Endocrine changes after laparoscopic ovarian drilling in clomiphene citrate-resistant women with polycystic ovarian syndrome

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ABSTRACT

Objectives: To study the effects of laparoscopic ovarian drilling on the serum hormone levels in clomiphene citrate resistant women with polycystic ovarian syndrome (PCOS) and to determine the criteria which influenced their clinical response.

Methods: A prospective study that was carried out at Salmaniya Medical Complex in Bahrain. One hundred and eighty-one women with clomiphene citrate-resistant PCOS were treated with laparoscopic ovarian drilling, all procedures were performed over a 4-year period between June 1996 and June 2000. Fasting blood samples for determination of the serum levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), LH-FSH ratio, testosterone and prolactin were taken during the follicular phase before and one month after laparoscopic ovarian drilling.

Results: Responders who ovulated spontaneously after the drilling were obese and had higher preoperative LH levels and the LH-FSH ratio. Both responders and non-responders showed a significant decline in LH, LH-FSH ratio and testosterone with a significant increase in FSH but no significant change in prolactin mean values compared with pretreatment levels. The magnitude of change was significantly higher for LH and the LH-FSH ratio ($p<0.05$) in responders, while there were no significant differences in the corresponding values of the other hormones between the 2 groups. Moreover, the decrease in LH ($p<0.01$) and the LH-FSH ratio ($p<0.05$) was significantly greater in obese than non-obese women and this was only observed in the responders group.

Conclusion: Laparoscopic ovarian drilling is an effective procedure in women with clomiphene citrate resistant PCOS. It produces significant endocrine changes with better results in obese patients with higher preoperative LH values and LH-FSH ratio. The magnitude of these changes was the highest in obese responders.

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Polycystic ovarian syndrome (PCOS) is the most common cause of anovulatory infertility in women of reproductive age.[1] Its prevalence seems to be higher than expected[2] and the classical description of the obese, virilized patients with this syndrome cannot be maintained.[3] However, it is a spectrum of disorders that ranges from individuals with normal body weight, regular menstrual cycles with ultrasonic features of polycystic ovaries to those with the full clinical picture of oligomenorrhea, obesity, hirsutism and hyperandrogenemia. There are several treatment options. Clomiphene citrate (CC) is well accepted as the first line of treatment for infertile women with PCOS. Women who are clomiphene resistant can be treated either surgically or medically with human menopausal gonadotrophin (HMG), purified follicle stimulating hormone (FSH), or combinations of gonadotrophins with gonadotrophin releasing hormone agonist. However, this medical treatment

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is costly, stressful, requires monitoring and carries a risk of ovarian hyperstimulation syndrome, multiple pregnancies and miscarriages.[4-6] Furthermore, some slur has been put upon the medical stimulation treatment, as it has been connected with the late development of ovarian malignancy. Even if this connection is not at present clear, the point should probably not to be ignored.[7]

Laparoscopic ovarian drilling was first described in 1984 by Gjonnaess[8] as an alternative method to ovarian wedge resection for treating patients with anovulatory PCOS. Since then, a number of studies reported the success and utility of this procedure that resulted in good ovulatory and pregnancy rates.[9-11] The endocrine changes induced by ovarian drilling were found to be very similar to those obtained by ovarian wedge resection, while avoiding the risk of significant postoperative adhesion formation with subsequent mechanical subfertility.[8,12,13] The main goal of our study was to examine the biochemical and the biophysical attributes of both responders and nonresponder women with PCOS following unsupplemented laparoscopic ovarian drilling, we considered this may assist in the selection of patients to be treated with this procedure. At the same time, in an attempt to determine the mechanism of action, we studied the endocrine changes produced by ovarian drilling in these women with CC resistant PCOS. More recently, we showed a strong positive correlation between the clinical outcome of this procedure and obesity.[11] Therefore, the second goal of this study was to investigate the impact of body weight on these endocrine changes, if they occurred, in both responders and nonresponders PCOS women.

Methods. The women included in this study had been referred to the author's morning or evening (private) clinic at Salmaniya Medical Complex (SMC), the main tertiary referral hospital in Bahrain, and had anovulatory infertility. However, the majority of these patients were private ones and referred mainly from other private clinics or hospitals either for diagnostic laparoscopy as a part of the infertility investigations or for laparoscopic ovarian drilling after they have reached almost the end of their medical treatment options. It should be noted that the 2 main reasons for referral particularly to our hospital were; firstly, although these private subjects have to pay for their investigations and medications, most of the required surgical procedures including laparoscopies will be carried out for them at free of charge as per norms at SMC; secondly, most of these patients were obese who required to be cared for in a hospital with advanced facilities. The increasing number of cases managed in our unit accounts for higher figure in this study in view of the facts mentioned above. This increase is also due to the fact that our colleagues in the surgical department are conducting laparoscopic gastric banding for patients with morbid obesity and hence, our subjects are motivated. However, we have to be honest with our patients and explain to them the potential benefits and risks of various treatments options. In this study, we considered ovarian drilling in carefully selected subjects who were CC-resistant and who are unable or unwilling to undergo other treatment option.

All women had PCOS, diagnosed on the basis of the presence of at least 3 of the following criteria: 1) menstrual abnormalities and anovulation, 2) clinical evidence of hyperandrogenemia (hirsutism) or biochemical hyperandrogenemia (testosterone ≥ 2.9 nmol/L), 3) presence of typical appearances of PCOS on ultrasound examination, and 4) elevated luteinizing hormone (LH) concentration or LH-FSH ratio >2. Other known disorders, such as Cushing's syndrome, thyroid disease and congenital adrenal hyperplasia were excluded by appropriate tests. All patients had previously failed to respond to CC, and various other treatments had been tried unsuccessfully in several cases (including gonadotrophin, metformin, bromocriptine, dexamethasone, and in-vitro fertilization). CC-resistant was defined as failure to ovulate with increasing doses of CC up to a maximum of 200 mg per day for at least 6 consecutive cycles.

All subjects were informed clearly about the nature and purpose of the study and the potential benefits and risk of the procedure. If the subject agreed, a detailed medical history was obtained according to a standardized prepared questionnaire with emphasis on menstrual dating and regularity, duration and type of infertility, hirsutism, gynecological history, medications and family history. Amenorrhea was defined as the absence of menstruation for more than 6 months. Oligomenorrhea was defined as less than 8 cycles per year, and regular menstrual cycle as 26-34 days in length. The degree of hirsutism was determined using a Ferriman and Gallwey (F-G) score and those who had a F-G score of ≥8 were considered to be hirsute. The body mass index (BMI) was documented and those who had a BMI of ≥30 kg/m^2 were considered to be obese. Preoperative transabdominal or transvaginal ultrasound examination was performed on all patients and typical appearances of PCOS were considered if the ovaries were enlarged with a thickened abnormal stroma and more than 10 cysts of 2-8 millimeters (mm) in diameter, arranged peripherally around a dense core of stroma or scattered throughout an increased amount of stroma or both.[1,14] Any medication known to affect the hormone milieu was withheld 3 months before the procedure. The serum hormone levels of these subjects were studied on 2 occasions, before and after ovarian drilling. Venous blood samples were taken before the drilling, after an overnight fast between 0800 and 1000 hour for the measurement of serum LH, FSH, LH-FSH ratio, testosterone and prolactin between day 3 and 5 of the spontaneous or progestin-induced cycle. Unfortunately, serum androstenedione, fasting blood glucose and fasting insulin or other parameters level was not measured for the majority of these patients due to economical reasons.

To maximize uniformity of the surgical technique, all patients included in this study were operated upon by the author between June 1996 and June 2000. Laparoscopic ovarian drilling was performed as described previously[11] using 3-puncture technique. The patient was put in moderate (30^{O}) Trendelenburg position. A subumbilical incision was made and the Verres needle (CooperSurgical Inc, Lake Forest, CA, USA) introduced through it. A longer needle was used in obese patients. Whereas, in the average patients the Verres needle was angled at 45 degrees, an approach closer to the vertical was carried out in the obese ones to ensure the intraperitoneal position of the needle tip. Thereafter, a pneumoperitoneum was created, the needle was then removed and a 10-mm trocar inserted intraperitoneally. The trocar sleeve was left in situ and a 10-mm 0 degree telescope was inserted and connected to a camera with a video monitor system. A preliminary laparoscopic evaluation was performed before making the incisions for instrumentation. The abdominal cavity, especially the pelvic area was carefully inspected. Two further 5-mm trocars were inserted through small incisions in each of the iliac fossae, one for a grasping forceps and the other for a unipolar diathermy electrode. The ovary was stabilized by grasping the ovarian ligament with a grasping forceps, then the ovarian cortex was pierced to a depth of 6 mm using a unipolar electrode set to a power of 30-50 watts and cauterized for 2-4 seconds. The number of punctures made depended on the ovarian size and number of subcapsular cysts visible at laparoscopy. All punctures were done a way from the hilum and mesovarium to protect against damage to the ovarian blood supply. Adequate care was taken to avoid overly aggressive drilling, which may lead to excessive tissue destruction, adhesion formation, and even ovarian failure. At completion of the procedure, 200 ml of normal saline was then introduced into the pouch of Douglas in order to enhance ovarian cooling after diathermy. As a prophylaxis of deep venous thrombosis, all patients were encouraged for early ambulation especially obese ones who were also received subcutaneous injections of low molecular weight heparin (Innohep) 4500 IU once daily starting either at the time of pre-medication or in the theatre immediately before surgery and continuing for 7 days. Clear instructions were given to the senior resident who will review all the cases postoperatively to discharge home those who were fully conscious, with stable pulse and blood pressure readings and mobile without significant pain or bleeding, otherwise an overnight stay would be considered. All women were asked to report if any complications arise such as significant pain, bleeding, breathing difficulty, persistent vomiting, faint or collapse. In addition, all patients were advised to see the author one week postoperatively to reassess them, inspect their wounds, and discuss the operative findings and plan for further management.

Serum hormone levels were reexamined after the first spontaneous menstruation, approximately 4-6 weeks after ovarian surgery. We considered one month postoperatively is a reasonable interval for hormonal reassessment allowing us to control the follow-up of these patients more closely and at the same time achieving a reasonable recovery of the ovarian tissue from the drilling. Therefore, blood sampling was carried out between day 3 and 5 of the cycle for the measurement of serum concentrations of LH, FSH, LH-FSH ratio, testosterone and prolactin. Another blood sample was taken at the mid luteal phase (day 21) of the same cycle in order to measure the serum concentration of progesterone. Those who had a progesterone level of ≥30 nmol/L were considered to be ovulating. However, if the spontaneous menstruation did not occur during the 6 weeks following surgery, a random blood sample was taken to measure LH, FSH, LH-FSH ratio, testosterone and prolactin. The serum concentrations of these hormones were measured by the electrochemiluminescence immunoassay (ECLIA) using the Roche Elecsys 1010/2010 and modular analytics E170 (Elecsys module) immunoassay analyzers. All patients were followed regularly for up to 2 years and their ovulation was monitored by plasma progesterone levels estimations, as described previously.[11] Women who did not ovulate spontaneously or failed to conceive within 3 months after surgery were treated with CC, and those who failed to respond to CC received gonadotrophins. The so-called "responders" are women who either ovulated spontaneously or became pregnant immediately after the drilling. When the spontaneous ovulation or spontaneous pregnancy was not achieved, the patient was recorded as a "nonresponder".

Data were analyzed using Statistical Package for Social Sciences (SPSS) computer program. Independent samples T-test was used to compare continuous variables, chi-square tests were used to compare discrete variables and paired samples T-test was used to examine the difference between 2 mean values for the same hormone before and after surgery. Significance was taken as $p<0.05$.

Results. The study was conducted initially on 213 CC-resistant women with PCOS. However, 32 women were excluded from the study as they discontinued the follow-up. The characteristics of the remaining 181 women who underwent laparoscopic ovarian drilling and continued this study are presented in **Table 1**. Obesity was noted in 93 (51.4%) women and 99 patients (54.7%) were hirsute. The LH-FSH ratio was found to be elevated (>2) in 83 (45.9%) women, however, LH levels (>10 IU/L) were elevated in 114 (62.9%). The testosterone levels were raised (≥2.9 nmol/L) in 54 (29.8%) women and 42 patients (23.2%) had hyperprolactinemia (range 28-91.5 ng/ml). Computerized tomography or magnetic resonance imaging of the pituitary did not reveal either a microadenoma or macroadenoma in any patient. As noted above, all patients had previously failed to respond to CC for at least 6 cycles and various other treatments had been tried unsuccessfully in several cases including 173 women who had received over 6 cycles of CC. Of these, 69 patients had received additional gonadotrophin therapy for 4-6 cycles including 18 women who had additional an in-vitro fertilization treatment. With or without gonadotrophin therapy; 56 women had received additional metformin, 24 patients had additional bromocriptine, and 11 women had additional dexamethasone treatment. Five patients had previously experienced moderate to severe ovarian hyperstimulation syndrome with gonadotrophin therapy, which required hospitalization.

The number of punctures drilled on each ovary varied from 5-15 (mean 9.1). There were no significant intraoperative or immediate postoperative complications. After surgery, 167 women (92.3%) were discharged home within 6 hours and the remaining 14 (7.7%) after 24 hours. The clinical results related to this study have already been published elsewhere[11] and can be summarized as follows: 127 patients (70.1%) ovulated spontaneously after the drilling and the remaining 54 (29.9%) patients were nonresponders; of these, 51 (28.2%) women ovulated after surgery with CC, but 3 (1.7%) remained persistently anovulatory even after treatment with HMG. One hundred and fifty three patients (84.5%) eventually conceived after the drilling. Of these, 59 women (32.5%) who conceived spontaneously after surgery, 83 women (45.9%) conceived with the help of CC (54 women in responders group and 29 women in the nonresponders), and 11 (6.1%) patients conceived with HMG (2 patients in responders group and 9 patients in the non-responders). **Table 1** shows the attributes of the responders (n=127) compared to those of the non-responders (n=54). The BMI (p=0.04) and pretreatment LH value (p=0.002) and the LH-FSH ratio (p=0.003) was significantly higher in the responders than in the nonresponders. However, there were no significant differences between the two groups in their age, duration of infertility, ultrasonographic findings, menstrual cycle pattern, basal serum FSH, testosterone or prolactin levels. The serum hormone levels before and after laparoscopic ovarian drilling are presented in **Table 2 and Table 3**. Both responders and non-responders showed a significant increase in FSH values (p<0.0001 and p<0.01) and a significant decrease in LH values (p<0.0001 and p<0.001), the LH to FSH ratio (p<0.0001 and p<0.001) and testosterone levels (p<0.0001 and p<0.01) but prolactin values showed no significant change compared with the pretreatment levels. The magnitude of change in these values was significantly greater for LH (p=0.02) and the LH-FSH ratio (p=0.04) in the responders than in the nonresponders, whereas there were no significant differences between the 2 groups in the corresponding values of the other hormones.

Table 2 shows the biochemical response of the responders and the endocrine profiles of the obese responders (n=72) are compared with those of the nonobese responders (n=55). Before drilling, there were no significant differences between the 2 groups in all the measured hormone levels. After drilling, although LH levels and the LH-FSH ratio reduced significantly (p<0.0001) in both groups, the magnitude of reduction was significantly higher in the obese responders than in the nonobese responders (p<0.01 for LH and p<0.05 for LH-FSH ratio). Both obese responders and nonobese responders showed a significant increase in FSH values (p<0.0001 for obese and p<0.001 for nonobese responders) with a significant decrease in testosterone values (p<0.01 for obese and p<0.05 for nonobese responders); however, the magnitude of these changes was not significantly different between the 2 groups. No significant changes occurred in the serum prolactin levels compared with the pretreatment values in both groups.

Table 3 shows the biochemical response of the nonresponders and the endocrine profiles of the obese-nonresponder (n=21) are compared with those of the nonobese-nonresponders (n=33). There was a significant postoperative increase in FSH levels with a significant decline in LH, LH-FSH ratio and testosterone but no significant changes occurred in prolactin values in both groups. On the other hand, no statistically significant differences were observed between the 2 groups either in preoperative or in postoperative serum concentrations of all the studied hormones.

Discussion. Polycystic ovarian syndrome encompasses a heterogeneous group of condition and the diagnosis is based on different parameters by different investigators. Accordingly, the response

Table 1 - Basal clinical and endocrine attributes of women who underwent laparoscopic ovarian drilling.

Parameter	**All patients (n=181)**	**Responders (n=127)**	**Non-responders (n=54)**	***p*-value***
Age (years)	30.4 ± 5.7	30.5 ± 5.8	30 ± 5.7	0.61
BMI (kg/m^2)	29.9 ± 6.7	30.6 ± 6.6	28.3 ± 6.6	0.04
Duration of infertility (years)	4.4 ± 3.5	4.4 ± 3.4	4.4 ± 3.8	0.93
			11.2 ± 4	
LH (IU/L)	13.2 ± 5.7	14.0 ± 6.2	5.9 ± 1.6	0.002
FSH (IU/L)	6.2 ± 3.1	6.3 ± 3.6	1.9 ± 0.6	0.47
LH-FSH ratio	2.2 ± 1	2.4 ± 1	2.2 ± 1.6	0.003
Testosterone (nmol/L)	2.4 ± 1.4	2.5 ± 1.3	22.2 ± 15.7	0.26
Prolactin (ng/ml)	21.2 ± 14.5	20.8 ± 14		0.56
Hirsutism				0.25
Yes (%)	99 (54.7)	73 (57.5)	26 (48.1)	
No (%)	82 (45.3)	54 (42.5)	28 (51.9)	
Ultrasonography				0.27
Typical of PCOS (%)	105 (58)	77 (60.6)	28 (51.9)	
Atypical of PCOS (%)	76 (42)	50 (39.4)	26 (48.1)	
Infertility				0.53
Primary (%)	87 (48.1)	63 (49.6)	24 (44.4)	
Secondary (%)	94 (51.9)	64 (50.4)	30 (55.6)	
Menstrual cycle pattern				0.21
Regular (%)	19 (10.5)	10 (7.9)	9 (16.7)	
Oligomenorrhea (%)	124 (68.5)	90 (70.9)	34 (63)	
Amenorrhea (%)	38 (21)	27 (21.3)	11 (20.4)	

Values are given as number (%) and mean ± standard deviation, BMI - body mass index, PCOS - polycystic ovarian syndrome, LH - luteinizing hormone, FSH - follicle stimulating hormone; *comparison between responders and nonresponders women.

Table 2 - Serum hormone levels before and after laparoscopic ovarian drilling in responders.

Parameter	**All patients (n=127)**		**Obese patients (n=72)**		**Nonobese patients (n=55)**	
	Before	**After**	**Before**	**After**	**Before**	**After**
LH (IU/L)	14.0 ± 0.6	8.4 ± 0.3*	13.9 ± 0.8	7.7 ± 0.3*	14.3 ± 0.8	9.4 ± 0.5*
FSH (IU/L)	6.3 ± 0.3	7.1 ± 0.3*	6.1 ± 0.2	7.1 ± 0.2*	6.6 ± 0.7	7.3 ± 0.7†
LH-FSH ratio	2.4 ± 0.1	1.4 ± 0.1*	2.3 ± 0.1	1.2 ± 0.1*	2.5 ± 0.2	1.5 ± 0.1*
Testosterone (nmol/L)	2.5 ± 0.1	2.3 ± 0.1*	2.7 ± 0.2	2.4 ± 0.1‡	2.3 ± 0.1	2.1 ± 0.1§
Prolactin (ng/ml)	20.8 ± 1.2	19.8 ± 0.7	20.7 ± 1.3	20.0 ± 0.9	20.9 ± 2.3	19.6 ± 1.1

Values are given as mean ± standard error of the mean.
The probability of chance difference: **p*<0.0001, †*p*<0.001, ‡*p*<0.01, §*p*<0.05; comparing values before and after drilling in each group separately.
LH - luteinizing hormone, FSH - follicle stimulating hormone.

Table 3 - Serum hormone levels before and after laparoscopic ovarian drilling in non-responders.

Parameter	**All patients (n=54)**		**Obese patients (n=21)**		**Nonobese patients (n=33)**	
	Before	**After**	**Before**	**After**	**Before**	**After**
LH (IU/L)	11.2 ± 0.6	9.7 ± 0.5*	12.3 ± 1.0	10.1 ± 0.6†	10.5 ± 0.6	9.5 ± 0.7‡
FSH (IU/L)	5.9 ± 0.2	6.7 ± 0.3†	6.4 ± 0.3	7.0 ± 0.4‡	5.6 ± 0.3	6.6 ± 0.3‡
LH-FSH ratio	1.9 ± 0.1	1.6 ± 0.1*	1.9 ± 0.1	1.5 ± 0.1‡	2.0 ± 0.1	1.7 ± 0.2‡
Testosterone (nmol/L)	2.2 ± 0.2	2.0 ± 0.2†	2.0 ± 0.2	1.8 ± 0.2‡	2.4 ± 0.3	2.1 ± 0.3‡
Prolactin (ng/ml)	22.2 ± 2.1	20.3 ± 1.2	25.7 ± 4.3	22.3 ± 2.0	19.9 ± 2.2	19.1 ± 1.5

Values are given as mean ± standard error of the mean. The probability of chance difference: **p*<0.001, †*p*<0.01, ‡*p*< 0.05; comparing values before and after drilling in each group separately. LH - luteinizing hormone, FSH - follicle stimulating hormone.

of these patients in different series may be different in quality or magnitude following different types of treatment including ovarian drilling. In this study, we tried to establish the biophysical and endocrine factors that influenced the outcome of laparoscopic ovarian drilling in carefully diagnosed subjects with CC-resistant PCOS based on the criteria mentioned above. Confirming previous reports, we found a better clinical and endocrine response in obese patients[11] and those with high preoperative LH levels.[11,15] We also showed a good outcome in women with higher preoperative LH-FSH ratio. Although previously reported better pregnancy rates in younger women,[11] this was not the case in this series, whereas, there was no significant difference between responders and nonresponders with regard to their age.

Our endocrine data are comparable with those previously described,[16-18] showing a significant decrease in testosterone and LH values along with significant reduction in LH-FSH ratio after the drilling. It also showed a significant postoperative increase in FSH levels, and this was consistent with that reported by others.[15,19] In this context, it has been suggested that the destruction of the androgen-producing stroma of the ovaries with the drilling will lead to the reduction of serum androgen levels, decreasing the amount of substrate available for peripheral aromatization to estrogens. This will restore the feedback mechanism to the hypothalamic-pituitary axis, allowing appropriate gonadotrophin stimulation for follicular development and ovulation.[17] Another suggestive mechanism is a reduction of the circulating levels of inhibin after the procedure, resulting in secondary rise in the FSH level accompanied with decreased intrafollicular androgen levels with subsequent appropriate follicular growth.[20] Furthermore, it has been reported a 40% increase in the concentrations of sex hormone binding globulin (SHBG) following the drilling, which associated with significant decrease in the free androgen levels.[21]

Both responders and nonresponders, in this study, showed a significant increase in FSH levels with a significant decrease in LH, LH: FSH ratio and testosterone values. These results are similar to those previously described,[15] although others found a significant postoperative endocrine changes only in the responders.[22] The significant improvement in the endocrine profile observed in our patients, responders and nonresponders, may explain the improved response of these women in both groups to CC following ovarian drilling as previously reported, despite earlier failure of this therapy in the same women.[11,19] However, the magnitude of change in the LH values along with LH-FSH ratio was significantly higher in responders than nonresponders but there were no significant differences between the 2 groups with regard to FSH and testosterone. This demonstrates the importance of LH in the genesis or maintenance of anovulation in these patients. The role of LH in PCOS has been emphasized in terms of development of the growing follicle, maturation of the oocyte and outcome of the pregnancy.[23] The decrease in LH level after ovarian drilling has been verified in several reports.[16-19,21,22] This reduction seems to last for more than 18 years.[21] It has been advocated that the decrease in LH after ovarian electrocautery is an indication that the high LH level seen in PCOS is probably secondary to the ovarian dysfunction.[21]

Low calorie diet should be the first choice of treatment for obese PCOS subjects. However, the compliance of these patients with diet is often poor. Obesity in women with PCOS was found to be associated with insulin resistance and a compensatory hyperinsulinemia, which may further contribute to ovarian hyperandrogenism and may directly interfere with ovulation.[24] Improvement in insulin resistance through the use of insulin-sensitizing agents such as metformin has been described and may have an important role in the management of these cases.[25] Nevertheless, laparoscopic ovarian drilling may offer greater scope for practical application in these women who were CC-resistant and who are unable or unwilling to undergo other medical treatment option. The impact of obesity or high BMI on the outcome of the drilling is disputable. Both reduced ovulation or pregnancy rates[26,27] and normal ovulation or pregnancy rates compared with those in non-obese patients were reported.[15,17,21] However, in agreement with our previous study,[11] we found a strong positive correlation between the outcomes of surgery and obesity. In this series, the obese women (BMI $\geq$30 kg/m^2) had a spontaneous ovulation rate of 56.7%, compared with 43.3% for nonobese (p=0.035). With this encouraging result, we suggest that obesity should not be considered a contraindication to laparoscopic ovarian drilling, although, obese patients are at higher risk of anesthetic and surgical complications such as difficult tracheal intubation, respiratory complications, deep venous thrombosis, wound infection and may be also more difficulties in creating a pneumoperitoneum during laparoscopic procedures. However, adequate precautions should be taken to obviate these complications as previously mentioned and all obese women should be cared for by an expert anesthesiologist and an expert gynecologist who can deal with such cases.

The mechanism by which laparoscopic ovarian drilling could induce a better response in our obese PCOS women compared with non-obese subjects is not clear. A possible explanation is that our obese women may have less severity or inherent sensitivity of the condition than nonobese ones. In this study, there were no significant differences between obese and nonobese women in their preoperative serum concentration of all the measured hormone values. This finding is in disagreement with others who found a higher plasma LH levels[28,29] and the LH-FSH ratio in nonobese PCOS subjects with respect to that of obese PCOS women.[28] It has been demonstrated that the response of laparoscopic ovarian drilling is highly correlated with the preoperative plasma LH levels.[11,15] Therefore, following the drilling, if the differences observed between obese and nonobese PCOS groups, it may reflect the respective preoperative plasma LH values. On the other hand, it has been reported that the body weight did not influence the endocrine changes after ovarian electrocautery significantly,[21] and this was comparable with our nonresponders group only. However, in the responders, the obese patient showed a greater decline in their LH values along with their LH-FSH ratio than nonobese ones in this series. Therefore, obesity per se in these patients seems to induce an LH decrease after ovarian drilling of prevalently greater magnitude. The mechanism of this reaction has yet to be determined.

The behavior of LH secretion in the blood of obese PCOS subjects could be the consequence of a sex steroid imbalance due to body fat excess. Obesity per se leads to reduced SHBG concentrations,[29,30] resulting in increased levels of free testosterone and estrone of extraglandular production, which may induce inappropriate feedback regulation on the hypothalamic-pituitary unit. Insulin receptors have been identified on the pituitary cells,[31] and the hyperinsulinemia of obesity may operate at a pituitary level to dampen LH pulse amplitude.[32] Alternatively, another fat associated factor, such as leptin, with a hypothalamic or pituitary site of action could mediate a feedback effect on LH secretion. This hypothesis is clarified earlier by reporting an elevated serum leptin levels in PCOS patients compared with weight matched normal women.[33] On the other hand, the decreased circulating LH levels in obese patients could be explained by an increase in renal gonadotrophin clearance that is unique to PCOS women and not seen in normal obese ones.[34] However, so far, the current knowledge of these aspects is too limited to encourage the formation of precise hypothesis and the exact interrelationship between body weight, hormones, and the ovarian response to electrocautery remains unclear. Further studies are needed to support these hypotheses by examining such factors before and after drilling in these patients, together with long-term follow-up after the procedure.

In conclusion, our results demonstrate that laparoscopic ovarian drilling is very useful when CC fails in patients with PCOS. Most of the endocrine abnormalities associated with this condition are corrected by the procedure, and the outcome is more likely to be successful in obese women with higher preoperative LH levels and LH-FSH ratio. The magnitude of endocrine changes was significantly greater for LH and the LH-FSH ratio in responders compared with non-responders and particularly more in obese responders ones.

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