Impact of laparoscopic ovarian drilling on anti-Müllerian hormone levels and ovarian stromal blood flow using three-dimensional power Doppler in women with anovulatory polycystic ovary syndrome

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Objective: To evaluate the effect of laparoscopic ovarian drilling (LOD) on plasma levels of anti-Müllerian hormone (AMH) and ovarian stromal blood flow changes, by using three-dimensional power Doppler ultrasonography, in polycystic ovary syndrome (PCOS).
Design: Prospective controlled study.
Setting: Taiba hospital, Kuwait.
Patient(s): Twenty-three anovulatory clomiphene citrate (CC)-resistant women with PCOS and 20 fertile women as a control group.
Intervention(s): Laparoscopic ovarian drilling.
Mean Outcome Measure(s): Serum levels of AMH, ovarian three-dimensional power Doppler indices (vascularization index, flow index, and vascularization flow index) and occurrence of ovulation or pregnancy.
Result(s): Plasma AMH and power Doppler indices of ovarian stromal blood flow were significantly higher in the PCOS group than in the control group. Plasma AMH and ovarian stromal blood flow Doppler indices were significantly reduced in the PCOS group after LOD. Women who ovulated after LOD had a significantly lower preoperative AMH compared with the nonresponders. There was a significant positive correlation between AMH and power Doppler flow indices before and after LOD in PCOS group.
Conclusion(s): Measuring AMH and ovarian stromal three-dimensional power Doppler blood flow for women with anovulatory PCOS undergoing LOD may provide a useful tool in evaluating the outcome of LOD. (Fertil Steril® 2011;95:2342–6. ©2011 by American Society for Reproductive Medicine.)

Key Words: Polycystic ovary syndrome, laparoscopic ovarian drilling, ovulation, anti-Müllerian hormone

Polycystic ovary syndrome (PCOS), one of the most common endocrine disorders in women of childbearing age, is characterized by a marked increase in preantral follicle number arranged peripherally around a dense core of stroma or scattered throughout an increased amount of stroma (1). This is coupled with menstrual disturbance, hyperandrogenism, and anovulation (2).

Ovarian stromal peak systolic blood flow velocity and time-averaged maximum velocity were found to be significantly greater in women with PCOS than in infertile women with healthy ovaries (3). Power Doppler ultrasound is more sensitive than color Doppler imaging at detecting low velocity flow, thus it overcomes the angle dependence of standard color Doppler and provides improved visualization of small vessels (4).

Anti-Müllerian hormone (AMH) is a member of the transforming growth factor-β (TGF-β) family. In women, AMH is mainly secreted by the granulosa cells (GC) of ovarian early developing follicles (5). The expression of AMH is localized in GCs of primary, preantral, and small antral follicles, suggesting an important role of AMH in human folliculogenesis. Anti-Müllerian hormone has been shown to lower the sensitivity of follicles to circulating FSH (6), an effect that is important for normal folliculogenesis and it has been shown to be two to threefold increased in serum from women with PCOS than in women with healthy ovaries (7). At present, controversial data are available regarding whether the AMH excess in PCOS is secondary to the increase in preantral follicles number, or if an intrinsic increased AMH production by the GCs is the cause of follicular arrest in PCOS (8, 9). However, increased concentrations of AMH may be a consequence of other factors in PCOS, the most obvious being hyperandrogenism (7, 10, 11) and insulin resistance (12). Increase in ovarian stromal blood flow in women with PCOS may result from the overexpression of ovarian vascular endothelial growth factor (VEGF), which probably modulates the vascular permeability of theca cells, and increased insulin-like growth factor I (IGF-I) (13, 14), which enhances gonadotropin-stimulated steroid production in GC and theca cells, resulting in increased ovarian androgen production and subsequently increased AMH production (12).

Identifying factors that determine the response of women with PCOS to laparoscopic ovarian drilling (LOD) will help in selecting patients who are likely to benefit from this treatment, thus avoiding fruitless treatment and improving success rates. A previous study (15) has reported on factors affecting the success of LOD. The AMH has been found to correlate with ovarian responsiveness to ovulation induction with clomiphene citrate (CC) (16) and to FSH ovarian hyperstimulation for IVF treatment (17, 18). The consistency of the serum levels of AMH throughout the menstrual cycle, with very little intercycle variability, makes it an attractive marker of response to treatment. The mechanism of action of

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TABLE 1

Clinical, hormonal, and power Doppler study of both PCOS and control groups.

Variable	Control group (n = 20)	PCOS group (n = 23)	
		Pre-LOD	Post-LOD
Age (y)	27.4 ± 2.8	28.8 ± 3.1	—
BMI (kg/m^2)	26.7 ± 2.4	29.2 ± 2.6	28.4 ± 2.3
LH (IU/L)	4.9 ± 1.2	11.7 ± 1.3[a]	10.8 ± 1.8
FSH (IU/L)	3.9 ± 1.1	4.2 ± 1.3	4.1 ± 1.4
LH:FSH	1.2 ± 0.2	2.8 ± 0.4[a]	2.5 ± 0.6
T (nmol/L)	1.1 ± 0.3	4.2 ± 0.4[a]	2.6 ± 0.6[b]
SHBG	48	31	34
FAI	2.3	11.6	7.6
AMH (ng/mL)	1.9 ± 0.3	7.4 ± 4.6[a]	4.2 ± 2.5[b]
Ovarian volume (mL)	6.9 ± 1.1	13.8 ± 2.1[a]	7.4 ± 2.9[b]
Mean number of follicles (both ovaries)	13.0 ± 1.9	29.0 ± 2.4[a]	15.0 ± 2.2[b]
Vascularization index	1.7 ± 0.34	4.8 ± 1.3[a]	2.4 ± 0.75[b]
Flow index	43.9 ± 5.9	52.4 ± 4.3[a]	44.3 ± 2.5[b]
Vascularization flow index	0.97 ± 0.38	2.9 ± 0.43[a]	1.2 ± 0.59[b]

Note: Values are given as mean ±SD, $P < .05$. AMH = anti-Müllerian hormone; LOD = laparoscopic ovarian drilling; SHBG = sex hormone-binding globulin; FAI = free androgen index.
[a] Significance indicated in this column refers to comparison of the pre-LOD PCOS and control values.
[b] Significance indicated in this column refers to comparison of the post-LOD and pre-LOD PCOS values.

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LOD is largely unexplained. In particular, it is not known whether LOD exerts its action through a direct effect on the ovary or through a systemic endocrine mechanism (19). The aim of this study was to determine the effect of LOD on plasma level of AMH and ovarian stromal blood flow changes, by using three-dimensional (3D) power Doppler ultrasonography in anovulatory women with PCOS and whether this could explain the mechanism of action of LOD.

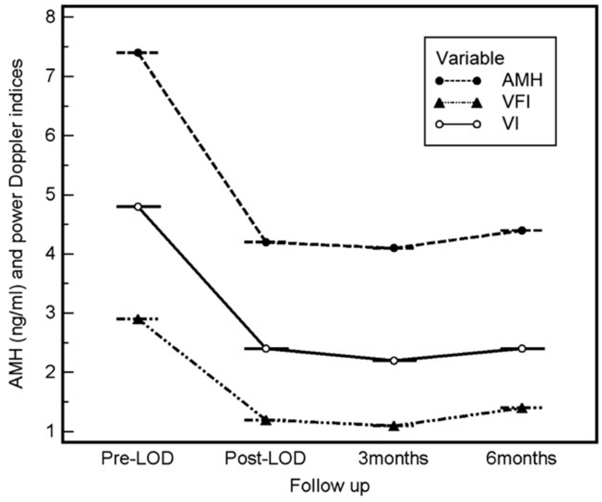
MATERIALS AND METHODS

This prospective controlled clinical study included 23 infertile anovulatory women with CC-resistant PCOS who underwent LOD (PCOS group), and a control group comprised of 20 healthy fertile women with a regular menstrual cycle and normal ovaries (by ultrasound examination) who were attending an outpatient clinic for contraception. The study was conducted in the Obstetrics and Gynecology Department, Taiba hospital, Kuwait, from January 2008 to August 2009. Clomiphene citrate resistance was defined as failure to ovulate after CC administration up to a daily dose of 150 mg from cycle days 2–6 for at least three consecutive cycles (20). Age and body mass index (BMI) were recorded for all study participants. Diagnostic criteria for PCOS included at least two of the following three features: [1] amenorrhea or oligomenorrhea with chronic anovulation, [2] clinical and/or biochemical evidence of hyperandrogenism, and [3] ultrasonographic appearance of PCOS (2). All patients with PCOS in the current study had amenorrhea or oligomenorrhea. Exclusion criteria were age <18 or >35 years; tubal or male factor infertility investigated with hysterosalpingography and standard semen analysis; current or previous use of metformin; any organic pelvic diseases at laparoscopy or diseases potentially affecting the ovarian environment and/or function (including endometriosis and leiomyomas); women with single ovary; previous ovarian cystectomy; hyperprolactinemia; and thyroid disease and diabetes. Ultrasound examinations were performed using three-dimensional (3D) transvaginal 7.5-MHz power Doppler ultrasound (Voluson 530D; Kretztechnik-Medison, Zipf, Austria) as previously described (3, 10, 13), to assess the ovarian volume, morphology, the mean antral follicle number in both ovaries (measuring 2–9 mm), and to monitor the evidence of ovulation at each visit to the clinic. Power Doppler measurements were performed on the early follicular phase before LOD and repeated in the early follicular phase of the first postoperative cycle, at 3- and 6-month follow-up. In the control group, examination was done in the early follicular phase of any cycle (3). Three indices quantifying the power Doppler signal were determined—vascularization index (VI), flow index (FI), and vascularization flow index (VFI). The VI measures the ratio of color voxels to all the voxels in the defined volume, providing an indication of the number and/or size of vessels within the region of interest. It represents the density of the vessels in the tissue and is expressed as a percentage. The FI, the mean value of the color voxels, represents the average intensity of flow (range 0–100) and this value is considered to reflect volume flow rate. The VFI is the mean color value in all the voxels in the defined volume and is a feature of both vascularization and volume flow (range 0–100). It has been suggested to be representative of tissue perfusion (13). Blood samples were collected on day 2 of the cycle before and 1 week after LOD to measure plasma concentrations of AMH, LH, FSH, T, sex hormone-binding globulin (SHBG), and the free androgen index (FAI) [T/SHBG × 100]. Additional blood samples were collected 3 and 6 months after LOD for the measurement of AMH. Plasma samples were assayed for AMH in duplicate using a commercial ELISA kit (Immunotech, Beckman–Coulter UK Ltd., High Wycombe, Buckinghamshire, United Kingdom) according to the manufacturer's protocol. The sensitivity of the assay was 0.24 ng/mL. The intra-assay and interassay variabilities were 5% and 8%, respectively. Assays for LH, FSH, T, and SHBG have previously been described (19). Assays for LH and FSH were performed by an automated microparticle enzyme immunoassay (Abbott Axsym analyser; Abbott Diagnostics). Assays for SHBG were performed by an automated chemiluminescent immunoassay (Immulite analyser; Diagnostic Products Corporation). The assay used for T was coated tube radioimmunoassay (Coat-A-Count; Diagnostic Products Corporation).

The LOD was carried out using the laparoscopic technique as described by Amer et al. (21). The procedure was always conducted by either A.I.E. or a laparoscopic staff in the presence of A.I.E. to ensure that the same technique was used in each patient. The LOD was carried out using a monopolar electrocautery needle and four punctures were made per ovary at a power setting of 30 W applied for 4–6 seconds at each point. If the patient did not ovulate after LOD, CC would be started 6–8 weeks after surgery on days 2–6 of

FIGURE 1

Plasma anti-Müllerian hormone (AMH) levels and three-dimensional power Doppler flow studies in women with polycystic ovary syndrome (PCOS) before and after treatment with laparoscopic ovarian drilling (LOD). There was a significant reduction both in the plasma levels of AMH and ovarian stomal power Doppler flow indices after LOD in the PCOS group and remained low at 3- and 6-month follow-up. VI = vascularization index; VFI = vascularization flow index.



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a menstrual cycle. Mean outcome measures were serum AMH levels, ovarian 3D power Doppler indices, and occurrence of ovulation or clinical pregnancy during the 6-month period. Monitoring for ovulation was systematic for all patients. Ovulation was diagnosed by serial sonographic monitoring of follicular growth and follicular collapse with elevated serum P levels 7 days later. Pregnancy was diagnosed by positive quantitative β-hCG and a gestational sac by ultrasound examination. Informed consent was obtained from all study participants, and the study was approved by the Institutional Review Board of the hospital.

Statistical Analysis

Statistical analysis was performed by using the Statistics Package for Social Sciences (SPSS Inc., Chicago, IL). Comparisons of the measured parameters between the two groups were carried out by Student's t-test. Comparisons of values before and after LOD in the PCOS group were done by using a paired t-test. For comparison of not normally distributed data, nonparametric statistical tests (Mann- Whitney U-test and Wilcoxon signed ranks test) were used. A P value $<.05$ was considered statistically significant. The correlation between AMH levels with other variables was evaluated by Spearman's rank correlation.

RESULTS

Participants in PCOS and control groups were comparable regarding age and BMI. Plasma levels of AMH, T, LH, and the LH:FSH ratio were significantly higher in the PCOS group before LOD than in the control group. The 3D power Doppler blood flow indices were significantly higher in the PCOS group before LOD than in the control group (Table 1).

After LOD in the PCOS group, there was a significant reduction in the plasma levels of AMH and the ovarian stomal power Doppler flow indices and remained low at 3- and 6-month follow-up (Fig. 1). Further analysis revealed that the significant reduction of AMH had occurred in women who ovulated in response to LOD. Similarly, ovarian stomal power Doppler flow indices were significantly decreased after LOD in the PCOS group. Power Doppler flow indices were decreased in women who ovulated in response to LOD; however, the change was not significant (Table 2). Ovulation rate was 73.9% and spontaneous pregnancy rate (PR) was 26.1% in the 6-month period after LOD.

There was a significant positive correlation between AMH and power Doppler flow indices before (r = 0.55, P=.001; r = 0.60, P=.001; r = 0.016, P=.03 for VI, FI, and VFI, respectively), and after LOD (r = 0.55, P=.006; r = 0.60, P=.002; r = 0.016, P=.013 for VI, FI, and VFI, respectively) in the PCOS group. Similarly, there was a significant positive correlations between plasma AMH levels and ovarian volume, the mean follicle number (r = 0.594; P=.001) and plasma T concentrations (Fig. 2). No significant correlation was found between plasma AMH and age, BMI, FAI, LH, or FSH.

DISCUSSION

The obtained results in the present study confirmed previous reports (19, 22, 23) of significant high levels of plasma AMH in women with anovulatory PCOS compared with healthy controls. A direct and significant correlation between follicle number and serum AMH levels has been demonstrated by some investigators (10), suggesting that the increased AMH levels in PCOS are the results of the increased number of early antral follicles (23). However, other reports demonstrated that the increase in AMH concentration is largely due to the increase in production of AMH by each follicle and not just a consequence of an increase in follicle number (24). The AMH may constitute a marker for ovarian aging as it correlate with the number of early antral follicles, which might in turn represent the size of the resting pool of follicles (10), therefore if the level of AMH is being reduced, ovarian reserve may be compromised.

Current results observed a significant positive correlation between plasma AMH levels and both ovarian volume and the antral follicle number in PCOS, which was not surprising as ovarian volume is a reflection of the number of small antral follicles present in PCOS, which are the only source of AMH. There was also a positive correlation between AMH and circulating androgens in PCOS. These findings are consistent with the results of previous studies (6, 7, 10). This positive association between T and AMH could be explained by the stimulatory effect of androgens on primordial follicular growth and GC proliferation, which in turn could increase AMH secretion (19), or the inhibitory effect of AMH on aromatase activity, resulting in an increase in androgens (11). In addition, androgen production per theca cell was equally increased in anovulatory and ovulatory polycystic ovaries (PCOs); however, the total number of follicles found in the anovulatory ovary is higher, resulting in increased total androgen level (5). Another cause of the increase in AMH and androgens in PCOS is hyperinsulinemia, which has been shown to enhance gonadotropin-stimulated steroid production in GCs and theca cells. Therefore the increased AMH concentrations may be secondary to an effect of insulin on androgen levels (12). There has been no evidence to suggest a direct stimulatory effect of T on AMH production by GCs (7).

Results of the present study revealed that, the 3D power Doppler ovarian stromal VI, FI, and VFI were significantly higher in women with PCOS than in healthy fertile women. Similar results have been previously reported (13, 25). This increased vascularity demonstrated in PCOS may result from overexpression of ovarian VEGF

TABLE 2

Preoperative and postoperative plasma levels of AMH, power Doppler flow studies, and other hormones in women with PCOS who ovulated in response to LOD (responders) versus nonresponders.

LOD	Variable	Responders (n = 17)	Nonresponders (n = 6)	*P* value[a]
Pre-LOD	AMH (ng/mL)	6.3 (5.1–6.9)[b]	11.9 (11.1–13.6)	.003
	FSH (IU/L)	4.8 (2.8–5.1)	4.7 (2.7–5.2)	.437
	LH (IU/L)	11.8 (8.1–13.2)	12.4 (11.31–6.8)	.243
	T (nmol/L)	3.4 (3.2–3.6)	4.1 (3.8–4.2)	.116
	SHBG	36.0 (34.1–38.0)	34.7 (34.1–37.1)	.721
	FAI	9.7 (8.4–10.3)	11.0 (10.3–11.3)	.218
	Vascularization index	4.7 (4.5–4.9)	5.1 (4.5–5.2)	.183
	Flow index	50.9 (49.4–53.4)	51.3 (49.7–53.9)	.872
	VFI	2.8 (2.3–3.1)	3.1 (2.8–3.2)	.170
Post-LOD	AMH (ng/mL)	4.2 (2.6–4.9)[b]	11.2 (10.4–14.0)	.002
	FSH (IU/L)	4.7 (2.7–5.2)	4.9 (4.2–5.4)	.129
	LH (IU/L)	10.9 (7.8–12.7)	12.1 (11.1–17.5)	.241
	T (nmol/L)	3.3 (3.1–3.5)	3.8 (3.6–4.1)	.578
	SHBG	38.1 (35.1–39.2)	36.2 (35.3–38.5)	.258
	FAI	8.8 (7.9–9.9)	10.3 (9.7–10.9)	.063
	Vascularization index	2.4 (2.2–2.7)	2.5 (2.3–2.7)	.610
	Flow index	44.3 (42.1–45.2)	44.8 (41.7–45.8)	.364
	VFI	1.3 (1.2–1.4)	1.7 (1.4–1.1.8)	.412

Note: Values are given as median (interquartile range). AMH = anti-Müllerian hormone; LOD = laparoscopic ovarian drilling; FAI = free androgen index; SHBG = sex hormone-binding globulin; VFI = vascularization flow index.
[a] *P* value for responders versus nonresponders (Mann–Whitney test).
[b] $P = .00273$ (pre-LOD versus post-LOD values; Wilcoxon signed ranks).

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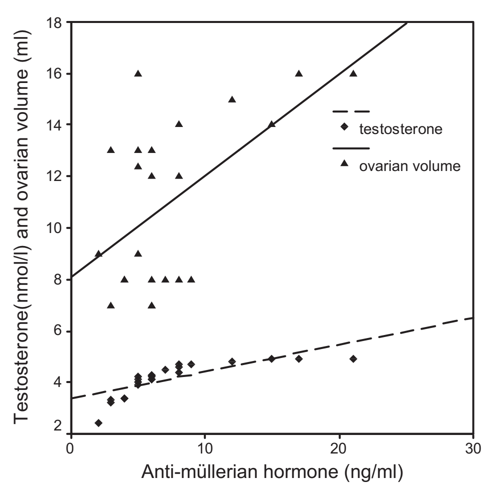
secondary to higher levels of LH in these women (13). Also, in the current study, a significant positive correlation between plasma AMH levels and power Doppler indices of ovarian stroma was observed. A plausible hypothesis is that the increased ovarian stromal blood flow in PCOS may result from increased ovarian VEGF and IGF-I (10, 11), which in turn could result in increased AMH secondary to increased ovarian androgen production (12). However, there was no significant correlation found between plasma AMH and age (possibly owing to the small age range included in the study), BMI, FAI, LH, or FSH. Current results showed that LOD significantly reduced both AMH level and power Doppler blood flow velocities. Interestingly, women who ovulated in response to LOD (responders) had a significantly lower preoperative AMH compared with the nonresponders. These findings are consistent with previous reports (19). Preoperative measurements of serum AMH levels for women who are candidates to undergo LOD was suggested to be beneficial to determine their likelihood of response and can be used a useful marker for prediction of no ovulation after LOD (19). It is thought that normal levels of AMH are necessary to achieve optimal ovarian responsiveness to ovulation induction. Both low and high levels of AMH seem to be detrimental to ovarian responsiveness to stimulation (17, 18).

In addition, the preoperative power Doppler indices were lower in the responders compared with nonresponders, but the difference was not significant. Current results showed a 73.9% ovulation rate and 26.1% spontaneous PR in the 6-month period after LOD. This is in agreement with previous studies (8, 11).

The mechanism of action of LOD is unclear and its beneficial effect is apparently due to destruction of the androgen-producing stroma that results in a decrease in ovarian stromal blood flow and subsequently, in serum levels of VEGF and IGF-I, which are significantly higher in PCOS (25). The reduction of AMH after LOD could be the result of destruction of some small follicles

FIGURE 2

Correlation between plasma anti-Müllerian hormone (in nanograms per milliliter) and both plasma T level (nanomoles per liter) and ovarian volume (milliliter) in polycystic ovary syndrome (PCOS) group. There was a significant positive correlation between plasma anti-Müllerian hormone and both T concentrations ($r = 0.973$, $P < .001$) and ovarian volume ($r = 0.514$, $P = .016$).



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(which are the only source of AMH) during LOD (21). It was speculated that the decrease in AMH after LOD could lead to ovulation by increasing the sensitivity of the follicles to circulating FSH (19, 21).

Failure of LOD in women with relatively high power Doppler indices along with high levels of AMH may be due to severity of the PCOS condition in these women. It is possible that the extent of follicle destruction by LOD in these women was not enough to reduce intraovarian AMH to a level consistent with resumption of ovulation (18).

In the present study, the levels of T in the PCOS group were significantly lowered by LOD, whereas LH was reduced but did not reach significance. A reduction in LH and T levels after LOD has been reported by other investigators (13, 21). In conclusion, measuring AMH and ovarian stromal 3D power Doppler blood flow for women with anovulatory PCOS undergoing LOD may provide a useful tool in evaluating the outcome of LOD. Further clinical studies are needed to clarify the underlying mechanisms controlling ovarian stromal blood flow and AMH.

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SUPPLEMENTAL TABLE 1

Correlation between plasma AMH and other factors in women with PCOS before and after LOD.

Variable	Pre-LOD r	Pre-LOD *P* value	Post-LOD r	Post-LOD *P* value
Age	−0.34	.87	—	—
BMI	0.16	.45	0.21	.35
LH	−0.07	.72	−0.16	.46
FSH	0.07	.74	0.05	.81
FAI	−0.42	.4	−0.37	.18
Vascularization index	0.67	.001[b]	0.55	.006[b]
Flow index	0.62	.001[b]	0.6	.002[b]
Vascularization flow index	0.43	.03[a]	0.016	.016[a]

Note: LOD = laparoscopic ovarian drilling level; FAI = free androgen index; BMI = body mass index; AMH = anti-Müllerian hormone; PCOS = polycystic ovary syndrome.

[a] Correlation is significant at the .05 level.

[b] Correlation is significant at the .01 level.

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