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QRLISTAT (THE LIPASE INHIBITOR) THERAPY IN OVERWEIGHT AND OBESE SUB-FERTILE WOMEN

By

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ABSTRACT

Background: Obesity remains an important risk factor for women planning for pregnancy because of its adverse effects on reproductive outcome. In individuals who experience difficulty in reducing significant weight with lifestyle intervention alone, the use of anti-obesity drugs can be an adjunct.

Objective: To evaluate the efficacy of Orlistat (a pancreatic lipase inhibitor) therapy on achieving pregnancy in overweight and obese sub-fertile women.

Patients and methods: This prospective study was carried out, involving 120 case of obese and overweight sub-fertile and primary infertility women that attend to antenatal care in obstetrics and gynecology clinics in both Al- Hussein Hospital and Kom-Hamada Hospital, They were divided into 2 groups: Group I: Patients received Orlistat (120 mg) twice daily for 6 months period, and Group II: Patients counseled for life style modification only. The duration of the study ranged between April 2019 and October 2020.

Results: In group I with BMI less than 30, there were 9(30%) with pregnancy outcome, 5(16.7%) with pregnancy outcome with BMI more than 30. In group II with BMI less than 30, there were 2(6.9%) with pregnancy outcome, 2(6.5%) with pregnancy outcome with BMI more than 30. There was a significant difference between 2 groups as regard pregnancy outcome.

Conclusion: Orlistat improved ovulation as it acted indirectly by weight reduction more than life style modification alone.

Keywords: Obesity, Orlistat, Infertility, Pregnancy outcome.

INTRODUCTION

Obesity and overweight are a common problem among women in reproductive age, the prevalence of obesity as a worldwide epidemic has increased dramatically over the past two decades *(Flegal et al., 2012).*

Obesity and overweight involves an abnormal and excessive fat accumulation that negatively affects the health of the body. According to the World Health Organization (WHO) categories of adult obesity are based upon body mass index (BMI) *(WHO, 2010).*

Most of the pregnancies occur in the first six cycles with intercourse in the fertile phase (80%). After that, serious subfertility must be assumed in every second couple (10%) although- after 12 unsuccessful cycles- untreated live birth rates among them will reach nearly 55%

in the next 36 months. Thereafter (48 months), approximately 5% of the couples are definitive infertile with a nearly zero chance of becoming spontaneously pregnant in the future *(Vahratian, 2010).*

The association between obesity and lower fertility rate has been shown in several studies, and it has been shown that obesity in early adulthood alters the reproductive functions, although many obese multiparous women are able to get pregnant despite their obesity, there is an increased prevalence of infertility in obese women. *Vahratian (2010)* have found that a larger portion of women who are seeking medical help to get pregnant are obese.

The studies demonstrated that the duration required achieving a spontaneous pregnancy rate increased and pregnancy rates decreased in obese women, including regular ovulatory obese women *(Gesink et al., 2010).*

Weight loss interventions studies in obese subfertile woman showed that modest weight loss in these patient category might increase the chance of spontaneous conception ant as result may decrease the for fertility treatment *(Sim et al., 2014).*

Orlistat (Xenical) is the only fat absorption inhibitor, and acts as a lipase inhibitor, which decreases the absorption of fats from the human diet by 30%. It is intended for use in conjunction with a healthcare provider-supervised regimen of caloric restriction *(Siebenhofer et al., 2013).*

The aim of this study was to evaluate the efficacy of Orlistat (a pancreatic lipase inhibitor) therapy on achieving pregnancy in overweight and obese sub-fertile women.

PATIENTS AND METHODS

This was prospective study was carried out, involving 120 case of obese and overweight sub-fertile and primary infertility women that attend to antenatal care in obstetrics and gynecology clinics in both Al- Hussein Hospital and Kom-Hamada Hospital, the duration of the study was April 2019 to October 2020.

They study followed the ethical and medical committee of the hospital, and written consents were obtained from the participating patients who were informed about the aim and method of the study.

All women between 21-35 years, BMI 25-40 Kg/M2 were divided into two equal groups: Group I received Orlistat (120 mg) twice daily for 6 months, and **Group II** was counseled for life style modification only on reducing energy intake and increasing physical activity through diet, exercise and behavioral measures.

Inclusion criteria: Subfertile obese and overweight female patients with BMI (25-40) Kg/M2, age (21-35) years, normospermic husband, normal HSG, no history of taking medication or dietary modification for weight loss, and primary infertility.

Exclusion criteria: Medical disorders, subfertile patients who had laparoscopic ovarian drilling and metformin treatment during Orlistat therapy, structural abnormalities in reproductive tract, and missed patients during study period.

All patients were subjected to:

a. **History taking:** Age, residency, occupation, period of infertility, previous abortion, family history of PCO, and early menarche, presence of comorbidities, such as hypertension were evaluate.

b. **Clinical examination:**

- Physical examination, general examination, abdominal examination and local (pelvic) examination.
- Investigations: General: CBC, urinalysis, Random blood sugar and Specific: FSH, LH, prolactin, midluteal progesterone, and anti-mullerian hormone (AMH).
- Transvaginal sonography (TVS) on day 3, 11 and 14 of menstrual cycle was done for evaluation of ovulatory status of patients and making a progesterone analysis in mid luteal phase.

Method of randomization: Randomization was ensured using closed sealed envelope with the method containing letter "O" indicating Orlistat group, letter "C" indicating life style modification group, the 2 groups received the same conventional hospital care. Then, pre and post-treatment parameters was done between two groups, according to weight reduction, ovulation improvement by sonar and midluteal progetrone, menstrual irregularitys and increase the chance of conception.

Statistical analysis:

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value < 0.05 was considered significant.

RESULTS

In group I there were 14(23.3%) with age between 21 and 25, 17(28.3%) with age between 25 and 30, 29(48.3%) with age more than 30. The mean age 28.57(±4.57 SD) with range (22-35), and the mean weight 83.88(±9.5 SD) with range (68-106.5), the mean height 164.8(±5.08 SD) with range (157-173), 30 (50%) with BMI less than 30, 30(50%) with more than 30, the mean BMI 30.91(±3.26 SD) with range (25.3-37). In group II there were 9(15%) with age between 20 and 25, 16(26.7%) with age between 25 and 30, 35(58.3%) with age more than 30, the mean age 29.78(±4.21 SD) with range (22-35), the mean weight 82.68(±10.37 SD) with range (62.7-105.9), the mean height 165(±4.76 SD) with range (157-173), 29(48.3%) with BMI less than 30, 31(51.7%) with more than 30, the mean BMI 30.38(±3.5 SD) with range (25.1-36.9). There was no significant difference between 2 groups **(Table 1)**.

Table (1): Comparison between the two studied groups according to demographic data

Groups / Demographicdata	Group I (n = 60)		Group II (n = 60)		p
	No.	%	No.	%	
Age (years)					
20 – < 25	14	23.3	9	15.0	0.432
25 – < 30	17	28.3	16	26.7	
≥ 30	29	48.3	35	58.3	
Min. – Max.	22.0 – 35.0		22.0 – 35.0		0.132
Mean ± SD.	28.57 ± 4.57		29.78 ± 4.21		
Median (IQR)	29.0 (25.0 – 33.0)		31.0 (26.0 – 33.50)		
Weight (kg)					
Min. – Max.	68.0 – 106.50		62.70 – 105.90		0.511
Mean ± SD.	83.88 ± 9.50		82.68 ± 10.37		
Median (IQR)	82.65(76.70 – 90.60)		81.80(74.55 – 89.70)		
Height (cm)					
Min. – Max.	157.0 – 173.0		157.0 – 173.0		0.839
Mean ± SD.	164.8 ± 5.08		165.0 ± 4.76		
Median (IQR)	165.0(161.0 – 169.0)		165.0(161.0 – 169.0)		
BMI (kg/m^2)					
<30	30	50.0	29	48.3	0.855
≥ 30	30	50.0	31	51.7	
Min. – Max.	25.30 – 37.0		25.10 – 36.90		0.395
Mean ± SD.	30.91 ± 3.26		30.38 ± 3.50		
Median (IQR)	30.0 (28.45 – 33.10)		30.45(27.40 – 32.95)		

p: p value for comparing between the two studied groups
Group I: patients were receiving capsule Orlistat 120 mg twice daily for 6 months period.
Group II: patients were counseled for life style modification only.

In group I, the mean period of infertility was 3.45(±1.83 SD) with range (1-7), in group II the mean period of infertility was 3.5±2.02 SD with range (1-7). There was no significant difference between 2 groups **(Table 2)**.

Table (2): Comparison between the two studied groups according to period of infertility

Groups / Period of infertility	Group I (n = 60)	Group II (n = 60)	p
Min. – Max.	1.0 – 7.0	1.0 – 7.0	0.907
Mean ± SD.	3.45 ± 1.83	3.50 ± 2.02	
Median (IQR)	3.0 (2.0 – 4.0)	4.0 (1.50 – 5.0)	

p: p value for comparing between the two studied groups

There was significant difference between 2 groups as regard LH post treatment, pre and post treatment free testosterone LH and LH/FSH ratio midluteal progesterone anti-mullerian hormone **(Table 3)**.

Table (3): Comparison between the two studied groups according to hormonal profile

Hormonal profile / Groups		Group I (n = 60)	Group II (n = 60)	p
Free Testosterone (pg/ml)	**Pre treatment**			
	Min. – Max.	0.49 – 2.45	0.47 – 2.43	0.330
	Mean ± SD.	1.46 ± 0.58	1.35 ± 0.56	
	Median (IQR)	1.43 (0.89 – 1.96)	1.22 (0.87 – 1.87)	
	Post treatment			
	Min. – Max.	0.28 – 2.26	0.45 – 2.47	0.077
	Mean ± SD.	1.06 ± 0.56	1.23 ± 0.53	
	Median (IQR)	0.98 (0.60 – 1.54)	1.12 (0.81 – 1.56)	
	Z (p_0)	6.275 (<0.001)	2.056 (0.040)	
FSH (mIU/ml)	**Pre treatment**			
	Min. – Max.	2.40 – 7.80	2.50 – 7.80	0.821
	Mean ± SD.	5.05 ± 1.71	4.98 ± 1.53	
	Median (IQR)	5.25 (3.45 – 6.45)	4.80 (3.60 – 6.25)	
	Post treatment			
	Min. – Max.	3.0 – 7.30	2.50 – 7.80	0.549
	Mean ± SD.	5.17 ± 1.30	5.32 ± 1.55	
	Median (IQR)	5.25 (4.0 – 6.35)	5.20 (4.15 – 6.95)	
	Z (p_0)	0.366 (0.714)	1.170 (0.242)	
LH (mIU/ml)	**Pre treatment**			
	Min. – Max.	1.30 – 9.70	1.20 – 9.80	0.461
	Mean ± SD.	5.37 ± 2.45	5.68 ± 2.49	
	Median (IQR)	5.70 (3.05 – 7.75)	5.90 (3.60 – 7.85)	
	Post treatment			
	Min. – Max.	2.10 – 5.70	1.20 – 9.60	0.002
	Mean ± SD.	3.80 ± 1.11	5.59 ± 2.81	
	Median (IQR)	3.90 (2.60 – 4.80)	6.55 (2.65 – 8.05)	
	Z (p_0)	3.948 (<0.001)	0.202 (0.840)	
LH/FSH ratio	**Pre treatment**			
	Min. – Max.	0.20 – 3.20	0.20 – 3.20	0.751
	Mean ± SD.	1.56 ± 0.91	1.60 ± 0.87	
	Median (IQR)	1.45 (0.80 – 2.20)	1.55 (0.80 – 2.25)	

	Post treatment			
	Min. – Max.	0.40 – 1.40	0.20 – 2.50	0.001
	Mean ± SD.	0.80 ± 0.29	1.26 ± 0.71	
	Median (IQR)	0.80 (0.60 – 1.0)	1.30 (0.60 – 1.80)	
	Z (p_0)	4.989 (<0.001)	3.058 (0.002)	
Midluteal progesterone	**Pre treatment**			
	Min. – Max.	5.20 – 9.50	5.0 – 9.40	0.286
	Mean ± SD.	7.54 ± 1.12	7.33 ± 1.03	
	Median (IQR)	7.25 (6.65 – 8.40)	7.35 (6.60 – 8.10)	
	Post treatment			
	Min. – Max.	12.0 – 17.0	9.0 – 14.0	<0.001
	Mean ± SD.	14.33 ± 1.63	11.21 ± 1.41	
	Median (IQR)	14.20 (12.80 – 16.10)	10.80 (10.15 – 12.20)	
	t_1 (p_0)	25.578 (<0.001)	18.514 (<0.001)	
Anti-mullerian hormone AMH (ng/ml)	**Pre treatment**			
	Min. – Max.	1.80 – 8.20	0.70 – 8.30	0.931
	Mean ± SD.	4.85 ± 1.85	4.77 ± 2.22	
	Median (IQR)	4.80 (3.15 – 6.30)	4.65 (3.0 – 7.10)	
	Post treatment			
	Min. – Max.	1.40 – 5.60	0.70 – 8.50	<0.001
	Mean ± SD.	3.23 ± 1.22	4.89 ± 2.36	
	Median (IQR)	2.95 (2.30 – 4.35)	5.15 (3.10 – 7.25)	
	Z (p_0)	4.801 (<0.001)	0.720 (0.472)	

p: p value for comparing between the two studied groups
p0: p value for comparing between pre and post treatment in each group

There was significant difference between 2 groups as regard post treatment ovulation. In group I there were 16.7% with nausea and vomiting, 6.7% with headache. In group II there were no one with complication. There was a significant difference between 2 groups as regard complication **(Table 4)**.

Table (4): Comparison between the two studied groups according to ovulation and complications

Groups / Parameters	Group I (n = 60)		Group II (n = 60)		p
	No.	**%**	**No.**	**%**	
Ovulation:					
Pretreatment:					
No	10	16.7	13	21.7	0.721
Ovulte size less than 18	43	71.7	39	65.0	
Ovulte size more than 18	7	11.7	8	13.3	
Post treatment:					
No	0	0.0	12	20.0	0.001
Ovulte size less than 18	39	65.0	35	58.3	
Ovulte size more than 18	21	35.0	13	21.7	
$x2(MH p_0)$	3.893*(<0.001*)		0.926(0.355)		
Complications:					
Non	46	76.7	60	100.0	<0.001
Nausea and vomiting	10	16.7	0	0.0	
Headache	4	6.7	0	0.0	

p: p value for comparing between the two studied groups
p0: p value for comparing between pre and post treatment in each group

In group I with BMI less than 30 there were 9(30%) with pregnancy outcome, 5(16.7%) with pregnancy outcome with BMI more than 30. In group II with BMI less than 30 there were 2(6.9%) with pregnancy outcome, 2(6.5%) with pregnancy outcome with BMI more than 30. There is significant difference between 2 groups as regard pregnancy outcome **(Table 5)**.

Table (5): Comparison between the two studied groups according to pregnancy outcome

Groups / Pregnancy outcome	Group I (n = 60)				Group II (n = 60)				χ^2	^{MC}p
	BMI <30 (n=30)		BMI ≥30 (n=30)		BMI <30 (n=29)		BMI ≥30 (n=31)			
	No.	%	No.	%	No.	%	No.	%		
No	21	70.0	25	83.3	27	93.1	29	93.5	7.740	0.044
Yes	9	30.0	5	16.7	2	6.9	2	6.5		

χ2: Chi square test, MC: Monte Carlo
p1: p value for comparing between the four studied groups

DISCUSSION

In group I there were 23.3% with age between 20 and 25, 28.3% with age between 25 and 30, 48.3% with age more than 30. There was no significant difference between 2 groups as regard age, weight, height and BMI.

Our results were supported by study of *Ghandi et al. (2011)* and *Rahman et al. (2017)* and reported that there was no significant difference among the studied groups as regard age, weight, height and BMI.

In the study of *Ghandi et al. (2011),* the mean age was 27 ± 4.92 and the mean body mass index was 33.68 ± 4.2 kg/m2.

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age. It is estimated to affect 1 in 10 women of childbearing age. This disorder is characterized by the symptoms of dysmenorrhea, infertility, hirsutism, and is strongly associated with weight gain, especially central obesity *(Pal et al., 2014).*

The present study showed that no significant difference between 2 groups. In group I, there were 35% with family history of PCOS, 41.7% with high sugar diet, 13.3% with early menarche. In group II, there were 36.7% with family history of PCOS, 33.3% with high sugar diet, 18.3% with early menarche. There was no significant difference between 2 groups.

Moini et al. (2015) conducted a randomized, double-blind, controlled trial. All participants received hypocaloric diet consists of 1,200-1,800 kcal/day and were encouraged to walk for 30 minutes each day.

The current study showed that there was a significant difference between 2 groups as regard LH post treatment. There was significant difference between pre and post treatment free testosterone in group I and significant difference between pre and post treatment free testosterone in group II. There was significant difference between pre and post treatment LH in group I.

Our results were supported by study of *Panidis et al. (2011)* as they reported that Orlistat reduced FSH and serum testosterone levels in both groups without any statistically significant difference between the two groups. The LH level in the PCOS group was observably higher than that in control group and was not obviously changed after treatment.

Furthermore, *Song et al. (2018)* demonstrated that significant reductions in serum LH and total testosterone were observed in all groups compared with baseline. However, *Ghandi et al. (2011)* revealed that treatment with Orlistat resulted in 3.9% reduction in serum LH, but the difference was not significant.

Our results were supported by study of *Vosnakis et al. (2013)* was stated that serum levels of AMH in the PCOS group was significantly increased compared with the control group, while there was remarkable correlation with serum LH.

The present study, in group I, there were 71.7% with pretreatment ovulate size less than 18, 11.7% with size more than 18, 65% with post treatment ovulate size less than 18, 35% with ovulate size more than 18. In group II, there were 65% with pretreatment Ovulate size less than 18, 13.3% with size more than 18, 58.3% with post treatment Ovulate size less than 18, 21.7% with ovulate size more than 18. There was significant difference between 2 groups as regard post treatment ovulation. There was significant difference between pre and post treatment endometrial thickness in group I and in group II.

There was significant difference between pre and post treatment in group A with BMI less than 30 and in group A with BMI more than 30. There was high significant difference between 2 groups as regard post treatment endometrial thickness. There was high significant difference between pre and post treatment endometrial thickness in each group.

In contrary with our results, *Rahman et al. (2017)* reported that ovulation was higher in Group I than that of Group II, but the difference was not statistically significant.

The randomized studies have also tried to compare the effects of Orlistat and metformin in obese PCOS patients, but they have not reported the ovulation rate and had a small number of cases *(Cho et al., 2012).*

Kumar and Arora (2014) randomly divided 90 overweight/obese PCOS patients into orlistat, metformin and control groups. The first two groups were given the corresponding drugs combined with the same lifestyle intervention for 3 months. The control group was only given the lifestyle intervention. Both BMI and WHR in the Orlistat and metformin groups were significantly lower than those in the control group. Compared with the control group, ovulation rates in both Orlistat and metformin groups were dramatically increased without significant differences between them (33.3% vs 23.3%).

The current study showed that there was significant difference between pre and post weight, and between pre and post treatment in group I and group II.

Our results were supported by a meta-analysis conducted by *Wang et al. (2018)* of pharmacological therapies to induce weight loss in PCOS women who are

overweight or obese covered 23 clinical trials, and compared the effectiveness of metformin, inositol, liraglutide, and Orlistat. According to subgroup analysis, only Orlistat significantly reduced participants' BMI after treatment for 12 weeks, while waist circumference showed no improvement.

Jayagopal et al. (2010) showed that the reduction in weight and after treatment with Orlistat was more significant than seen in the metformin-treated group. Similarly, according to *Kujawska-Łuczak et al. (2016)* the percentage change of weight loss and BMI was more in orlistat-treated group than that of metformin for weight loss and BMI. On comparison, the difference between the groups was found to be statistically significant for the concerned parameters.

However, *Rahman et al. (2017)* reported that reduction of weight (%) was significantly higher in Group I than that of Group II in BMI.

In the study of *Kumar and Arora (2014)*, conception rates were 40% and 16.7% and 3.3% in Orlistat, metformin group and control group respectively.

The present study showed that in group I there were 16.7% with Nausea and vomiting, 6.7% with headache. In group II, there were no complications. There was high significant difference between 2 groups as regard complication.

In the study of *Kumar and Arora (2014)*, patients in the metformin group reported side-effects such as nausea, epigastric pain. However, those in Orlistat group tolerated the drug well. Gastrointestinal symptoms were present in 6.7% of patients who received metformin and none of the Orlistat group had any symptoms. *Song et al. (2018)* demonstrated that side effects were less with Orlistat than metformin.

CONCLUSION

Orlistat can improve ovulation as it acted indirectly by weight reduction more than life style modification alone.

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العلاج بأورليستات (كابح إنزيمات المعدة والبنكرياس) لدى النساء اللآتى يعانين من تأخر الخصوبة بسبب السمنة وفرط الوزن

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خلفيـــة البحـــث: أصـــبح مـــرض الســـمنة مـــن أمـــراض العصـــر المصـــاحبه لأســـاليب الحيـــاة المعاصـــرة والناتجـــة عنهـــا, ولقـــد أصـــبح مـــرض الســـمنة وزيـــادة الـــوزن يمثـــل مشـــكلة كبيـــرة علـــى الصـــحة العامـــة بشـــكل عـــام وعلـــى الصـــحة الانجابيـــة بشـــكل خـــاص حيـــث أنـــه يـــؤدى إلـــى تـــأخير الحمـــل ومشـــاكل فـــى الخصـــوبة, كمـــا يزيـــد مـــن فـــرص الاصـــابه بـــامراض الحمـــل التـــى تـــنعكس بالآثار السلبية على الأم وجنينها.

الهـــدف مـــن البحـــث: دراســـة تـــأثير العـــلاج بأورليســـتات علـــى النســـاء اللآتـــى يعانين من تأخر الخصوبة بسبب السمنة وفرط الوزن.

المريضـــات وطـــرق البحـــث: أجريـــت الدراســـة علـــى 120 ســـيدة مـــن اللاتـــى يعـــانين مـــن تـــأخر الخصـــوبة بســـبب الســـمنة وفـــرط الـــوزن واللاتـــى يتـــرددن علـــى عيـــادات النســـاء والتوليـــد بمستشـــفى الحســـين الجـــامعى ومستشـــفى كـــوم حمـــادة المركـــزى, وتـــم تقســـيمهمن الـــى مجمـــوعيتن : المجموعـــة الاولـــى تنـــاولن كبســـولة اورليســـتات (120مجـــم) مـــرتين يوميـــا لمـــدة ســـتة أشـــهر, والمجموعـــة الثانيـــة تـــم نصـــح المريضـــات بتعـــديل الـــنمط الغـــذائى. وقـــد أجريـــت هـــذه الدراســـة مـــن أبريـــل 2019 حتـــى أكتـــوبر 2020 , وقـــد تـــم متابعـــة الحـــالات بواســـطة الموجـــات فـــوق الصـــوتية وتحليـــل الهرمونـــات والوزن قبل وبعد العلاج.

نتـــائج البحـــث: فـــي المجموعـــة الأولـــى مـــع مؤشـــر كتلـــة الجســـم أقـــل مـــن 30، كـــان هنـــاك 9 (30٪) مـــع نتيجـــة الحمـــل، 5 (16.7٪) مـــع نتيجـــة الحمـــل مـــع مؤشـــر كتلـــة الجســـم أكثـــر مـــن 30. وفـــي المجموعـــة الثانيـــة مـــع مؤشـــر كتلـــة الجســـم أقـــل مـــن 30 كـــان هنـــاك 2 (6.9٪) مـــع نتيجـــة الحمـــل 2 (6.5٪) مـــع نتيجـــة الحمـــل مـــع مؤشـــر كتلـــة الجســـم أكثـــر مـــن 30. وهنـــاك فـــرق كبيـــر بـــين العـــلاج باورليســـتات وتغييـــر الـــنمط الغـــذائى حيـــث تبـــين وجـــود فـــرق كبيـــر فـــى تحسين الخصوبة وفرص حدوث الحمل.

الاســـتنتاج: إســـتخدام اورليســـتات كعـــلاج للســـمنة وزيـــادة الـــوزن لـــه تـــأثير واضح على تحسين معدل الخصوبة وزيادة فرص الحمل.

الكلمات الدالة: السمنة، أورليستات، العقم، نتائج الحمل.