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Could Anti-Mullerian Hormone be a Useful Predictor of the Success of Laparoscopic Ovarian Drilling?

Abstract

Aim: To assess the correlation between pre-ovarian drilling patients' demographic data and hormonal profile and subsequent spontaneous ovulation and conception following the procedure.

Methods: Prospective observational study including 145 primary infertility, clomiphene resistant patients with polycystic ovary syndrome, undergoing laparoscopic ovarian drilling (LOD). The selected patients were directed to have LOD. Ovulation was diagnosed by serial follow up ultrasonography in the subsequent cycles confirmed by day 21 progesterone. Antimullerian hormone (AMH), lutenizing hormone (LH) and prolactin assays were done before and 3 months after the procedure. Receiver operator curve was used to correlate between demographic and hormonal data and spontaneous ovulation following the procedure.

Results: There was a significant reduction of AMH, LH and prolactin after LOD in both groups (P<0.001) but the decrease in post-LOD AMH and prolactin is less pronounced in the non-ovulatory group which is significantly higher than in the ovulatory group (P<0.001). The logistic regression analysis revealed that pre-LOD AMH is highly predictive of non-ovulation at a cut off value of 8.8ng/ml with sensitivity of 77% and specificity of 72% (P<0.001). Other demographic and hormonal data was not significant.

Conclusion: AMH could be used as a good predictor of ovarian response to LOD. Larger trials are warranted to confirm or refute this finding.

Keywords: Polycystic ovary syndrome; Antimullerian hormone; Laparoscopic ovarian drilling

Research Article

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Abbreviations: PCOS: Polycystic Ovary Syndrome; LOD: Laparoscopic Ovarian Drilling; AMH: Anti Mullerian Hormone; LH: Lutenizing Hormone; ESHRE: European Society of Human Reproduction and Embryology; ASRM: American Society for Reproductive Medicine; ROC: Receiver-operating characteristic; BMI: Body Mass Index

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders and the leading cause of infertility in women of reproductive age [1]. The first line of infertility treatment is clomiphene citrate, the second line includes gonadotrophins or laparoscopic ovarian drilling (LOD) and the third is IVF [2]. The mechanism of action of LOD is not fully understood and therefore it is not exactly clear why some PCOS patients do not respond to this treatment [3]. The aim of this study was to assess the correlation between patients' demographic data and hormonal profile and poor ovarian response to LOD.

Materials and Methods

A prospective Observational study was designed taking 145 primary infertility, clomiphene resistant patients, admitted to the Department of Obstetrics and Gynecology, Menoufia University hospital, Menoufia, Egypt in the period between October 2008 to March 2011.

The respective approvals of the review board and the ethics committee of the Menoufia Faculty of medicine were obtained before commencing the study. The study protocol and its benefits and complications were explained to all participants, and all recruited patients completed and signed the 'informed consent' form. The assumed total sample size of the study was actually calculated according to a proposed type I error of 5% with an expected difference between rates of spontaneous ovulation of 50-90%. Type II error was proposed to be 20% (β = 20%) hence the power was set at (1-β, 80%). Accordingly, 120 patients were needed after adding a 10% for possible drop out of cases.

Included patients with PCOS were diagnosed according to the revised European Society of Human Reproduction and Embryology (ESHRE) and American Society for Reproductive Medicine (ASRM) criteria of 2004 which were based on the Rotterdam criteria [4].

Clomiphene citrate resistance was defined as the absence of developing follicles after ovarian stimulation with 150 mg clomiphene citrate/day given for five days beginning with the 2nd day of the menstrual cycle. Patients were stimulated with clomiphene for a minimum of three and a maximum of six cycles [5]. A normal semen analysis, normal uterine cavity and bilateral tubal patency were the criteria of inclusion.

Patients with FSH>15 mIU/ml, medical disorders such as Diabetes Mellitus and hypertension, contraindications for laparoscopy, Endocrine disorders: hyperprolactinaemia (prolactin ≥ 22 ng/dl), Thyroid disorders, Cushing's syndrome and Acromegaly, husband semen abnormalities and patients having organic pelvic disease (endometriosis, leiomyoma, PID, endometrioma or ovarian cyst) upon laparoscopy were excluded from the study. Patients baseline blood samples were obtained before laparoscopic ovarian drilling (2–3 days after the commencement of spontaneous or progesterone induced menstrual bleeding) to assess serum levels of AMH, LH and prolactin. The second blood sample was obtained in the early follicular phase (days 2-3) of the menstrual cycle after 3 months of the operation.

AMH assay was done using a commercial ELISA kits (Immunotech, Beckman-coulter UK Ltd, High Wycombe Buckinghamshire UK), according to the manufacturer, the sensitivity of the assay is 0.24 ng/mL. LH assay was performed using automated microparticles enzyme immunoassay (Abbott Axsyem analyzer, Abbott Diagnostics). Mid-luteal serum progesterone was measured via Radioimmunassay (Immunotech, Westbrook, ME, USA) and prolactin (Immunotech, Westbrook, ME, USA).

Pelvic sonography (Acuson 128 XP 10, computed sonography system, Mountain View, California, USA) was carried out on day 12-16 for folliculometry before and after the operation. Ovulation is defined as the presence of at least one dominant follicle measuring ≥ 18 mm. Laparoscopic ovarian drilling (LOD) was performed using three-puncture technique. The laparoscope was introduced through a subumblical incision. After assessment of the pelvic structures and tubal patency, an insulated needle connected to a unipolar electro-cautery with four to six cautery points 3-4 mm in diameter was created in each ovary with a current of 4 mA applied through the laparoscopic insulated needle.

Ovulation was diagnosed by serial follow up ultrasonography in the subsequent cycle confirmed by day 21 progesterone. If no menses occurred within 6 weeks, withdrawal bleeding was done and the patients were followed up for 3 months and considered as non-ovulatory. Patients were categorized into two groups, ovulatory (n=98) and non-ovulatory (n=47) groups. Patients in both groups were followed via regular visits to the outpatient clinic every 2-4 weeks to record the pregnancy rate.

Outcome measures

a) The primary outcome was to assess the utility of patients' demographic criteria and hormonal profile for the prediction of poor ovarian response to LOD.

b) Secondary outcome was to record the pregnancy rate in the ovulatory group during the subsequent 15 months.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences Version 16 (IBM Corp., Armonk, NY, USA). Quantitative data are expressed as means and standard deviations. Chi-squared test and t-test were used to compare the two groups. $p \leq 0.05$ was considered to indicate significance and $p \leq 0.001$ was considered to indicate strong significance. Receiver-operating characteristic (ROC) curve analysis was used to evaluate the prognostic value of demographic and hormonal data.

Results

Table 1 displays the patients' demographic data. No significant difference between the ovulatory and non-ovulatory groups regarding age, body mass index (BMI) and duration of infertility. Table 2 reveals the hormonal profile before and three months after LOD. There is a significant reduction of AMH, LH and prolactin after LOD in both groups ($P<0.001$). Post-LOD AMH and prolactin are higher in the non-ovulatory group than in the ovulatory group ($P<0.001$).

Table 1: Patients' demographic data.

	Ovulatory Group (n=98)	Non-ovulatory Group (n=47)	Student t-test	P-value
Age (in years)	29.7±1.5	29.8±1.4	0.38	>0.05
Body Mass Index	27.9±2.1	28.4±1.8	1.4	>0.05
Duration of Infertility (in years)	5.4±0.7	5.2±0.5	1.75	>0.05

Table 3 shows the logistic regression analysis of patients' characteristics and hormonal profile among the participants (total no 145). Pre-LOD AMH is highly predictive of non-ovulation at a cut off value of 8.8ng/ml with sensitivity of 77% and specificity of 72% ($P<0.001$). Table 4 shows the pregnancy rate in the ovulatory group over 15 months (82/98). Pregnancy rate within the first 6 months was 60/82 (74.4%) with 22 women (25.6%) conceived in the subsequent 6 months.

Table 2: Hormonal profile before and after LOD.

	Ovulatory Group (n=98)	Non-Ovulatory Group (n=47)	Student t-test	P-value
AMH				
Before LOD	14.2±4.7	14.6±4.6	0.48	>0.05
After LOD	8.6±3.2	12.2±3.2	6.43	<0.001
	P<0.001	P<0.05		
LH				
Before LOD	21.1±4.8	21.7±4.5	0.72	>0.05
After LOD	15.3±3.4	15.8±3.2	0.84	>0.05
	P<0.001	P<0.001		
Prolactin				
Before LOD	28.2±5.1	28.8±4.9	0.67	>0.05
After LOD	8.5±3.7	15.2±6.3	8.04	<0.001
	P<0.001	P<0.001		

AMH: Antimullerian hormone; LH: Leutinizing hormone

Table 3: The logistic regression analysis of patients' characteristics and hormonal profile among the participants (Total no 145).

	AUC	Sensitivity	Specificity	Cut-off value	P-value
Age	0.586	63%	69%	-	>0.05
BMI	0.658	55%	61%	-	>0.05
Infertility Duration	0.642	64%	52%	-	>0.05
AMH	0.714	77%	72%	8.8ng/ml	<0.001
LH	0.66	61%	69%	-	>0.05
Prolactin	0.626	58%	62%	-	>0.05

Table 4: Pregnancy rate (n=82) in the ovulatory group over 15 months (n=98).

	Category	Pregnancy Rate After 6 Months (n=60)	Pregnancy Rate After 12 Months (n=22)
Age	<25 years	42	16
	≥25 years	18	6
BMI	<25	52	18
	≥25	8	4
Infertility duration	<5 years	54	20
	≥5 years	6	2
AMH	<8.8	56	21
	≥8.8	4	1
LH	<10	19	10
	≥10	41	12
Prolactin	<10	50	17
	≥10	10	5

BMI: Body Mass Index; AMH: Antimullerian hormone; LH: Leutinizing hormone

Discussion

In this series, 47 patients out of 145 were anovulatory (32.4%) with ovulation reported in 98 patients (77.6%). The reported ovulation rate after LOD varies between 50% and 90% in the literature [6]. There is some disparity between hormonal improvement and ovulation rate following LOD [7].

In this study, the amount of decrease in post-LOD AMH and prolactin is less pronounced in the non-ovulatory group since AMH and prolactin levels were significantly higher in the pre-LOD non-ovulatory group than in the ovulatory group.

Gjonness et al. [8] in their study on 17 women showed a transient hyperprolactinemia immediately after LOD, they believed that this phenomenon was due to operative stress. Hyperprolactinemia as a complication of operation, and/or anesthesia was previously described with the peak prolactin levels always occurring during surgery. Prolactin remained elevated in 62.5% when measured 6–10 weeks after operation [9-11].

Another possible explanation of anovulation following LOD is that the amount of ovarian tissue destroyed during LOD is not sufficient to produce an effect in some patients. However, others believe that ovarian diathermy works by increasing the sensitivity of the ovaries to endogenous FSH, and that only a minimal amount of thermal injury is required [3].

In this study, Pre-LOD AMH is highly predictive of non-ovulation at a cut off value of 8.8ng/ml with sensitivity of 77% and specificity of 72% ($P<0.001$). On the other hand, other demographic and hormonal data has no significant impact on the ovarian response to LOD.

A previous smaller study was conducted in UK to measure circulating AMH before laparoscopic ovarian diathermy (LOD) to evaluate its prognostic value for an ovulatory response and to investigate AMH changes after LOD to further explore the effects of LOD. This study included anovulatory women with PCOS undergoing LOD ($n = 29$) or receiving clomiphene citrate ($n=18$). Plasma AMH concentrations were measured before and 1 week after treatment. Further measurements of AMH were made at 3- and 6-month follow-up. AMH was found to be a useful predictor of no ovulation after LOD with area under the curve of 0.804 ($P = 0.025$). Using a cut-off of 7.7ng/ml, AMH had a sensitivity of 78% and a specificity of 76% in the prediction of no ovulation after LOD [12].

In our series 82(56.5%) patients get pregnant within 15 months in the ovulatory group. Pregnancy rate within the first 6 months was 60/82 (74.4%) and 22 women (25.6%) conceived in the subsequent 6 months. Pregnancy rate was higher in women younger than 25 years, with BMI less than 25 and infertility duration less than 5 years.

Many authors have reported high ovulation (about 80%) and pregnancy (about 60%) rates following LOD [13-16]. Duleba et al. [17] reported that lean PCOS women (BMI <25 kg/m2) achieved higher conception rates than overweight women (BMI >25 kg/m2) after laparoscopic wedge resection using a harmonic scalpel in 33 PCOS patients [17].

In our series, ovulatory women with higher LH levels (>10 IU/l) have a significantly higher chance of conception than those with lower LH levels which is consistent with previous studies [3,18]. Failure of LOD in women with relatively 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 intra-ovarian AMH to a level consistent with resumption of ovulation [12]. Future research should explore the use of dose adjusted LOD in relation to the serum levels of AMH and subsequent ovulation and pregnancy rates. From the results obtained in this clinical study, AMH could be used as a good predictor of ovarian response to LOD. Larger trials are warranted to confirm or refute this finding.

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