenism. Remarkably, this study shows that overweight women have lower inhibin B, FSH, and LH levels. Consistently, circulating levels of these hormones were negatively correlated with indices of body mass and fat distribution, i.e., BMI and waist circumference. Estradiol showed a tendency to be lower in overweight than in normal-weight women and to be inversely correlated with BMI in the whole study population ($n = 32$). Moreover, estradiol was independently associated with BMI (or waist circumference), after adjustment for possible confounders, such as age, gonadotropins, FBG, and insulin resistance (or insulin levels).

We also sought to determine whether the inhibitory effect of obesity is exerted primarily on the hypothalamus-pituitary axis, on the ovary, or both. When multiple regression analyses were performed, FSH and LH levels maintained an inverse association with BMI (or waist circumference), independently of age, insulin resistance (or insulin levels), estradiol, and inhibin B. This indicates that body mass per se may have an inhibitory effect on gonadotropin secretion. These findings are consistent with previous studies showing an altered pulsatile gonadotropin secretion in obese patients (6). In addition, the negative relationship between estradiol and BMI (or waist circumference) was maintained independently of FSH and LH levels, thus indicating that body mass may have a direct inhibitory effect on estradiol production by the ovary, independently of LH and insulin levels. On the other hand, inhibin B seems to be less sensitive to the effects of obesity. In fact, its negative correlation with BMI and waist circumference was not retained after adjustment for possible confounders.

It is noteworthy that all study subjects had regular menstrual cycles and progesterone levels, regardless of possible effects of excess body fat on FSH, LH, estradiol, and inhibin B. Therefore, we may speculate that, despite possible negative effects of obesity on hormonal secretions, additional defects, such as genetic and/or psychological factors, hyperandrogenism, or insulin resistance, are needed to impair folliculogenesis and fertility in overweight and obese women. This suggestion is reinforced by the finding that follicle count was not significantly different between normal-weight and overweight women, thus confirming that ovarian follicle reserve is less influenced by obesity than ovarian endocrine activity.

A second important issue is the relationship between insulin resistance and the pituitary-ovary axis. Insulin is commonly believed to inhibit folliculogenesis (13). In the present study, insulin or $HOMA_{IR}$ did not show any significant relationships with inhibin B or estradiol levels, either in simple correlation or in multiple regression analyses. These findings are consistent with previous in vitro studies on human granulosa cells from small antral follicles showing that insulin has no direct effects on inhibin B secretion (17). These data, obtained in women with normal FBG and normal glucose tolerance, seem to exclude a direct role of hyperinsulinemia on inhibin B or estradiol production, at least in women without PCOS.

Hence, we suggest that hyperinsulinemia and/or insulin resistance may exert an inhibitory effect on estradiol secretion but is not sufficient to cause infertility or diseases, such as PCOS, that possibly need additional factors (genetic disturbances of steroidogenesis, etc.) to become clinically overt.

The cross-sectional design and the lack of a direct measurement of body fat are possible limitations of this study.

In conclusion, the present study shows that overweight women have lower gonadotropin, estradiol, and inhibin B levels and suggests a direct inhibitory effect of body mass on FSH, LH, and estradiol production. However, it shows that these alterations are not sufficient to reduce the number of follicles and fertility in women with simple obesity and normal menstrual cycles.

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