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Ovarian Reserve in a Population of Obese Infertile Patients in Kinshasa

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Abstract

Background: The ovarian reserve, which is an important marker in the management of couple infertility, undergoes depletion over time. This depletion could accelerate in the presence of certain circumstances, such as obesity. The contradictory results of studies on the impact of obesity on the ovarian reserve throughout the world accelerated ovarian ageing in infertile women from Kinshasa, as well as the high rate of obese women in this population, seemed necessary to undertake this study to find out if this obesity impacted the ovarian reserve of Kinshasa women. The objective of this study was to identify the profile of markers of ovarian reserve in obese infertile patients according to certain characteristics. **Method:** A case-control study with retrospective data collection on 439 obese infertile patients (cases) and 439 normal-weight infertile patients (controls) who had consulted for the desire to conceive at the University Hospital of Kinshasa and the Edith Medical Center between January 2016 and December 2021. **Results:** The average age of the patients was 33.6 years ± 4.3 years, with 47.8% of patients aged at least 35 years. Menarche and menstrual duration were correlated with AMH in linear regression ($p = 0.043$ and 0.021, respectively). Late menarche and irregular cycle were risk factors for ovarian ageing [OR: 4.6; 95% CI: (1.052 - 20.636); $p = 0.043$ and OR: 4.8; 95% CI: (1.633 - 14.566); $p = 0.005$] while PCO was a protective factor for ovarian ageing [OR: 0.109; 95% CI: (0.182 - 0.652); $p = 0.015$]. **Conclusion:** Within the limits of our study, we found that the more obese the patients were, the faster the ovaries aged.

Keywords

Ovarian Reserve, Obesity, Infertility, AMH, FSH

1. Introduction

The ovarian reserve, which is the follicular capital available to the woman at a given moment in life [1], is an important marker in the management of infertile couples [2] [3]. This follicular capital, composed of primordial, intermediate, and small primary follicles [4], is estimated at 2 million at birth [5]. The ovarian reserve undergoes a depletion in quantity and quality to such an extent that at menopause, there are only a few thousand follicles [6]. The ovarian reserve, therefore, constitutes an indirect index of a woman's reproductive age [7]. It is evaluated using markers, the most predictive of which are AMH and antral follicle count [8] [9]. However, due to the difficulties in supplying reagents in our set, many patients benefited more from the FSH dosage than from the AMH. This follicular depletion could accelerate in certain circumstances, such as obesity [6] [9]. Obesity (body mass index (BMI) ≥ 30 kg/m^2) is defined as an abnormal or exaggerated accumulation of body fat that can disrupt the proper functioning of the body [10]. More than 20% of women aged 25 to 44 are obese [11]. In Saudi Arabia, the USA, and Türkiye, they constitute 44%, 40% and 26%, respectively [12]-[14]. In Africa, the rate of female obesity is around 30% [15]. In the Kinshasa population, the obesity rate among adult women was 22.4% [16]. In addition to these numerous comorbidities [17], obesity through the peripheral aromatization of excess androgens [18], the leptinoresistance of neurons to Kisspeptin [19], the inhibition of AMH mRNA synthesis by leptin [20], insulin resistance [21], increased oxidative stress for oocytes [22], poor regulation of proinflammatory cytokines [23], adiponectinemia [24] and lipotoxicity [25], hamper the Ovarian follicular recruitment, oocyte development and quality [26]. Several studies carried out to evaluate the impact of obesity on ovarian reserve have produced contradictory results. Indeed, some authors, such as Vitek W. *et al*., found that AMH was lower in obese infertile women [27], while others, such as U. Gorken *et al*. and Simoes-Peirera J. *et al*., reported that BMI did not seem to affect AMH level as well as other ovarian reserve parameters [6] [28]. Even more, Albu *et al*. showed that an increase in BMI is accompanied by an increase in AMH [29]. In the DRC, Mboloko *et al*. found that in the Kinshasa population, overweight and obesity were associated with a reduced chance of conception compared to thinness [30]. Faced with the contradictions on the association of obesity and ovarian reserve throughout the world, accelerated ovarian ageing in infertile patients in Kinshasa as well as the high rate of obese patients in the infertile population of Kinshasa, it seemed necessary to undertake this study to find out whether obesity impacted ovarian reserve. The objective of this study was to describe the epidemiological and paraclinical profile of obese infertile patients to identify the profile of markers of ovarian reserve according to certain characteristics and the factors associated with ovarian ageing.

2. Material and Method

The sample size was calculated according to the formula: $n \geq ((1 + 1/c) \times p(1 - p)(Z\alpha + Z2\beta)^2)/(p1 - p0)^2$. The minimum size was 207 cases and 207 controls. It

was a case-control study that took place at the University Clinic of Kinshasa (UCK) and the Edith Medical Center (EMC) of Lemba, DRC, from January 2016 to December 2021. During this period, 878 patients who sought clinic for infertility and whose files contained more than half of useful variables were enrolled. The variables of interest were sociodemographic, clinical, and paraclinical (age, parity, menarche, menstrual cycle features, infertility duration, Body Mass Index (BMI), ultrasound findings, Anti Mullerian Hormone (AMH) and Follicle Stimulating Hormone (FSH) dosages). Indeed, 439 obese patients (cases) were paired with 439 normal weights (controls) according to their age. The ones with a history of smoking, oophorectomy, chemotherapy, and hormonotherapy during the last three months were excluded.

The data were recorded in Microsoft Access 2013 software and analysed with STATA IC.18 software. The quantitative variables were summarized as mean plus minus standard deviation and qualitative variables as proportions. After checking the normality of the distribution, the comparison of means was made by the student's t test, and the comparison of proportions with the Pearson chi-square test. Simple linear regression was used for prediction between certain quantitative variables, and Logistic regression was used to determine the strength of association between the variables via the Odds Ratio (OR). The p-value less than 0.05 was considered significant. The study project received approval from the Ethics Committee of the Kinshasa Public Health School Board (approval note: ESP/CE/138/2022).

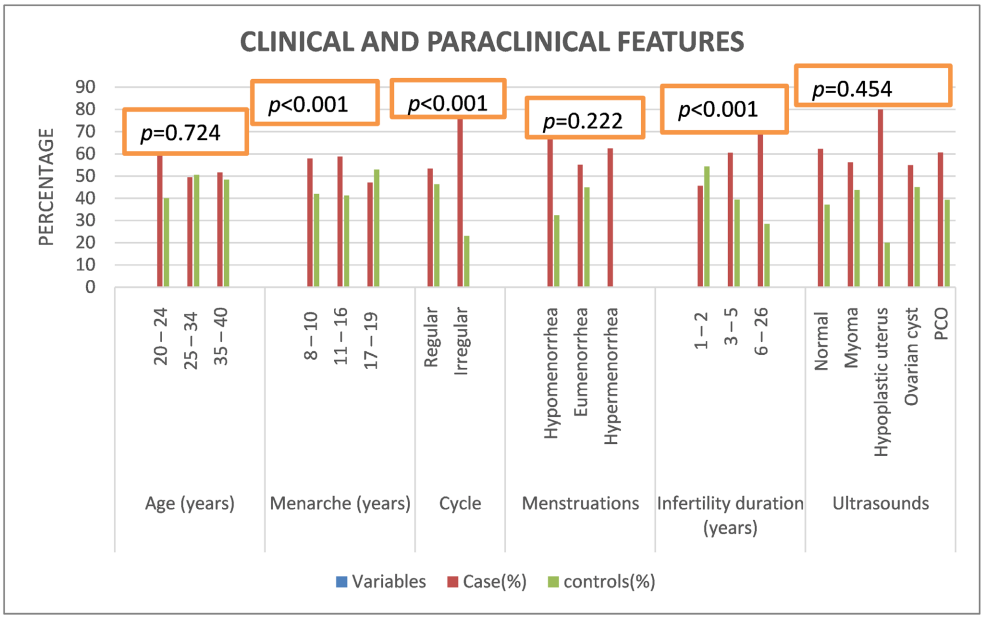
3. Results

3.1. Clinical and Ultrasound Characteristics of Patients

The age of the patients ranged from 20 to 40 years, with an average of 33.6 years ± 4.3 years. Almost half of them (47.8%) were at least 35 years old. The mean age of menarche was 13.5 years ± 1.8 years, ranging from 8 to 19 years. Menarche was significantly ($p = 0.0004$) earlier in the obese group (13.3 years ± 1.8 years) than the controls (13.6 years ± 1.8 years). The average duration of infertility was 4.4 years ± 3.8 years, longer in the case group than the controls ($p = 0.000$). A quarter of patients (24.9%) had an irregular menstrual cycle, predominant significantly ($p = 000$) in the case group (76.9%). The mean duration of the menstruation was 4.0 days ± 1.2 days. Hypomenorrhea and hypermenorrhea were more observed in the case group (67.6% and 62.5% respectively). In ultrasound exploration, a third of patients (35.5%) had uterine myoma, and one-tenth (11.5%) had PCO; the two seemed ($p = 0.454$) more frequent in the case group (**Figure 1**).

3.2. Ovarian Reserve Markers

AMH levels ranged from 0.1 to 11.6 ng/ml with a mean level of 3.7 ng/ml ± 3.1 ng/ml. Cases had a lower mean AMH level (3.3 ng/ml ± 2.9 ng/ml) than controls (6.3 ng/ml ± 3.2 ng/ml). This difference was statistically significant ($p = 0.020$). More than a quarter of the patients (26.8%) had an AMH level below the normal value and were exclusively made of cases (100%).



Legend: PCO = Poly Cystic Ovaries.

Figure 1. Clinical and ultrasound characteristics of patients.

The average FSH level was 12.6 mIU/ml ± 16.1 mIU/ml, with 13.4 mIU/ml ± 16.9 mIU/ml for the case group and the controls 10.1 mIU/ml ± 13.1 mIU/ml. Almost a third of the patients (31.6%) had a pathological FSH level, and the majority (66.2%) were made of case patients (**Figure 2**).

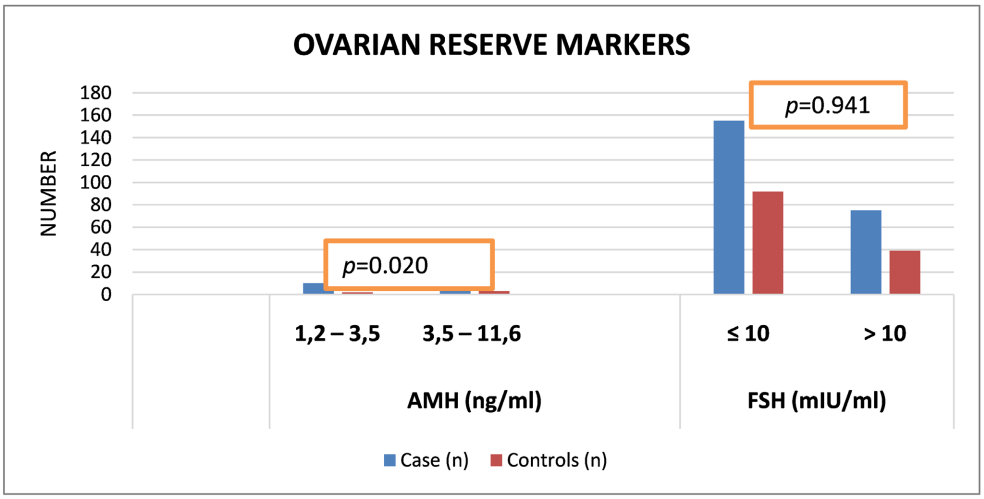


Figure 2. Ovarian reserve markers.

3.3. Relationship between Patient's Characteristics

Evolution of AMH with BMI

According to **Figure 3**, a negative, non-significant correlation (p = 0.280) was found between AMH level and BMI. An increase of 1 Kg/m² of BMI was associated with a decrease in AMH level of 11.5%.

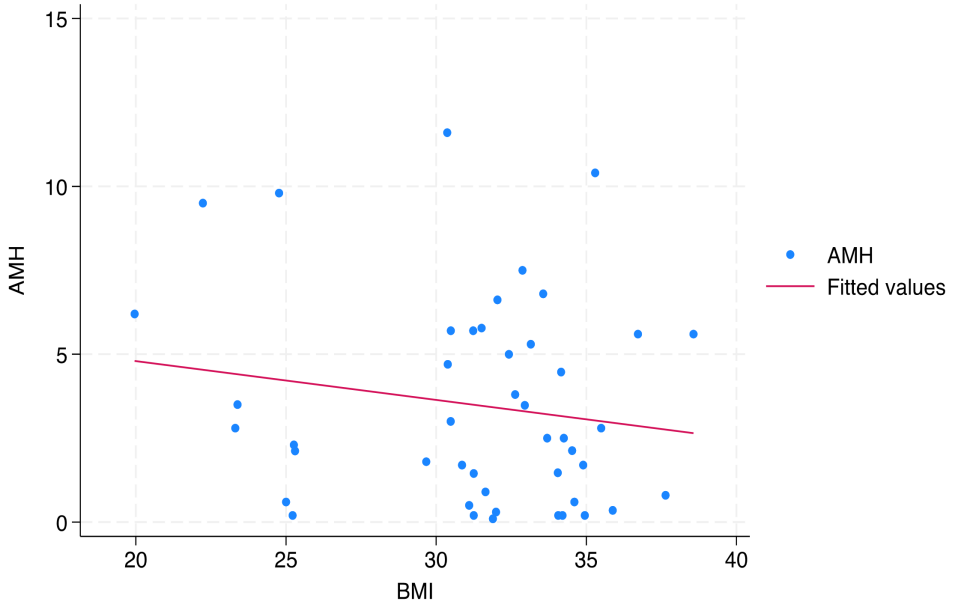


Figure 3. Evolution of AMH with BMI.

Evolution of AMH with age

It appears from **Figure 4** that AMH had a negative, non-significant correlation (p = 0.063) with age. The increase in age by one year was accompanied by a decrease in the AMH rate of 21.8%.

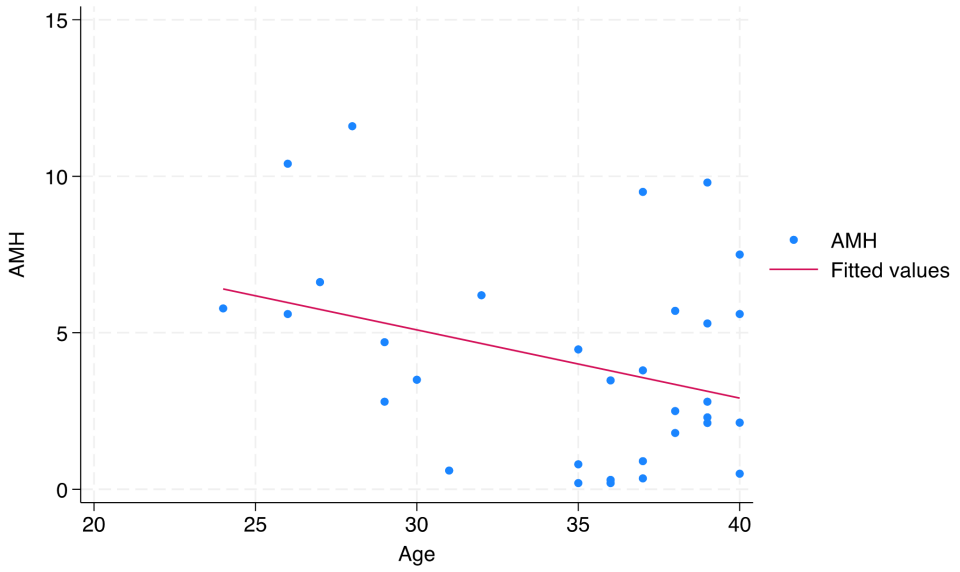


Figure 4. Evolution of AMH in relation to age.

3.4. Evolution of AMH with Menarche

The AMH had a negative and statistically significant correlation (p = 0.043) with menarche (**Figure 5**). The one-year increase in menarche was accompanied by a 59.0% decrease in the AMH rate.

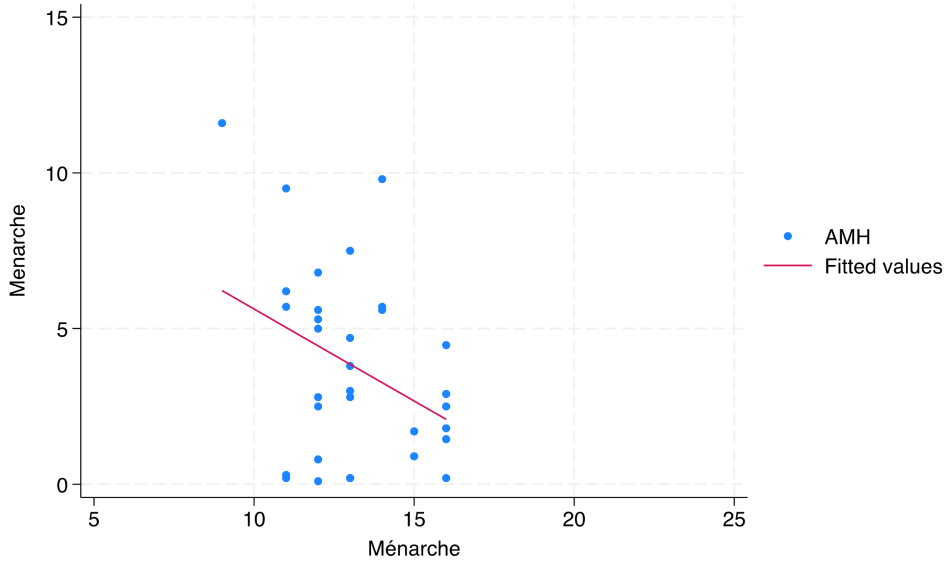


Figure 5. Evolution of AMH with menarche.

Evolution of AMH with the duration of menstruation

The AMH had a positive, statistically significant correlation (p = 0.021) with the duration of periods. The increase in one-day periods was accompanied by an increase in the AMH rate of 61.6% (**Figure 6**).

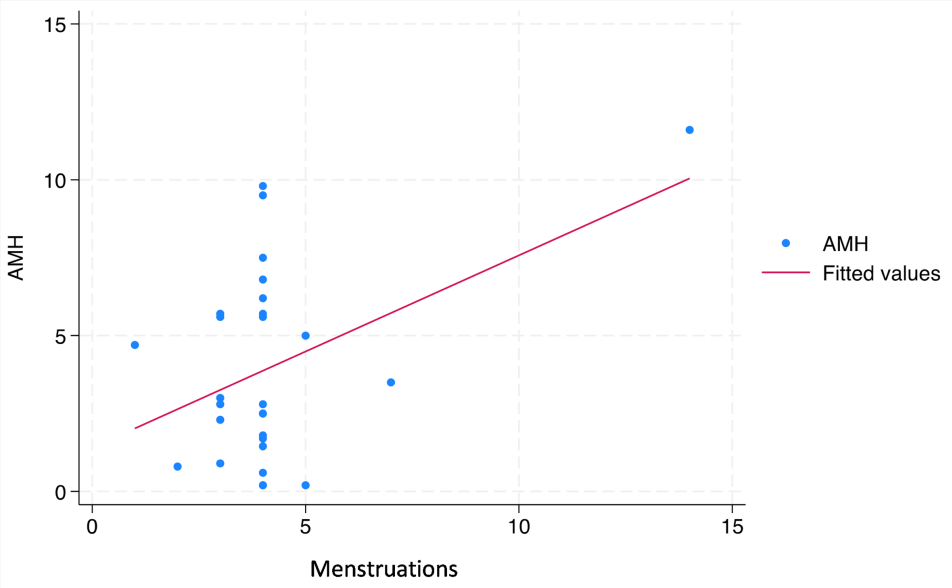


Figure 6. Evolution of AMH with duration of menstruation.

3.5. Factors Associated with Ovarian Ageing in Univariate Analysis

According to **Table 1**, the univariate analysis did not reveal a particular association between the BMI categories and the ultrasound findings. On the other hand, patients with a duration of infertility of more than 5 years had twice the risk (p = 0.037) of ovarian ageing compared to those less than two years old compared to

patients with a regular cycle, patients with an irregular cycle were twice as likely to have ovarian ageing (p = 0.003). Patients with hypermenorrhea were 35 times more likely (p = 0.021) to have ovarian ageing compared to patients with hypomenorrhea.

Table 1. Factors associated with ovarian ageing in univariate analysis.

Variables	OR	95% CI		p
BMI				
Controls	1			
Case	1.195	0.686	2.081	0.527
Duration of infertility (years)				
1 - 2	1			
3 - 4	1.656	0.917	2.990	0.094
5 - 26	1.961	1.041	3.694	0.037
Type of cycle				
Regular	1			
Irregular	2.130	1.295	3.501	0.003
Duration of menstruation				
Oligomenorrhea	1			
Eumenorrhea	4.344	0.553	34.097	0.162
Hypermenorrhea	35.999	1.710	757.788	**0.021**
Ultrasound findings				
Normal	1			
Myoma	1.058	0.595	1.881	0.846
Uterine Hypoplasia	2.25	0.433	11.689	0.335
Ovarian Cyst	0.75	0.191	2.934	2.934
PCO	0.460	0.203	1.042	0.063

Legend: OR = Odd Ration; CI = Confidence Interval; p = Significance Level; BMI = Body Mass Index.

3.6. Factors Associated with Ovarian Ageing in Multivariate Analysis

After adjustment, BMI, menstrual duration, infertility duration and PCO were not associated with ovarian ageing. Late menarche and irregular menstrual cycle were found to be determinants of ovarian ageing (OR: 4.6; 95% CI: 1.052 - 20.636; p = 0.043 and OR: 4.8; 95% CI: 1.6 - 14.565, respectively) (Table 2).

Table 2. Factors associated with ovarian ageing in multivariate analysis.

Variables	OR	95% IC	p
BMI			
Control	1		
Case	1.7	0.476 - 6.127	0.411

Continued

Parity			
Nulliparous	1		
Primiparous	1.6	0.419 - 6.498	0.474
Multiparous	1.3	0.270 - 6.737	0.714
Gestity			
Nulligeste	1		
Multigeste	1.0	0.314 - 3.512	0.935
Menarche			
Early	1		
Normal	0.049	0.066 - 3.512	0.489
Late	4.6	1.052 - 20.636	0.043
Type of cycles			
Regular	1		
Irregular	4.8	1.6 - 14.566	**0.005**
Duration of menstruation			
Oligoménorrhea	1		
Euménorrhea	1.5	0.149 - 15.655	0.719
Hyperménorrhea	30.7	0.950 - 992.007	0.053
Duration of infertility (year)			
0 - 2	1		
3 - 4	0.7	0.227 - 2.688	0.688
5 - 26	2.5	0.678 - 9.874	0.164
Ultrasound funding			
Normal ultrasound	1		
Myoma	0.7	0.258 - 2.21	0.612
Uterine Hypoplasia	3	0.136 - 67.873	0.481
PCO	0.109	0.182 - 0.652	**0.015**

Legend: OR: Odd Ration; CI: Confidence Interval; p: Significance Level; BMI: Body Mass Index.

4. Discussion

The present study aimed to analysed the ovarian reserve in a population of infertile obese patients. The discussion focuses on the characteristics of the patients, the relationships between the different characteristics of ovarian reserve markers, and finally, the factors associated with ovarian ageing.

The average age of the patients was 33.6 years ± 4.3 years. Therefore, those patients are located, according to the diagram by F. Broekmans, at the pivotal level of the beginning of ovarian ageing [31]. This average age is in agreement with the previous study carried out in the same area by E. Mboloko *et al*.: 33.2 years ± 5.6 years [30] and with Belaïsch's assertion that worldwide, the age at first motherhood

is constantly increasing [32] [33]. Almost half (47.8%) of patients were aged at least 34 years, with the majority of cases (51.6%) above 35 years. However, advanced age is a major risk factor for obesity and an indirect marker of ovarian ageing. The average duration of infertility in this study was 4.4 years ± 3.8 years and corroborates the results of C. Mckinnon *et al*. and S. Esmaeilzadeh *et al*. which highlights that infertile patients consult late [34] [35]. In the sub-Saharan setting, the itinerary of infertile patients is characterized by loss of time in errance across traditional healers, general practitioners before consulting the specialist [35]. To reinforce that statement, the durations of infertility in the current study are very long, with more than half (60.7%) having a duration of infertility more than 2 years, especially in case group patients (p = 0.037).

According to the ovarian reserve markers during the current study, FSH was previously and more frequently used (**Figure 2**), and AMH was more recent and more expensive than FSH. So, FSH was used instead of AMH for the association analyses. Comparing the average level of ovarian reserve markers AMH and FSH in the cases to controls, they are within the pathological limits for FSH (13.4 mIU/ml ± 16.9 mIU/ml vs 10.1 mIU/ml ± 13.1 mIU/ml), especially in the case group. That is consistent with the previous finding: the population was aged and at the stage of the decline of ovarian function, whose clinical expression includes irregular cycles and hypermenorrhea [36].

Concerning AMH, the cases had an average level lower than controls (3.3 ng/ml vs 6.3 ng/ml; p = 0.021). Our results corroborate those of V. Vitek *et al*., I. Su *et al*. and N. Moslehi *et al*. (p = 0.001, 0.02, and 0.001, respectively) [27] [37] [38]. Obesity, due to its pathophysiology, leads to insulin resistance, leptin resistance and inhibition of AMH mRNA synthesis, the hormone known for its opposition to follicular depletion by counteracting both initial and cyclical recruitment [20] [39]. On the other hand, the controls had a high average AMH level (6.3 ng/ml ± 3.2 ng/ml), suggestive of PCOS which, compared to patients with a normal ultrasound, emerged as a non-risk factor (OR: 0.46; 95% CI: 0.182 - 0.652; p=0.015) of ovarian aging. Indeed, the multifollicular nature of this pathology leads to increased secretion of AMH which, currently, is being considered as one of the diagnostic elements of PCOS [40].

Compared to characteristics that have an association with obesity, AMH was negatively correlated with menarche (p = 0.043) and positively correlated with menstrual duration (p = 0.021). Menarche is known to occur at a certain level of weight gain, favoring those with significant weight gain. Patients who had had early menarche were mainly made up of cases (57.9%). However, early menarche is associated with depletion of the OR by increasing the frequency of ovulation [41] [42]. Obesity is also known to be associated with heavy menstrual bleeding [43] and irregular menstrual cycles [44]. In the present study, the irregular cycle was 10 largely found among the cases (76.9%) and which, compared to patients with a regular cycle, increased the risk of ovarian aging by 5 (OR: 4.8; p=0.005; 95% CI: 1.6 - 14.566). This trend was also observed in the British study by M. Seif

et al. of 2015 [43]. Indeed, high BMI was associated with elevated estrogen levels due to peripheral conversion of androgens to estrogens in adipose tissues through aromatization [45] and decreased SHBG levels [46]. Low levels of SHBG are associated with the high likelihood of irregular menstrual cycles through anovulation [47].

5. Conclusion

Within the limits of our study, the patients were at the pivotal level of the beginning of ovarian ageing. There was a negative correlation between weight gain and the decrease in ovarian reserve. The more obese the patient, the faster the ovary ages. Age and late menarche are risk factors for ovarian ageing, and the irregular cycle is the main expression of ovarian ageing. Furthermore, more structured studies are required to elucidate the fundamentals of the relationship between weight gain and ovarian ageing.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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