Impact of laparoscopic ovarian drilling on anti-mullerian hormone levels in women with clomiphene resistant polycystic ovary syndrome

Monica Saraswat[1], Tony Jose[2,*], Meenakshi Rajput[3], Nilopher Siddique[4]

[1]Assistant Professor, [2]Associate Professor, [3,4]Resident, Dept. of Obstetrics & Gynecology, AFMC, Pune, Maharashtra

*Corresponding Author:
Email: oncotango@gmail.com, ltcoltony@gmail.com

Abstract

Introduction: Patients with PCOS not only have raised androgen levels which leads to anovulation but may also have high AMH levels. When ovulation induction fails, androgen levels are reduced by laparoscopic ovarian drilling (LOD) thereby effecting ovulation and thus improving fertility. Studies have suggested that LOD also reduces AMH levels and the degree of its fall may forecast the success of LOD.

Materials and Method: The study objective was to evaluate baseline AMH levels and its change post LOD in patients with clomiphene resistant infertility, and correlate with spontaneous rates of ovulation and pregnancy.

Results: AMH levels were found to be high in clomiphene resistant PCOS. LOD was found to be safe and effective in the management of these patients and it caused statistically significant drop in AMH levels effecting spontaneous ovulations and pregnancies. Though the degree of fall did not correlate statistically with the success of the procedure, the chances of pregnancy were found to better in patients whose pre-LOD AMH levels were higher.

Conclusion: AMH levels could be a useful marker in PCOS related infertility with clomiphene resistance and LOD could be a safe and effective option for management of patients with high AMH levels and fall in AMH levels may emerge as a prognostic indicator. Randomized studies with adequate sample size would bring out the utility AMH as a prognostic marker in PCOS related infertility.

Keywords: Anti-Mullerian Hormone(AMH), Polycystic Ovarian Syndrome(PCOS), Laparoscopic Ovarian Drilling(LOD)

Introduction

Polycystic ovarian Syndrome(PCOS) as defined by the Rotterdam consensus criteria is a common cause of infertility and is managed initially by ovulation inducing agents as first line of treatment.[1] Recent studies have demonstrated that AMH levels also tend to be high in PCOS and response to ovulation inducing agents are inversely proportional to the levels of AMH.[2,3] Laparoscopic Ovarian Drilling(LOD) has been used as an option for management of the group of patients not responding to ovulation induction. The success of LOD too is unpredictable but it has been observed recently that patients with very high AMH levels respond better when the AMH levels reduce after LOD. It is also seen that patients with normal and low baseline AMH levels do not benefit from LOD possibly because it indicates low ovarian reserve. AMH therefore has the potential to be used not only in the initial evaluation of PCOS related infertility but also in the selection of patients for LOD during laparoscopy and also in predicting the success of LOD in managing infertility in these patients. The consistency of the serum levels of AMH throughout the menstrual cycle, with very little inter-cycle variability, makes it an attractive marker of response to treatment as well.[4,5,6] The present study has been conducted to study the effect of laparoscopic ovarian drilling, as one of the treatment options to treat infertility caused by PCOS resistant to ovulation inducing agents on the levels of anti-Mullerian hormone. The primary objective of this study was in addition to finding out change in AMH levels after LOD, to look for any correlation between this change in AMH levels and fertility as evidenced by spontaneous ovulation and spontaneous conception levels.

Materials and Method

The objective of this prospective study was to study the impact of Laparoscopic ovarian drilling on anti-Mullerian hormone levels in infertile women with clomiphene resistant PCOS by comparing AMH levels before and after LOD and documenting ovulation and spontaneous pregnancy rates for three subsequent cycles. Thirty patients of primary infertility less than 35 years with clomiphene resistant PCOS reporting to Armed forces medical college for treatment and planned for LOD who consented to be included in the study after counselling formed the study population. PCOS was defined by Rotterdam consensus criteria and clomiphene resistance was defined as failure to ovulate after Clomiphene Citrate(CC) administration up to a daily dose of 150 mg from cycle days 2–6 for at least three consecutive cycles. Patients above 35 years, h/o ovarian cysts or surgery on the ovary in the past, any other organic pathology detected at USG or laparoscopy, known endocrine diseases (diabetes, thyroid disorder and hyperprolactinemia) and known tubal and male factor infertility were excluded from the study. Ethical clearance was obtained from institutional ethics

committee of the hospital before the start of study. Written informed consent was obtained from each patient before being included in the conduct of the study.

Preoperatively AMH levels were done on Day 2 of the cycle, along with FSH, LH, Prolactin and TSH that were done as a part of endocrine survey. Additional pre op work up in addition to the routine, also included an HSG (day 6-11) of the cycle and USG pelvis. Serum AMH levels were done using ELISA kit from Bioassay Technology Laboratory based on the principle of Biotin double antibody sandwich technology with an assay range from 0.05ng/ml-20ng/ml with a sensitivity of 0.021ng/ml. The patients underwent diagnostic hysteron-laparoscopy and LOD between day 5 to 10 of their menstrual cycle. LOD by standard technique using a monopolar needle point electrocautery with current set at 40 W (pure cutting) for a duration of 4-6 seconds with total of four to six drills made in each ovary several millimeters apart through the ovarian cortex (exposure time equal to or less than four to six seconds per drilling) as shown below. Hilum of the ovary was avoided for prevention of bleeding. Post operatively patients were called on day 7 of LOD for suture removal and a post LOD AMH levels. AMH levels were again checked on day 2 of the first cycle or on the 35th post op day whichever was earlier. They were followed up for three menstrual cycles by TVS follicular monitoring for spontaneous ovulation as evidenced by sudden disappearance or regression in the size of the follicle, intra-follicular echoes or free fluid in POD was documented and timed intercourse advised. Amenorrhoeic patients underwent pregnancy test by standard UPT kits (Pregakem, ALKEM Laboratories with a sensitivity of 25 mIU/ml) or B-HCG (if indicated). The patients continued treatment as per hospital protocol after culmination of 3 month follow up. The results were tabulated and analyzed using SPSS software.

Results

A total of 30 patients were included in study aged 21yrs – 41yrs and a mean age of. 28.15 ± 5.78 (mean ± SD) years. The duration of infertility ranged between 2 to 16yrs and the average number marital life was 5.45 ± 3.42(mean ± SD) years. Out of the 30 patients who underwent LOD, only 2 patients, i.e. 6.6 percent of the population, had regular menstrual cycles and others (93.4%) had irregular cycles mostly oligo-menorrhea. Preoperative USG done as part of the infertility evaluation showed that 27 out of 30 patients (90 percent) o had evidence of PCOS (increased ovarian volume or multiple cysts in cortex). The level of pre-operative AMH ranged between 19.12 – 2.32 ng/ml the mean ± SD being 9.86± 6.028. (Table 1) Post LOD, the reduction in AMH levels ranged from 0.33 ng/ml to 13.94 ng/ml with the mean reduction in AMH levels being 3.64ng/ml on 7th post op day and 3.87 ng/ml on day 2 of the subsequent cycle (or on the 35th day post LOD in patients who did not menstruate). The difference in values between day 7 and Day 2 of next cycle/35th pod were not found to be statistically significant and hence the values on D2 of subsequent cycle(of 35th post op day)was considered for statistical calculations. (Table 1, 2)

Table 1: Levels of AMH Pre and post Laparoscopic ovarian drilling

	Range (ng/ml)	Mean	N	Std. Deviation	Mean Difference
Pre LOD AMH	19.12 – 2.32	9.86	30	6.028	1.348
	Range (ng/ml)	Mean	N	Std. Deviation	P-Value
Post LOD AMH (7th POD)	14.88-1.2	6.12	30	3.724	
Post LOD AMH (Day 2 of next cycle)	14.16 -1.2	6.03	30	3.742	0.837

Table 2: Levels of AMH pre and post-Laparoscopic ovarian drilling by paired t test

	Mean	N	Std. Deviation	Mean Difference	t-value	p-value
Pre LOD AMH	9.89	30	6.028	1.348		
Post LOD AMH	6.03	30	3.742	0.837	4.288	<0.001

After LOD, 11 out of 30 patients ovulated in the first cycle (35%) though none conceived. However, the number of patients who demonstrated ovulation increased to 70% during the second cycle (21out of 30 patients). 18 out of the remaining 24 patients (6 patients had already conceived) ovulated in the third cycle. Hence by the end of the third cycle a total of 24 patients had ovulated (80%) which also included the 6 patients who became pregnant in the second cycle. However, 6 patients (20%) remained anovulatory even after the third cycle and this included two who remained amenorrhoeic. Ovulation induction was started in these patients after the third cycle. None out of the 30 patients conceived during the first menstrual cycle post LOD. Six patients out of twenty (20%) achieved pregnancy at the end of second cycle. Four patients (6.6 %) out of the remaining twenty-four cases conceived by the end of third cycle thereby achieving a spontaneous pregnancy rate of 33.33%(10 /30).

The Outcomes of pregnancy vis-à-vis pre and post LOD AMH levels was also looked into. Mean value of pre and post LOD AMH levels were found to be 11.19ng/ml and 7.21ng/ml respectively in women who achieved pregnancy vis-a-vis 9.18ng/ml and 6.03ng/ml in those who did not. Though there was a significant reduction in the AMH levels post LOD both on 7th POD and on 2nd day of the next cycle, statistical tests did not show any significant correlation between these AMH values in the patients who achieved pregnancy as compared with those who did not. (Table 3) However, the patients who had higher pre LOD AMH levels were found to have better chances of pregnancy in this study suggesting that the subgroup of clomiphene resistant PCOS patients with high AMH levels may benefit more from LOD as compared to those in whom AMH is normal or only marginally raised.

Table 3: Correlation AMH levels post LOD with successful pregnancy outcome

Variable	Pregnancy	N	Mean	Std. Deviation	t-value	p-value
Pre LOD AMH	Yes	10	11.19	7.04	0.7	0.493
	No	20	9.18	5.59		
Post LOD AMH	Yes	10	7.21	3.32	1.034	0.315
	No	20	5.40	3.93		

Discussion

The present study, was to study the effect of laparoscopic ovarian drilling, on the levels of AMH, and its effect on anovulation and fertility. Review of literature shows that majority of studies were performed to compare clinical pregnancy, live birth and miscarriage rates after LOD with those after ovulation induction with clomiphene alone, or in combination with metformin and gonadotrophins but observed no statistically significant differences. However, these studies suggested a possibility that the success of LOD was possibly also dependent on the decrease in the high AMH levels in this groups of patients.[7] The present study was done to study AMH levels in PCOS patients resistant to ovulation induction and evaluate changes with LOD and its implications if any on the ovulation and pregnancy rates.

The mean plasma AMH values pre LOD, in our study, was 9.89 ± 6.02 ng/ml. **Amer SA** et al in a prospective study of anovulatory women with PCOS undergoing LOD or receiving clomiphene citrate found pretreatment median (range) plasma AMH concentrations as 6.1 (1.0–21.0) and 5.7 (1.3–9.5) ng/ml in women having LOD and clomiphene citrate treatment, respectively.[8] The higher levels in our study was possibly due to the selection of patients with clomiphene resistant PCOS. These patients are known to have high AMH levels which is cited as one of the reasons for not responding to medical methods of ovulation induction.

The mean postoperative AMH levels after 1 week were 6.03 ± 3.74 ng/ml with a mean reduction of 3.87ng/ml (0.33 ng/ml to 13.94 ng/ml). Amer SA et al found that following LOD, the median AMH concentration significantly decreased to 4.7 (0.3–15.1) ng/ml and remained low at three and six month follow-up. The higher post op levels in our study may be due to two factors - patients with only PCOS with Clomiphene resistance who have a higher AMH to start with and to the small sample size of the study.

Elmashad AI found that plasma AMH levels were significantly higher in the PCOS patients and AMH was significantly reduced after LOD. The mean pre LOD AMH level was 7.4 ± 4.6ng/ml and post LOD levels were 4.2 ± 2.5ng/ml. Women who ovulated after LOD had a significantly lower preoperative AMH compared with the non- responders. There was a significant positive correlation between AMH before and after LOD in PCOS group.[9] This study is comparable to our study, in terms of significant decrease in AMH levels in women with PCOS after laparoscopic ovarian drilling.

In our study 36.6% ovulated in the first cycle though none conceived. In the second cycle, 70% ovulated out of which six conceived. 80% had ovulated by the end of third cycle which included 6 who had already conceived. 20% however remained anovulatory after the third cycle out of which two were amenorrhoic and required withdrawal bleeding. These findings are in agreement with Farquhar et al, who in their meta-analysis studied ovulation rates as secondary outcome and found that, 71% ovulated after LOD.[10] Hamed HO et al in their study also showed statistically significant increase in ovulation following laparoscopic ovarian drilling in clomiphene resistant PCOS patients (50.8% vs 33.5%) with p value<.001. Amer SA et al found that women, who ovulated after LOD, had a significantly lower preoperative AMH [5.6 (1.0–21.0) ng/ml] compared with the non-responders [9.0 (6.1–17.1) ng/ml] and concluded that patients with pre LOD AMH >7.7 ng/ml were associated with significantly lower chances of ovulation and pretreatment circulating AMH level was a good predictor of the ovarian response to LOD.[11] The results were not comparable to our study, in which the mean plasma pre LOD AMH values were high i.e. 9.89±6.02 and the women who ovulated and achieved successful pregnancy had high mean preoperative values of AMH [11.18 (21.53-3.3) ng/ml] than who did not achieve pregnancy [9.8(18.95-2.32) ng/ml] though without any statistical significance. The findings of earlier studies could not be reproduced in the present study possibly because of small sample size, composed only of clomiphene resistant PCOS with higher mean

AMH levels.

33% patients conceived post LOD in subsequent three cycles though there was no statically significant correlation with conception and pre and post-operative AMH levels. Farquhar et al in their meta-analysis found that 25 to 51% conceived after LOD. Similar rates (50.7%) were documented by Zakerah et al.[12] The pregnancy rates in our study was 33% (26.6% radiologically confirmed rate) which is generally in agreement with the available literature. But there was no significant statistically drawn correlation between the degree of fall in post LOD AMH levels and achievement of pregnancy.

Our study had limitations; it was only a prospective observational study and did not have a control group, LOD was studied without addition of any medical ovulation techniques subsequently and the follow up period was short. Hence the long term effects of LOD on AMH and ovarian reserve could not be studied mainly due to logistic constraints. However, the novelty of this study was that it selected patients with Clomiphene resistant PCOS to study the effects of LOD on AMH levels which has not been done before.

Conclusion

LOD was found to be effective in the management of PCOS related infertility and led to a statistically significant drop in AMH with improved outcomes of spontaneous ovulation though no statistical significance could be found between the degree of fall of AMH and ovulation rates. Spontaneous pregnancy rates showed no statistically significant correlation between the degree of fall in AMH but the chances of successful conception possibly improved subsequent to LOD.

LOD does lead to a significant decrease in levels of circulating AMH, which has the potential to be used not only as a marker of ovarian reserve in patients with PCOS with primary infertility but may also emerge as a predictor for success in infertility treatment by LOD, ovulation induction and other ART techniques. All similar studies in literature are limited by the small sample size and limited follow up. Further studies need to be done with adequate sample size and longer follow up to address these issues.

References

1. Rotterdam ESHRE/ASRM- Sponsored PCOS Consensus Workshop Group, authors. Revised 2003 consensus on diagnostic criteria and long term health risk related to polycystic ovary syndrome. Fertil Steril. 2004;81:19-25.[Pubmed]
2. Mumford SL, Legro RS, Diamond MP, Coutifaris C, Steiner AZ, Schlaff WD et al. Baseline AMH Level Associated With Ovulation Following Ovulation Induction in Women With Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 2016 Sep;101(9):3288–3296.
3. La Marca A, Sighinolfi G, Radi D, Argento C, Baraldi E, Artenisio AC et al. Anti- Mullerian hormone (AMH) as a predictive marker in assisted reproductive technology (ART). Hum Reprod Update. 2010 Mar-Apr;16(2):113-30.
4. Nardo LG, Gelbaya TA, Wilkinson H. Circulating basal anti-Mullerian hormone levels as predictor of ovarian response in women undergoing ovarian stimulation for in vitro fertilization. Fertil Steril 2009;92:1586–93.
5. La Marca A, Volpe A. Aniti-Mullerian hormone(AMH) in female reproduction: is measurement of circulating AMH a useful tool? Clin Endocrinol (Oxf). 2006 Jun;64(6):603-10.
6. Dumont A, Robin G, Catteau-Jonard S, Dewailly D. Role of Anti-Müllerian Hormone in pathophysiology, diagnosis and treatment of Polycystic Ovary Syndrome: a review. Reproductive Biology and Endocrinology. 2015;13:137.
7. El-Halawaty S, Rizk A, Kamal M, Aboulhassan M. Clinical significance of serum concentration of anti-Müllerian hormone in obese women with polycystic ovary syndrome. Reprod Biomed Online. 2007 Nov;15(5):495-9.
8. Amer SA, Li TC, Ledger WL. The value of measuring anti-Müllerian hormone in women with anovulatory polycystic ovary syndrome undergoing laparoscopic ovarian diathermy. Human Reproduction, Vol.24, No.11 pp. 2760–2766, 2009.
9. Elmashad AI. 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 ovarian syndrome. Fertil Steril. 2011 Jun;95(7):2342-6, 2346.
10. Farquhar C, Brown J, Marjoribanks J. Laparoscopic drilling by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome. Cochrane Database of Systematic Reviews 2012, Issue 6. Art. No.: CD001122. DOI: 10.1002/14651858.CD001122.pub4.
11. Hamed HO, Hasan AF, Ahmed OG, Ahmed MA. Metformin versus laparoscopic ovarian drilling in clomiphene and insulin-resistant women with polycystic ovary syndrome. Int J Gynaecol Obstet. 2010 Feb;108(2):143-7.
12. Zakherah MS, Nasr A, El Saman AM, Shaaban OM, Shahin AY. Clomiphene citrate plus tamoxifen versus laparoscopic ovarian drilling in women with clomiphene-resistant polycystic ovary syndrome. Int J Gynaecol Obstet. 2010;108(3):240-243.