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**Serum FSH level is lower in dysovulating than in ovulating non-PCOS obese women, independently of body-mass index**  
**Les taux sériques de FSH sont diminués chez les patientes obèses dysovulantes sans SOPK, indépendamment de l'indice de masse corporelle**

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## **Abstract**

**Objectives:** The prevalence of ovulation disorder (OD) is 3-fold higher in obese than normal-weight women. Most ODs are associated with concomitant polycystic ovary syndrome (PCOS), but obesity by itself can cause OD, through mechanisms that remain poorly documented. The literature on obese non-PCOS women with OD is sparse. The aim of the present study was to analyze a population of obese non-PCOS women with OD to shed further light on the mechanism of ovulation disorder.

**Material and methods:** This retrospective observational study of infertile obese women without PCOS compared a control group without OD (n=45) to a study group with OD (n=30) (OD group). Clinical, hormonal, and ultrasound characteristics were collected between cycle days 2 and 5. Women older than 37 years and women with PCOM (polycystic ovarian morphology) or hormonal disorder were excluded.

**Results:** Body-mass index (BMI) was significantly higher in the OD group, as were waist circumference and insulin and leptin serum levels. Conversely, serum follicle stimulating hormone (FSH) levels were significantly lower. After adjustment for BMI, only serum FSH level remained significantly different between the 2 groups. Discriminant analysis suggested that FSH may have a much stronger effect on OD than BMI.

**Conclusion:** Low serum FSH level may contribute to OD in some obese women, independently of BMI. The pathophysiological mechanism of this finding and its impact on therapeutic strategies must be clarified.

## **Keywords**

Obese women; ovulation disorder; FSH; BMI; leptin

## **Résumé**

**Objectif :** La prévalence des troubles de l'ovulation (TO) est 3 fois plus élevée chez les femmes obèses que chez les femmes de poids normal. La plupart de ces TO sont liés à un syndrome des ovaires polykystiques concomitant (SOPK), mais l'obésité peut à elle seule provoquer un TO, à travers des mécanismes qui restent mal documentés. En effet, la littérature sur les femmes obèses sans SOPK avec TO est très faible. Le but de notre travail était d'étudier une population de femmes obèses dysovulantes sans SOPK afin de mieux préciser le mécanisme de la dysovulation.

**Matériels et méthodes :** Cette étude observationnelle rétrospective de femmes obèses infertiles sans SOPK a comparé un groupe témoin sans TO (n = 45) à celui avec TO (n = 30) (groupe TO). Les caractéristiques cliniques, hormonales et échographiques ont été recueillies entre les jours 2 et 5 du cycle. Les femmes âgées de plus de 37 ans ainsi que celles ayant des ovaires multifolliculaires ou des troubles hormonaux ont été exclues.

**Résultats :** L'indice de masse corporelle (IMC) était significativement plus élevé dans le groupe TO, tout comme le tour de taille et les taux sériques d'insuline et de leptine. À l'inverse, leur taux d'hormone folliculo-stimulante (FSH) était significativement plus bas. Après ajustement pour l'IMC, seul le taux de FSH sérique restait significativement différent entre les 2 groupes. L'analyse discriminante suggérait que la FSH pouvait avoir un effet beaucoup plus important sur la dysovulation que l'IMC.

**Conclusion :** Un faible taux de FSH sérique pourrait contribuer aux troubles de l'ovulation chez certaines femmes obèses, indépendamment de l'IMC. Le

mécanisme physiopathologique de ce résultat et son impact sur les stratégies thérapeutiques doivent être clarifiés.

**Mots-clés :**

Femmes obèses ; dysovulation ; FSH ; IMC ; leptine

**BACKGROUND**

According to the World Health Organization in 2014, around 1.9 billion people over 18 years of age were overweight, 600 million of them were obese, that is, 13% of the world's adult population [1]. Obesity is a real problem of modern society and is a major public health concern. Its frequency is steadily increasing: the world's obese population has more than doubled since 1980 [1]. According to a national epidemiological study on overweight and obesity in 2012, the prevalence of obesity in women of reproductive age in France was 6% for those aged 18 to 24 years and 11.1% of those 25 to 34 [2].

The negative impact of obesity on spontaneous fertility is well documented [3,4]. Obese women face a risk of infertility up to three times higher than women with normal body mass index (BMI) [5]. Time to conception is 3 months longer in overweight women and 9 months longer in obese women than in normal-weight women [6]. Obesity is also associated with a higher risk of failure of assisted reproductive technologies [7].

The negative impact of obesity on fertility occurs at different levels. Hormonal and inflammatory disorders due to obesity may impair oocyte quality and maturation, and endometrial quality, as well as aggravate the manifestations of polycystic ovary syndrome (PCOS) [3,8]. Obese women have a risk of ovulation disorders (OD) three times higher than normal-weight women [9], mostly due to PCOS.

Although the impact of obesity on male fertility has been studied extensively [10-12], data about cycle disorders in obese women with no disorders other than overweight are still sparse. Most studies do not differentiate between obese women with or without PCOS. Thus it is still unclear how obesity alone causes OD. The objective of this work was to compare 2 groups of obese women without PCOS, PCOM (polycystic ovarian morphology), or other hormonal issues: one group with OD (n=30) and the other without OD (n=45).

## **METHODS**

This descriptive, retrospective study analyzed data collected from the department of Endocrine Gynecology at our University Hospital between 2011 and 2014. It compares two groups of infertile obese women without PCOS: a group with OD (OD group, n=30) and another without OD (control group, n=45).

All women had previously consented to the use of their clinical, laboratory, and ultrasound data for research purposes. This study was approved by the Institutional Review Board of the University Hospital.

## **POPULATION**

Seventy-five obese women (BMI > 30 kg/m<sup>2</sup>) were included. Exclusion criteria were: age > 37 years (to prevent confounding by potential diminished ovarian reserve), premature ovarian failure (amenorrhea > 4 months and repeated basal FSH >25 IU/L) [13], PCOS (defined by the modified Rotterdam classification [14]), hyperprolactinemia, severe thyroid dysfunction, Cushing syndrome, follicle number per ovary (FNPO) > 18 (threshold values for PCOM/PCOS, according to our in-house threshold) [14].

The OD group included 30 obese women with OD, which was defined by: short cycles (<25 days) or long cycles (>35 days) or spaniomenorrhea (<8 cycles per year) or primary or secondary amenorrhea.

The control group included 45 obese women with regular cycles (25-35 days), normal ovarian assessment (laboratory and ultrasound), and with tubal or male infertility.

## METHODS

All women underwent a clinical examination between cycle days 2 and 5 (spontaneous cycle or triggered with a progesterone challenge test). Blood samples were collected on the same day for assays. Blood tests included the radioimmunoassay of serum LH, FSH, estradiol, AMH, androstenedione, DHAS (serum dehydroepiandrosterone sulfate), testosterone, sex hormone-binding protein, 17-hydroxyprogesterone, leptin, and insulin, as previously described [15,16]. Serum AMH levels were measured with the enzyme immunoassay AMH-EIA (ref A16507) from Beckman Coulter Immunotech (Villepinte, France), with an analytical range between 0 and 150 ng/ml and a functional sensitivity of 0.4 ng/ml. A pelvic ultrasound was performed at the same time with a Voluson E8 Expert (GE Systems) with vaginal probe frequency of 5-9 MHz. The ovarian area and FNPO (follicles between 2-9 mm in diameter) were measured as previously described [17].

## STATISTICS

Continuous variables had a non-Gaussian distribution and were compared with the non-parametric Mann Whitney test. Covariance analysis and discriminant analysis were also carried out to study the confounding effect of BMI. Data analysis was performed with SPSS software (Statistical Package for the Social Sciences, version 22.0, Chicago Il, USA). Results were considered significant when  $p < 0.05$ .

## RESULTS

Table 1 reports the clinical, laboratory, and ultrasound characteristics of the 2 groups. BMI, waist circumference, insulin and leptin levels were significantly higher in the OD group than in the control group, and FSH levels significantly lower. After covariance analysis to adjust for BMI, only serum FSH values were significantly lower in the OD group than in controls ( $P<0.001$ ). The other differences were no longer significant. Discriminant analysis, with OD as a binary (i.e., yes/no) dependent variable and BMI, FSH, leptin, insulin and waist circumference as independent variables yielded two significant models: the first included only FSH and the second FSH and BMI. The first model accounted, for 36% of the total variance of OD, and the second for 44%.

## DISCUSSION

To our knowledge, this study is the first to report significantly lower FSH levels in non PCOS obese women with, compared to without, OD, in infertile couples. Those women had also a higher BMI, which appeared to be independently associated with OD according to our discriminant analysis. The effect of BMI was, nonetheless, much weaker than that of FSH, as the model including both parameters increased the portion of the total variance of OD only slightly (+8%) over that of the model including only FSH (36%). Our analysis thus uncovered a relative FSH deficiency in obese women with OD that may contribute to OD independently of BMI and other markers of obesity.

This finding disagrees with experimental data from rodents. In obese murine models, OD has been linked to hypogonadotropic hypogonadism, mediated by hyperleptinemia [18,19]. Leptin is a satiety hormone, secreted by adipocytes [20, 21].

It affects reproductive functions via ovarian and hypothalamic receptors [22]. Obesity is associated with high serum leptin levels, which dysregulate GnRH secretion [23,24] and abnormalities in ovarian steroidogenesis [25] and folliculogenesis [26]. In obese rats, hyperleptinemia increases the secretion of neuropeptide Y, which in turn decreases pulsatile GnRH secretion [27] and leads to hypogonadotropic hypogonadism (low FSH and LH levels) [18]. In our study, however, the OD and non-OD groups did not differ for LH or leptin levels after adjustment for BMI.

Obesity is also associated with higher concentration of adipokines and inflammatory factors, such as adiponectin, interleukin 6, PAI1 (plasminogen activator inhibitor type 1), and TNF $\alpha$  [28]. Some authors report that these factors negatively affect gonadotropin secretion or ovulation or both [29-31]. According to Wang [32], women resistant to clomiphene citrate have higher levels of C-reactive protein and chemokine than women sensitive to it. Further studies are needed to confirm and explain the role of inflammatory factors in the OD of some obese women.

The difference in BMI does not by itself explain the difference in FSH levels between the 2 groups, as demonstrated by the discriminant analysis. BMI and FSH each independently explain OD. Previous studies have already shown significantly lower FSH levels in PCOS patients with OD, even in lean subjects [33,34].

This low concentration is still not completely understood. Some authors have suggested that a pathological increase in the frequency of GnRH pulses leads to higher levels of LH than FSH [35]. This relative deficit of FSH might thus attenuate the aromatization of androgens to estrogens and thereby inhibit follicular maturation and ovulation [36]. This subtle decrease in FSH might partially explain the OD. We can go further and hypothesize that low FSH levels might no longer be able to counteract folliculogenesis-inhibiting factors, such as AMH [37], which could cause

defective selection of the dominant follicle and thus result in OD. In this situation, the addition of exogenous FSH or anti-estrogens should restore ovulation in the same way as in patients with PCOS. The underlying problem is the management and safety of pregnancy in situations of high obesity. In addition, it is possible that the usual doses of the therapies are to be increased in these patients with a larger volume of distribution.

FSH levels may thus be the cause of OD in obese women with OD. Conversely, however, low FSH levels might be a consequence of OD. Because no corpus luteum is developed, no luteolysis occurs. Accordingly, there is no decrease in inhibin A and estradiol levels, no intercytic elevation of FSH, and therefore a low basal FSH level (cycle days 2-5) [38].

The women were very carefully selected to be PCOM-free. A weakness of this study, however, is the small number of women included in the groups. The number of obese women with OD unrelated to PCOS is small. The control group had a lower BMI, because it was difficult to find similarly overweight women without OD. Is OD inevitable above a certain BMI? In our experience, no patient over BMI 41 ovulates correctly, although we have not constructed a ROC curve to verify the cutoff. Another potential bias might be the prescription of the progesterone challenge test to the women who did not ovulate spontaneously, mainly to women from the OD group. Although dydrogesterone has no or a very small antigonadotropic activity [39], we cannot rule out its potential responsibility for a small artificial decrease in basal FSH levels.

## **CONCLUSIONS:**

In obese women without PCOS and with OD unrelated to PCOS, low serum FSH level may contribute to OD independently of BMI. This result, unreported until now,

requires further investigation to confirm and explore the pathophysiological mechanism of this finding and its impact on therapeutic strategies.

#### **ETHICAL STATEMENT, COMPLIANCE WITH ETHICAL STANDARDS:**

- Funding: no funding was received
- Conflict of Interest: The authors declare that they have no conflict of interest.
- Ethical approval: This study was approved by the Institutional Review Board of the University Hospital (DEC 16-185).
- Informed Consent: All women had previously consented to the use of their clinical, laboratory, and ultrasound data for research purposes.
- Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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**TABLE 1:**

	Group with <b>ovulation disorders</b> (n=30) MEDIAN (5 <sup>th</sup> -95th percentile)	Control group (n=45) MEDIAN (5 <sup>th</sup> -95th percentile)	<i>P</i> *	<i>P</i> ** with adjustment for BMI
Age (years)	29.5 (18.65-36.90)	30 (22.3-34.7)	1.000	NA
<b>BMI (kg/m<sup>2</sup>)</b>	<b>40.75 (30.26-54.25)</b>	<b>33.00 (30.00-40.5)</b>	<b>&lt;0.0001</b>	NA
<b>Waist circumference (cm)</b>	<b>112 (87.85 – 146.15)</b>	<b>98 (83-121.75)</b>	<b>&lt;0.0001</b>	<b>0.916</b>
Hirsutism (Ferriman & Gallway score)	0 (0-5)	0 (0-8.9)	1.000	NA
Estradiol (pg/mL)	36 (21.55-60.05)	34 (18.60-59.50)	1.000	NA
<b>FSH (IU/L)</b>	<b>4.4 (2.61-6.27)</b>	<b>5.60 (3.75-8.54)</b>	<b>&lt;0.0001</b>	<b>&lt;0.001</b>
LH (IU/L)	2.45 (1.10-6.46)	2.70 (1.30-5.64)	1.000	NA
AMH (pmol/L)	18.85 (8.4-42.89)	19.6 (10.06-33.35)	1.000	NA
Testosterone (ng/mL)	0.26 (0.11-0.57)	0.21 (0.07-0.40)	1.000	NA
Androstenedione (ng/mL)	0.92 (0.32-2.88)	1.15 (0.56-1.75)	1.000	NA
DHAS (μmol/L)	3.55 (1.57-8.53)	3.80 (1.83-8.01)	1.000	NA
17 OH-progesterone (ng/mL)	0.33 (0.13-0.95)	0.41(0.12-0.80)	0.423	NA
Sex-binding protein (nmol/L)	25.45 (11.70-49.25)	28.65 (14.2-60.23)	1.000	NA
<b>Insulin (mIU/L)</b>	<b>9.45 (3.71-34.31)</b>	<b>6.1 (1.4-17.66)</b>	<b>0.030</b>	<b>0.623</b>
<b>Leptin (ng/mL)</b>	<b>66.1 (19.2-166.9)</b>	<b>49.9 (28.7-129.2)</b>	<b>0.033</b>	<b>0.914</b>
Right ovarian area (cm <sup>2</sup> )	4.38 (2.66-6.87)	3.68 (2.63-5.20)	0.273	NA
Left ovarian area (cm <sup>2</sup> )	3.31 (1.74-5.76)	3.38 (2.21-5.01)	1.000	NA
<b>Follicle number per ovary</b>	<b>10.25 (0.00-17.10)</b>	<b>8.75 (6.00-13.43)</b>	1.000	NA

Legend: Clinical, laboratory, and ultrasound characteristics of the groups. \*Comparison between the 2 groups with non-parametric Mann Whitney test. \*\*Covariance analysis to adjust the comparison for BMI.