ORIGINAL ARTICLE

Effects of laparoscopic ovarian drilling in treating infertile anovulatory polycystic ovarian syndrome patients with and without metabolic syndrome

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Objective To compare the effects of laparoscopic ovarian drilling in treating infertile polycystic ovarian syndrome in patients with and without metabolic syndrome.

Design Retrospective review.

Setting A university-affiliated hospital in Hong Kong.

Patients A total of 89 infertile anovulatory polycystic ovarian syndrome patients, who underwent laparoscopic ovarian drilling with completed metabolic screening and seen over a 5-year period from 2002 to 2007.

Main outcome measures The clinical, hormonal, and metabolic characteristics as well as spontaneous ovulation rates, reproductive outcomes, and diabetes risks during pregnancy observed after laparoscopic ovarian drilling.

Results Approximately one fifth (21%) of polycystic ovarian syndrome patients had the metabolic syndrome. There were no differences in spontaneous ovulation rates (68% vs 61%, P=0.76), cumulative pregnancy rates (68% vs 61%, P=0.77), and diabetes risks during pregnancy (64% vs 42%, P=0.13) between patients with and without metabolic syndrome.

Conclusion Laparoscopic ovarian drilling was equally effective in inducing ovulation in polycystic ovarian syndrome patients with metabolic syndrome. Thus, patients with metabolic syndrome should not be precluded from laparoscopic ovarian drilling, which has the additional advantage of enabling full tubo-peritoneal assessment at the same time.

Introduction

Polycystic ovarian syndrome (PCOS) is the most common reproductive endocrinopathy affecting 6 to 12% of women during their reproductive age.[1,2] It is also the major cause of anovulatory infertility.[3] The first-line treatment of anovulatory infertility in PCOS patients is clomiphene citrate.[3-5] Laparoscopic ovarian drilling (LOD) has been shown to be an effective means of inducing ovulation in these patients when clomiphene citrate fails.[5,6]

Polycystic ovarian syndrome has diverse phenotypes whose aetiology remains unclear. Hyperandrogenism mediated through elevated luteinising hormone (LH) [endocrine pathway] and/or insulin resistance (metabolic pathway), which are both important pathophysiological features but the relative contribution of these pathways to the disease mechanism varies in different subjects, which possibly accounts for its clinical heterogeneity.[7,8] Emerging evidence suggests that a significant proportion of PCOS patients have central obesity,[9] glucose intolerance,[10,11] atherogenic dyslipidaemia[12,13] and hypertension,[14] which contribute to the development of metabolic syndrome (MetS). According to our earlier study,[15] patients with PCOS had a 5-fold increased risk of developing MetS.

While LOD seems to be more effective in inducing ovulation in LH-predominant patients,[6] after the procedure, both LH and androgen levels decrease[16] but there is no impact on metabolic parameters (including plasma glucose, insulin, and lipid levels).[17-19] In addition, LOD was noted to be less effective in inducing ovulation in obese PCOS women.[20] It was therefore unclear as to whether LOD would work effectively in PCOS patients with MetS.

Key words
Diabetes mellitus, type 2; Hyperandrogenism; Infertility, female; Metabolic syndrome X; Polycystic ovary syndrome;

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腹腔鏡卵巢打孔術治療有或無新陳代謝症候群的多囊卵巢綜合徵無排卵性不孕患者的成效

目的 比較有或無新陳代謝症候群的多囊卵巢綜合徵（PCOS）不孕患者，其腹腔鏡卵巢打孔術的治療成效。

設計 回顧研究。

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患者 2002至2007年的5年期間，共89位PCOS無排卵性不孕患者接受腹腔鏡卵巢打孔術治療及代謝篩查。

主要結果測量 臨床、激素和代謝特徵，以及接受治療後的自然排卵率、妊娠情況和糖尿病風險。

結果 約有五分之一（21%）PCOS患者出現新陳代謝症候群。將有新陳代謝症候群與無新陳代謝症候群兩組的結果比較，發現無論在自然排卵率（68%比61%，P=0.76）、累積妊娠率（68%比61%，P=0.77），以及妊娠期間的糖尿病風險（64%比42%，P=0.13）都沒有顯著分別。

結論 以腹腔鏡卵巢打孔術治療有新陳代謝症候群的PCOS患者，同樣能有效地刺激排卵。所以這些患者不應被抹剎接受上述治療的機會；患者也可於治療期間同時作全面的腹膜管檢查。

This retrospective study aimed to compare the clinical, hormonal, and metabolic characteristics, as well as the reproductive outcomes after LOD in PCOS patients with and without MetS. The primary outcome measure was the spontaneous ovulation rate after LOD, and secondary outcome measures were pregnancy outcomes and the diabetes risk during pregnancy.

Methods

Patient selection

All infertile Chinese PCOS patients who underwent LOD at the Prince of Wales Hospital, a university-affiliated hospital in Hong Kong, over a 5-year period from 2002 to 2007 were reviewed. In our unit, LOD was offered to patients with PCOS according to the Rotterdam consensus,[21] so they had to have evidence of chronic anovulation and sonographic appearance of polycystic ovaries when undergoing laparoscopic assessment for infertility.

Laparoscopic ovarian drilling

All operations were performed by a designated team, which comprised two surgeons. The procedure in our centre involved a three-puncture laparoscopy: a 10-mm laparoscope was inserted via the primary sub-umbilical port, with two additional 5-mm ports in the lower abdomen. A pair of grasping forceps was used to hold the ovarian ligament for manipulation of the ovary; a laparoscopic ovarian diathermy was introduced via the 5-mm port for drilling. A laparoscopic ovarian diathermy needle with a distal operating needle measuring 8 mm in length and 2 mm in diameter was used with a standardised monopolar coagulation current set at 30 watts. The output waveform of the current had a nominal frequency of 500 kHz and a maximum output of 99 watts at 300 Ω resistances. A total of 3 to 10 punctures 7 to 8 mm in depth were made in each ovary depending on its size. Each penetration lasted 4 to 5 seconds.[6,16]

Clinical, anthropometrical, and biochemical parameters

A standard data sheet was used to record the personal, medical and drug histories; regularity and length of the menstrual cycle; symptoms of hirsutism and acne; duration and cause of infertility and previous ovulation induction method and response. Sitting blood pressure was measured after 5-minute rest using a standard sphygmomanometer. Body weight, body height, and waist circumferences were measured. Waist circumference was taken as the narrowest measurement midway between the top of iliac crest and the lower rib margin.

Serum hormone assays were performed for LH, follicle stimulating hormone (FSH), and total testosterone using blood samples taken in the early follicular phase (defined as day 2 to 3 of the menstrual cycle) or after progestogen-induced menstruation. The concentrations were measured using validated assays on an Immulite 1000 semi-automated immunoassay analyser (Diagnostic Products Corporation, Los Angeles [CA], US) in our laboratory at the Department of Clinical Chemistry, Prince of Wales Hospital. We defined LH predominance as elevated LH-to-FSH ratio of ≥2.5 or increased basal concentration of LH to ≥10 IU/L. Biochemical hyperandrogenaemia was defined as elevated total testosterone of ≥3 nmol/L, which was the 97.5th percentile of the values of total testosterone of healthy women. Overnight fasting blood samples were taken on the same day as the hormonal assay for measurement of total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, fasting plasma glucose (FPG), and fasting insulin. A 2-hour plasma glucose concentration was also determined as part of a 75 g oral glucose tolerance test (OGTT).

Metabolic syndrome

Metabolic syndrome was defined according to the AHA/NHLBI (American Heart Association and the National Heart, Lung and Blood Institute)–modified

Adult Treatment Panel III criteria in 2005 (ATPIII 2005).[22] This entailed co-occurrence of three or more of the following risk factors:

(1) Impaired fasting glucose (FPG ≥5.6 mmol/L) or impaired glucose tolerance after 75 g OGTT (2-hour plasma glucose ≥7.8 and <11.1 mmol/L) or type II diabetes (FPG ≥7 mmol/L or 2-hour plasma glucose ≥11.1 mmol/L).[23]
(2) Elevated systolic and/or diastolic blood pressure of ≥130/85 mm Hg.
(3) Reduced fasting HDL-C of <1.3 mmol/L.
(4) Elevated fasting TG of ≥1.7 mmol/L.
(5) Central obesity with waist circumference of ≥80 cm in Asian women.[24] In cases where waist circumference was not measured, a body mass index (BMI) of 25 kg/m^2 was used as a surrogate, which corresponded to a waist circumference of 80 cm (r=0.92, P<0.001) in data derived from our previous studies.[15,25]

Postoperative reproductive outcomes

Following LOD, the regularity of the menstrual cycles was recorded. Ovulation was examined by mid-luteal phase progesterone; a serum progesterone level of >10 ng/mL was taken as confirming ovulation.[26] If spontaneous ovulation occurred, the women were advised to contemplate natural conception for 6 to 12 months if no other infertility factors co-existed. If the women failed to conceive during this period, they preceded to gonadotrophin ovulation induction with intrauterine insemination. If spontaneous ovulation failed to ensue after LOD, clomiphene citrate treatment was added as an ovulation induction adjuvant (starting from 50 mg/day for 5 days in the early follicular phase of menstrual cycle). Depending on the presence of other concomitant infertility factors, patients might receive gonadotrophin ovulation induction with intrauterine insemination for patients with co-existing borderline male factor, in-vitro fertilisation for patients with co-existing moderate-to-severe tubo-peritoneal factors or severe male factor. The reproductive outcomes in terms of spontaneous ovulation, pregnancy, method of conception, pregnancy outcome, multiple pregnancy, and diabetes complicating pregnancy were assessed. For diabetes complicating pregnancy, diagnosis was made by an FPG of ≥5.5 mmol/L or a 2-hour plasma glucose of ≥8 mmol/L according to the Australasian Diabetes in Pregnancy Society's criteria[27] after a standard 75 g OGTT. The screening for diabetes complicating pregnancy was usually performed early in the third trimester and in some patients, also in the first trimester.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (Windows version 16; SPSS Inc, Chicago [IL], US). Continuous variables were presented as mean (standard deviation [SD]) or median (interquartile range [IQR]), and analysed using independent sample t test for normally distributed data or Mann-Whitney U test for non-parametric variables. Categorical variables were expressed as proportions (percentages) and analysed by Chi squared or Fisher's exact tests as appropriate.

Results

A total of 109 consecutive anovulatory infertile PCOS Chinese patients underwent LOD over the 5-year study period with a median follow-up duration of 16 (range, 8-26) months were examined. Twenty women who had incomplete metabolic screening were excluded. There were no differences in the clinical and biochemical characteristics between those who were included and excluded from the study.

A total of 89 patients were included for data analysis. Their median age was 32 (IQR, 30-35) years, and the median duration of infertility was 60 (IQR, 36-84) months. In all, 59 (66%) of the patients had primary infertility and 18 (20%) had concomitant infertility factors apart from anovulation (10 had tubo-peritoneal factors including moderate-to-severe endometriosis, and 8 had borderline-to-severe male factors). Among these patients, 75 had had previous ovulation induction—46 (61%) had clomiphene citrate resistance (no ovulation despite clomiphene citrate of up to 150 mg/day for 5 days in the early follicular phase of menstrual cycle), and 29 (39%) had clomiphene citrate failure (no conception despite ovulatory response achieved with clomiphene citrate for more than 6 cycles). Among the whole cohort, the median serum concentration of LH was 7.7 (3.9-10.9) IU/L and 29 (33%) of the patients were found to have LH predominance. The median body weight and BMI were 58 (50-71) kg and 24 (21-27) kg/m^2, respectively. Thirty-five (39%) of the patients were noted to be obese using the Asian-specific cut-off BMI value of 25 kg/m^2 or greater.

Concerning reproductive outcomes, in our study 54 (61%) of the patients achieved spontaneous ovulation after LOD. A total of 56 patients achieved pregnancy in the whole cohort (cumulative pregnancy rate of 63%), and 31 (35%) achieved pregnancy within a 12-month period. For those who conceived spontaneously (n=31), the median duration to get pregnant was 11 (3-26) months after LOD. Eight women conceived with clomiphene citrate as supplementary treatment after LOD, eight conceived with the aid of gonadotrophin induction and intrauterine insemination because of associated borderline male factors, and nine conceived with the aid of in-vitro fertilisation (to overcome tubo-peritoneal factors). Among these pregnancies, 13

TABLE 1. Clinical and biochemical characteristics in polycystic ovarian syndrome patients with and without metabolic syndrome (MetS)

Characteristic*	Median (interquartile range) or No. (%)		P value
	Without MetS (n=70)	With MetS (n=19)	
Clinical and biochemical characteristics			
Age (years)	32 (30-35)	32 (30-34)	0.81†
Infertile duration (months)	60 (36-84)	60 (36-84)	0.89†
Concomitant factors	15/70 (21%)	3/19 (16%)	0.75‡
Response to previous ovulation induction			0.79‡
No clomid (therapy-naïve)	11/70 (16%)	3/19 (16%)	
Clomid resistance	35/70 (50%)	11/19 (58%)	
Clomid failure	24/70 (34%)	5/19 (26%)	
Operating time (mins)	30 (25-45)	40 (30-60)	0.31†
Follow-up duration (months)	17 (8-28)	17 (7-28)	0.66†
Total testosterone (nmol/L)	1.6 (1.3-2.3)	1.3 (0.8-1.9)	0.06†
LH level (IU/L)	6.9 (3.9-11.0)	9 (3.8-11.0)	0.44†
LH predominance	21/69 (30%)	8/19 (42%)	0.49‡
FSH level (IU/L)	6.0 (4.9-7.2)	5.8 (5.2-6.3)	0.76†
Body weight (kg)	55.7 (48.9-61.8)	75.0 (65.4-83.8)	<0.001†
BMI (kg/m^2)	21.4 (19.9-24.9)	28.7 (26.0-32.9)	<0.001†
WC (cm)	74.3 (69.0-81.8)	88.0 (85.0-98.0)	<0.001†
SBP (mm Hg)	108 (100-115)	134.0 (119-149)	<0.001†
DBP (mm Hg)	66 (60-74)	77 (70-87)	<0.001†
Fasting TG (mmol/L)	1.0 (0.7-1.5)	1.6 (1.1-2.2)	0.003†
Fasting HDL-C (mmol/L)	1.6 (1.3-2.0)	1.2 (1.0-1.3)	<0.001†
Fasting LDL-C (mmol/L)	2.7 (2.3-3.2)	2.9 (2.5-3.4)	0.29†
Fasting cholesterol (mmol/L)	4.9 (4.4-5.4)	4.7 (4.2-5.8)	0.69†
Fasting plasma glucose (mmol/L)	5.0 (4.8-5.3)	5.5 (5.2-6.8)	<0.001†
2-Hour plasma glucose after OGTT (mmol/L)	5.7 (4.8-6.7)	9.6 (6.5-14.1)	<0.001†
Fasting insulin (mIU/L)	7.6 (5.2-10.4)	19.0 (14.1-29.7)	<0.001†
Modified ATPIII criteria			
BMI ≥25 kg/m^2 or WC ≥80 cm	23/69 (33%)	17/19 (89%)	<0.001‡
SBP ≥130 or DBP ≥85 mm Hg	4/64 (6%)	12/19 (63%)	<0.001‡
Fasting TG ≥1.7 mmol/L	8/64 (13%)	8/18 (44%)	0.005‡
Fasting HDL-C <1.3 mmol/L	9/64 (14%)	15/18 (83%)	<0.001‡
Fasting glucose ≥5.6 mmol/L or IGT/DM	11/70 (16%)	14/19 (74%)	<0.001‡

* ATPIII criteria denotes Adult Treatment Panel III criteria, BMI body mass index, DBP diastolic blood pressure, DM type 2 diabetes, FSH follicle-stimulating hormone, HDL-C high-density lipoprotein cholesterol, IGT impaired glucose tolerance, LDL-C low-density lipoprotein cholesterol, LH luteinising hormone, OGTT oral glucose tolerance test, SBP systolic blood pressure, TG triglycerides, and WC waist circumference

† Mann-Whitney *U* test

‡ χ^2/Fisher's exact test as appropriate

(23%) ended in miscarriages. In all, 42 pregnant women had 75 g OGTTs performed, of whom 20 (48%) were diagnosed to have diabetes complicating pregnancy. There were four multiple pregnancies but none resulted from spontaneous conception.

Tables 1 and 2 show a comparison of clinical, hormonal, and metabolic parameters as well as postoperative reproductive outcomes in the PCOS patients with and without MetS. Based on the modified ATPIII 2005 criteria, 19 (21%) of the patients were diagnosed to have MetS. Their median age was 32 (30-34) years and their median body weight was 75 (65-84) kg. The remaining 70 (79%) of the women without MetS had a median age of 32 (30-35) years and a median body weight of 56 (49-62) kg. There were no significant differences between the two groups in terms of age, duration of infertility, response to previous ovulation induction, and serum hormone concentrations (including total testosterone and LH levels). When compared with patients without MetS, those with the syndrome were significantly more obese (with central obesity), had higher systolic and diastolic blood pressures, higher levels of fasting and 2-hour OGTT glucose, fasting insulin, fasting TG, but they had lower fasting HDL-C levels (P<0.001 for all differences). Reproductive outcomes after LOD in the two groups were comparable (Table 2), there being no differences in terms of ovulation rates (P=0.76), cumulative pregnancy rates (P=0.77), and diabetes risks during pregnancy (P=0.13).

Discussion

Increasing evidence suggests that PCOS is associated with MetS. The reported prevalence of MetS in PCOS patients varies from 1.6 to 46% in different countries and ethnic groups.[28-30] These differences are not solely accountable by the difference in definitions of MetS used in different reports; differences in genetic predisposition, diet, and environment factors also play a role. Besides, in the pathogenesis of PCOS there are different contributions due to elevated LH levels (endocrine pathway) and insulin resistance (metabolic pathway) that account for some of the clinical heterogeneity.

In the current study, about one fifth (21%) of PCOS women had MetS, which was comparable to an earlier report[15] in Hong Kong Chinese PCOS women. Apart from having more central obesity, higher levels of blood pressures and dysglycaemia, patients with MetS had significantly higher levels of fasting insulin and more dyslipidaemia.[30,31] The latter patients also had higher fasting TG and lower HDL-C levels, confirming the strong association with insulin resistance. The hormone levels (including serum concentrations of LH and total testosterone) in the two groups differed, which was also in accord with other reports.[15,30]

The LOD procedure has been widely used to induce ovulation in PCOS women after failure of clomiphene citrate treatment, and the spontaneous ovulation and pregnancy rates achieved in the current study were comparable to those reported in the literature.[6,16] The exact mechanism of how LOD induces ovulation is unclear. According to one hypothesis, it destroys androgen-producing ovarian tissue, which may correct the androgenic intra-ovarian environment and allow better follicular development and ovulation.[32] Following LOD, there was a reduction in circulating LH and androgen levels,[16,18,19] however, insulin sensitivity and serum glucose levels and lipoprotein profiles remained unchanged.[17-19] This possibly explained the favourable responses in PCOS patients with high preoperative LH level.[6] Our study, however, has demonstrated that LOD was equally effective in inducing ovulation in PCOS patients with predominant metabolic disturbances. This suggests that the endocrine aberration associated with anovulation is correctable locally at the ovarian level, without modulating the metabolic pathway. Therefore PCOS patients with MetS should not be precluded from LOD, which has additional advantage of allowing tubo-peritoneal assessment at the same time.

Notably, LOD had no impact on the metabolic pathway as supported by the high risk of diabetes during pregnancy, particularly in those with concomitant MetS. More than 60% of PCOS women with MetS in the current cohort were found to have gestational diabetes mellitus. In this context, adjuvant strategies like insulin sensitisers may confer additional benefits in those with metabolic disturbances. It was reported that the administration of metformin alone to overweight PCOS women resulted in higher pregnancy and live-birth rates when compared with those having LOD alone.[33] Moreover, such treatment was associated with reduced gestational diabetes mellitus rates during pregnancies.[34]

This study was limited by its retrospective nature and the small sample size. Our cohort involved heterogeneous PCOS patients with different concomitant infertility factors and previous ovulation induction treatments. These differences may have resulted in bias. There was also measurement bias as the anthropometric measurements were not blinded and data collection was incomplete. For example, waist circumferences were not retrievable from the medical notes of some patients and hence BMI was used as a surrogate for waist circumference in the diagnosis of MetS. Also, we only measured total testosterone concentrations which may be less sensitive markers for hyperandrogenism. Furthermore, the diabetes risk in PCOS patients might have been over- or under-estimated due to incomplete screening during pregnancy. Finally, multiple pregnancies may have been a confounding factor, biasing assessment of diabetes risk during pregnancy.

Notwithstanding these limitations, the present study serves as an exploratory attempt to examine the effect of LOD in PCOS patients with MetS. The results suggest that although LOD restores ovulation effectively in PCOS patients with MetS, the procedure does not improve the diabetes risk during pregnancy. While these patients should not be precluded from LOD, use of other adjuvant strategies like insulin-sensitising drugs to reduce metabolic risks should also be considered. Early screening and serial monitoring of diabetes is recommended for all PCOS patients during pregnancy.

TABLE 2. Reproductive outcomes after laparoscopic ovarian drilling (LOD) in polycystic ovarian syndrome (PCOS) patients with or without metabolic syndrome (MetS)

Post-LOD reproductive outcomes*	No. (%)		P value†
	PCOS without MetS (n=70)	PCOS with MetS (n=19)	
Spontaneous ovulation	41/67 (61%)	13/19 (68%)	0.76
Cumulative pregnancy	43/70 (61%)	13/19 (68%)	0.77
Method of conception			
Spontaneous pregnancy	24/70 (34%)	7/19 (37%)	0.95
Clomid-induced pregnancy	6/70 (9%)	2/19 (11%)	0.34
OI/IUI pregnancy	6/70 (9%)	2/19 (11%)	0.34
IVF pregnancy	7/70 (10%)	2/19 (11%)	0.33
Pregnancy outcome			
Delivered or ongoing	31/42 (74%)	11/13 (85%)	0.23
Miscarriage	11/42 (26%)	2/13 (15%)	0.23
Multiple pregnancy	4/42 (10%)	0/13 (0%)	-
Diabetes in pregnancies	13/31 (42%)	7/11 (64%)	0.13
Among singleton pregnancies	9/27 (33%)	7/11 (64%)	0.07
Among multiple pregnancies	4/4 (100%)	0/0 (0%)	-

* OI denotes ovulation induction, IUI intrauterine insemination, and IVF in-vitro fertilisation

† χ^2/Fisher's exact test

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