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Transvaginal Ovarian Drilling in Infertile Women with Polycystic Ovary Syndrome Resistant to Minimal Stimulation

Alieh Ghasemzad, Laya Farzadi and Ozra Ajalli

Polycystic ovary syndrome (PCOS) is the commonest cause of anovulatory infertility. Treatment modes available are numerous mainly relying on ovarian stimulation with FSH, a reduction in insulin concentrations and a decrease in LH levels as the basis of the therapeutic principles. Surgical management of anovulatory infertility also, has enjoyed a revival in recent years. The aim in present study was to evaluate the efficacy of transvaginal ovarian drilling (TVOD) in infertile women with PCOS resistant to minimal stimulation protocol. In this prospective study 30 infertile women with PCOS and resistant to clomiphene citrate and HMG were selected. After ovarian drilling, the number and size of dominant follicles was increased. Cumulative ovulation rate increased to 90.3% in the cycles after ovarian drilling. Cumulative pregnancy rate was 26.7% at 6 months after TVOD. Miscarriage rate in women who conceived after TVOD, was 6.7% in comparison with 12-20% in general population. With the excellent results after TVOD in difficult to treat patients with PCOS, routine use of this procedure is recommended in these patients before more expensive techniques such as IVF.

Key words: Polycystic ovary syndrome, transvaginal ovarian drilling, infertility

INTRODUCTION

Anovulatory infertility secondary to polycystic ovary syndrome (PCOS) is common, accounting for the majority of women with anovulation who attend fertility clinics (Balen *et al.*, 2003; Farquhar *et al.*, 2002). PCOS is a heterogeneous disorder with features including hyperandrogenism, menstrual irregularity and obesity (Tang *et al.*, 2006).

It is clear that the first approach taken for women with PCOS should be the administration of anti-estrogen therapy, but while Clomiphene Citrate (CC) is successful in inducing ovulation in 80% of the treated women, the cumulative pregnancy rate after 6 months of therapy is only 40% (Api *et al.*, 2005).

Those women who do not ovulate with increasing dose of CC are described as being clomiphene citrate resistant (Adashi *et al.*, 1981). The therapeutic option for patients with PCOS who fail to conceive with CC is gonadotropin therapy. Gonadotropin treatment in these patients offer a cumulative pregnancy rate of 70% after 4-6 cycles (Tadokoro *et al.*, 1997) but is associated with an increased risk of developing severe ovarian hyperstimulation syndrome (OHSS) and an increased rate of multiple pregnancy (Hamilton and Franks, 1990).

Wedge resection of the ovary was largely abandoned by the early 1980s, as the introduction of urinary gonadotropins and oral anti-estrogen agents such as CC has made this approach redundant (Farquhar *et al.*, 2002).

Laparoscopic Ovarian Drilling (LOD) is a relatively simple and it provides an alternative treatment option for PCOS patients anovulatory to CC. The mechanism of action of laparoscopic ovarian drilling is unclear; its beneficial effect is apparently due to destruction of the androgen-producing stroma. The majority (56-94%) of PCOS patients who are clomiphene citrate resistant ovulate after drilling and at least half of them go on to achieve a pregnancy. Younger age and lower body mass index are of predictive factors for pregnancy. The endocrine changes resulting from ovarian drilling last for an extended period of time. Exogenous gonadotropin treatment and laparoscopic ovarian drilling appear to yield comparable ovulation and pregnancy rate. However, multiple pregnancy is rare with drilling. There are several complications associated with the procedure, including post-operative peri-adnexal adhesion formation (Gomel and Yarali, 2004).

Studies suggest that transvaginal ovarian drilling (TVOD) is effective in improving IVF results in difficult to treat patients with PCOS and it is less invasive and less expensive when compared with laparoscopic ovarian diathermy (Ferraretti *et al.*, 2001). We conducted this

study to evaluate the efficacy of transvaginal ovarian drilling (TVOD) on the endocrinologic, clinical parameters and reproductive outcome of clomiphene-resistant anovulatory infertile patients with PCOS.

MATERIALS AND METHODS

We conducted this prospective study on 30 infertile women with PCOS and resistant to clomiphene citrate and HMG therapy (minimal stimulation protocol). The samples were selected consecutively from patients presenting to the Infertility Clinic of Tabriz Al-Zahra Hospital since Dec 2003 to Aug 2005. The sample size was achieved according the prior resemble studies and opinion of consultant statistics professor. The diagnosis of PCOS and infertility was made by three separate expert obstetrician and gynecologist. Ethical clearance from Research Vice-Chancellor of Tabriz University of Medical Sciences and informed consents from patients was achieved.

The information were collected by questionnaire including general characteristics, age, weight and height (for calculation of BMI [body-mass index]), duration and type of infertility, hormonal assays, size and number of follicles before and after drilling.

The diagnosis of PCOS was made according to the typical findings including the history of oligomenorrhea, hirsutism and obesity, together with a demonstration of enlarged polycystic ovaries (Speroff *et al.*, 2005). Of course, specific conditions (if any) were pursued and excluded, such as adrenal hyperplasia, thyroid diseases, Cushing's syndrome, hyperprolactinemia and androgen-producing tumors (Speroff *et al.*, 2005).

Anovulation was determined by the history of irregular menstruation and sonographic surveillance. The appearance of dominant follicle is confirmed by sonography and then ovulation was confirmed by US surveillance for decrease of dominant follicle size and appearance of fluid in Cul de sac (the dominant follicle was considered to have the size of ≥ 16 mm).

Minimal stimulation protocol: These patients who had no response to 3 cycles of clomiphene citrate alone (with daily dose of 150 mg) were treated for other 3 cycles with clomiphene citrate and HMG (CC with daily dose of 150 mg from day 3 to 7 and daily injection of HMG from day 8 for 3-5 days). Any injection of HMG was contained 75IU of FSH and 75IU of LH.

Then the non-responders for this minimal stimulation protocol were considered as candidate for TVOD. This consideration was made for reducing in therapy costs and prevention of complications of high-dose gonadotropin treatment such as OHSS and multiple pregnancy.

Patients underwent transvaginal ultrasonography prior to TVOD and a day after the procedure. The same ultrasound machine was used in our unit during the study period.

Semen fluid analysis of partners was normal and the patients had normal hysterosalpingography. The inclusion criteria include having PCOS and history of 6 failed cycles of ovulation induction by clomiphene citrate and HMG (minimal stimulation).

The exclusion criteria were irregular presentation of patients for follow up and discontinuation of therapy and late-onset congenital adrenal hyperplasia.

At first, the patients were informed about this new surgical intervention and an informed consent was signed, including the possible complications and some advantages of TVOD.

The patients underwent anesthesia by administration of propofol. Then, any of ovaries were drilled from various angles under transvaginal sonographic guide by using Wallace Oocyte Recovery Needle attached to suction pump and all small visible follicles were aspirated. We used from Wallace 16G with 33 cm length.

The patients were surveyed for 2-3 h after TVOD and checked for vital signs, vaginal bleeding and abdominal pain and tenderness. Then, the patients were discharged and followed by US, Hct, Hb, morning after.

Following TVOD, the patients underwent ovulation induction in next cycle rapidly, by using clomiphene citrate and HMG.

The difference of size (Size Difference) of medium-sized follicles and the difference of number (Number Difference) of medium-sized follicles were compared before and after TVOD. These comparisons were performed also about preovulatory follicles before and after TVOD.

For pregnancy testing, we used the serum β -hCG survey in days 28-35 of menstrual cycle. The laboratory method we used for this test was ELISA with detectability of 50 mIU/ml β -hCG in serum.

The cases with positive β -hCG were controlled for the miscarriage symptoms (vaginal bleeding, flank and abdominal pain). Then, at 5th and 6th weeks of pregnancy, the transvaginal sonography was performed and the Fetal Heart Rate (FHR) was checked to confirm clinical pregnancy.

The patients were followed until 12 weeks of pregnancy and the miscarriage rate were documented.

Statistical analysis: For statistical analysis the data were entered into the Statistical Package for Social Sciences (SPSS) for PC version 12.

For comparison of follicle numbers, follicle size before and after TVOD, we used paired t-test and for comparison

of abortion rate in patients became pregnant following TVOD with its rate among pregnant women of general population, we used χ^2 -test.

Correlation test was used for determination of effect of age and BMI and duration of infertility on the number and size differences of follicles before and after TVOD.

RESULTS

The average age of patients was 26.5 ± 4.61 years. The duration of infertility among the patients was 2-17 years with average of 5.5 ± 3.47 years.

The infertility was primary in 80% (24/30) and secondary in 20% (6/30) of cases. The average BMI of patients was 26.14 kg m^{-2} . Table 1 compares the average FSH, LH and testosterone values before and after the surgical procedure.

All patients had experienced 6 cycles of failed ovulation induction by clomiphene citrate and HMG (minimal stimulation protocol). Table 2 shows the average numbers of medium-sized (10-15 mm) and preovulatory (dominant) follicles with size of ≥ 16 mm before and after TVOD.

There was no complication following TVOD (bleeding, pain, or fever). The second day Hb and Hct were normal. The second day sonography showed the disappearance of small typical echo-free regions which had been distributed mainly in subcapsular area in initial sonography and showed that the subcapsular area has sonographically more homogenous views following TVOD.

Ovulation induction was initiated one month following TVOD by administration of clomiphene citrate and HMG and in the patients who did not become pregnant, this administration was continued for 6-9 cycles. After TVOD and ovulation induction, 26.67% (8/30) of patients became pregnant. The miscarriage rate among these patients was 12.5% (1/8). The cumulative ovulation rate after TVOD was 90% (27/30).

Figure 1 shows the average numbers of medium-sized and preovulatory follicles before and after TVOD.

The number of medium-sized follicles was not significantly different before and after TVOD but the difference of number of preovulatory follicles was significant before and after TVOD ($p < 0.05$).

According to the number difference and size difference of follicles before and after TVOD, the relation between the age of patients and response to therapy was not significant.

The difference of follicle size before and after TVOD was significant in both type of follicles ($p < 0.05$).

The number of preovulatory follicles was increased significantly after TVOD and this increase was related significantly with patients BMI ($p = 0.041$).

Table 1: Comparison of serum FSH[†], LH[‡] and testosterone levels before and after TVOD*

Hormone	Before TVOD	After TVOD	p-value
LH (IU)	8.64±4.03	4.96±1.8	<0.05
FSH (IU)	3.72±1.76	6.20±2.2	<0.05
LH/FSH	2.60±1.24	1.30±0.89	<0.05
Testosterone (ng mL ⁻¹)	0.74±0.17	0.40±0.09	<0.05

†LH: Luteinizing hormone; ‡FSH: Follicular stimulating hormone; *TVOD: Transvaginal ovarian drilling.

Table 2: The average number of medium-sized (10-15 mm) and preovulatory (dominant) follicles with size of = 16 mm in patients before and after TVOD*

Follicles	Average No. before TVOD	Average No. after TVOD	p-value
Medium-sized follicles	2.60±2.86	2.9±1.54	>0.05
Dominant follicles	0.13±0.43	1.4±0.76	<0.05

*TVOD: Transvaginal ovarian drilling

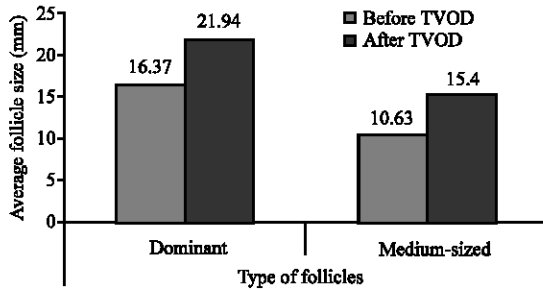


Fig. 1: The average size of medium-sized and preovulatory (dominant) follicles in patients before and after transvaginal ovarian drilling (TVOD)

The relation of the duration and type of infertility with response to therapy (the difference in number and size of medium-sized and preovulatory follicles before and after TVOD) was not significant.

The occurrence of pregnancy was not related significantly with the increase in number and size of preovulatory follicles following TVOD, but the relation between the occurrence of pregnancy and size difference of medium-sized follicles before and after TVOD was significant (p = 0.019).

Also, the relation between serum testosterone and LH:FSH ratio was significant (p = 0.002).

DISCUSSION

It has long been known that the polycystic ovary syndrome is an important cause of anovulation and hirsutism. In a study of 175 anovulatory women presenting consecutively to a reproductive endocrine clinic, 30% of those with amenorrhea and 75% of those with oligomenorrhea had ultrasonographic evidence of polycystic ovaries. These findings are supported by a study in which clinical and biochemical, rather than

ultrasonographic, criteria were used to make the diagnosis of polycystic ovary syndrome (Stephen, 1995).

Transvaginal ovarian drilling (TVOD) now presents a further treatment option for women with anovulatory infertility associated with polycystic ovary syndrome. In this study, TVOD resulted in size increase of all follicles and number increase of preovulatory follicles. This is due to drainage of small follicles or ablation of ovary stroma by this procedure. The mechanism of action of ovarian drilling is unclear; its beneficial effect is apparently due to destruction of the androgen-producing stroma which subsequently decreases androgen inhibitory effect on follicular development (Gomel and Yarali, 2004).

Also, decreased circulatory Inhibition following the decrease in ovary stroma, result in elevated FSH secretion which stimulate follicle growth. Therefore, the size of all follicles and as a result the number of preovulatory follicles increases (Speroff *et al.*, 2005). This is the best achievement in infertile PCOS patients. A study by Takahashi *et al.* (1974) showed that the mean ovarian volume and the number of small follicles were significantly larger in the Clomiphene Citrate (CC) nonresponders compared with those of the CC responders. Ovarian drilling causes to significant decrease of ovary volume after 3 weeks which increases the ovary response to ovulation induction (Al-Took *et al.*, 1999). The results of these two mentioned studies are compatible with our obtained results regarding to the increased number of follicles.

Another important finding in this study was the relation of follicles number and size with patients BMI. So that, the patients BMI was associated inversely with number difference of preovulatory follicles and size difference of medium-sized follicles before and after TVOD. Another finding of this study was the decrease of OHSS following TVOD. Patients with polycystic ovary syndrome (PCOS) treated with gonadotrophins often have a polyfollicular response and are exposed to the risks of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy (Api *et al.*, 2005; Fernandez *et al.*, 2003; Malkawi and Qublan, 2005).

PCOS women have more number of growing follicles in comparison with normal ovulating women and their ovulation induction cycles are in higher risk of OHSS. However, although in fertility-assisted methods, the ovary is stimulated very higher than usual ovulation induction, the frequency of OHSS not only is not more but also is less. For this reason it is believed that follicle aspiration prevent somewhat from OHSS (Speroff *et al.*, 2005).

A study by Kriplani *et al.* (2001) to analyze the efficacy of laparoscopic ovarian drilling in women with anovulatory infertility with clomiphene-resistant

polycystic ovary syndrome (PCOS) showed that laparoscopic ovarian drilling is an effective surgical procedure in women with clomiphene-resistant PCOS. Because they achieved a spontaneous ovulation rate of 81.8%, cumulative ovulation rate of 93.9% and pregnancy rate of 54.5% (Kriplani *et al.*, 2001). The high pregnancy rate and economic aspect of the procedure offer an attractive management for patients with PCOS (Ramzy *et al.*, 2001). These results are compatible with present study findings regarding the reduced rate of OHSS.

According to the results of this study it appears that TVOD can help the improvement of further follicle development as well as follicle growth and also maturation of oocyte under stimulation of clomiphene citrate and HMG. In this way the PCOS patients achieve a rate of pregnancy in a normal cycle of ovulation women.

Present results showed that the new technique, TVOD, can cause changes in ovary for improvement of further follicle development and oocyte maturation under ovary stimulation without increase in complications (adhesion and subsequent infertility).

Ramzy *et al.* (2001) used transvaginal ultrasound guided ovarian stroma hydrocoagulation (TOSH) in 52 anovulatory infertile females diagnosed as PCOS. Ovulation has been achieved in 73.1% of clomiphene citrate resistant PCOS cases and resulted in pregnancy in 26.9% of these cases. No adverse effects were recorded and the procedure was tolerable in most cases. They concluded that this method is a safe, economic and practical procedure that is acceptable by the patients. These results are compatible with present study findings.

The miscarriage rate among present studied patients who became pregnant following TVOD was very low (6.7%) in comparison with miscarriage rate in normal population (12-20%). This indicates that TVOD and aspiration of small follicles improve the subsequent development of oocytes, which decrease the miscarriage rate.

Fernandez *et al.* (2001) performed a same study in which the cumulative pregnancy rate was 33% at 3 months after TVOD and 71% at 6 months after TVOD. No miscarriages occurred. They concluded that TVOD appears to be an alternative minimally invasive method in patients with PCOS who are resistant to clomiphene therapy (Fernandez *et al.*, 2001; Amer *et al.*, 2002).

Casa *et al.* (2003) performed a study to verify the value, feasibility and reliability of TVOD. After the surgical procedure, ovulation occurred spontaneously in 66.7% of women. The cumulative pregnancy rate was 38% at 3 months and 76% at 6 months. No ovarian hyperstimulation or abortion occurred. They concluded that TVOD is a useful therapeutic option in these women (Casa *et al.*, 2003).

Fernandez *et al.* (2004) in another same study showed that during a mean follow-up of 18.1 months, 91% of women recovered regular and ovulatory cycles. The cumulative pregnancy rate was 60% for spontaneous and stimulated cycles, with 39.7% imputed to drilling alone. Although in their study the miscarriage rate was 2.6 times greater than present study, it was lower than general population. They concluded again that TVOD appears to be an effective minimally invasive procedure in patients with PCOS resistant to clomiphene citrate (Fernandez *et al.*, 2004).

Present study was encountered with time limitation and we recommend at least 6 months follow up of response to the therapy in future studies. Also, we recommend the comparison of efficacy of TVOD in CC-resistant and CC-sensitive infertile PCOS women.

CONCLUSION

Present data showed that TVOD normalizes ovarian function and morphology in women with PCOS. In choosing ovulation induction method in clomiphene resistant PCOS patients, TVOD may avoid or reduce the risk of OHSS and multiple pregnancy than gonadotrophins with the same success rate of conception. Also, the high pregnancy rate and economic aspect of the procedure offer an attractive management for patients with PCOS.

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