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Vaginal ultrasound-guided ovarian needle puncture compared to laparoscopic ovarian drilling in women with polycystic ovary syndrome

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Abstract

Study objective To compare pregnancy outcomes in PCOS women undergoing transvaginal ovarian injury (TVOI) and laparoscopic ovarian drilling (LOD)

Design 126 infertile patients with PCOS were included in this prospective cohort study

Canadian task force classification of level of evidence IIA.

Setting University-affiliated fertility center.

Patients Sixty-seven infertile patients with the history of failed in vitro maturation underwent follow-up as the TVOI group. Fifty-nine infertile women who underwent LOD acted as controls. All subjects had PCOS with menstrual irregularity and were anovulatory by repetitive serum progesterone levels.

Interventions The LOD group underwent six cauterizations of a single ovary with 30W for 4–6 s. Failed IVM subjects with 20–30 needle punctures per ovary acted as the TVOI group. Subjects were followed for six months.

Measurements and main results There was not a significant difference between the groups when the cases were evaluated in terms of spontaneous pregnancy or miscarriage rates. BMI levels decreased in both the TVOI and the LOD groups in a similar fashion. However, serum AMH and AFC decreased greater after LOD than they did with TVOI over the six-month duration of the study ($p < 0.001$ in both cases).

Conclusions Preliminary data suggest that TVOI likely represents a safer, less costly and equally effective manner of surgical ovulation induction in anovulatory PCOS women when compared to LOD.

Keywords Polycystic ovary syndrome · Laparoscopic ovarian drilling · Pregnancy · Transvaginal

Introduction

Polycystic ovary syndrome (PCOS) affects 4–10% of reproductive age women [1–3]. Many women with PCOS conceive with ovulation induction, which is most safely achieved with oral agents [4, 5]. However, many women with PCOS ultimately fail to conceive with ovulation induction and undergo in vitro fertilization (IVF). Withholding the injection of human chorionic gonadotropin combined with freezing all the oocytes makes severe ovarian hyperstimulation syndrome (OHSS) unlikely in these patients [6–8]. However, it has recently been shown that oocytes obtained in GnRH-agonist trigger cycles may have lower pregnancy potential than when hCG is given [9].

Another option for care in women with PCOS is in vitro maturation (IVM) [10]. IVM results in the collection of a variable number of mature and immature oocytes which are

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subsequently matured in the laboratory. IVM results in an extremely low rate of OHSS [11], but lower chances of pregnancy than IVF [12, 13].

Laparoscopic ovarian drilling can also be performed, to induce spontaneous ovulation [14–16] and changes in serum ovarian reserve parameters [17]. However, it requires laparoscopy to injure the ovary. IVM collections are different than IVF collections with multiple passes through the ovarian cortex and stroma often being performed [18]. This is performed trans-vaginally. This injury has been shown to alter pituitary hormone levels and function similar to laparoscopic ovarian diathermy [19]. Pregnancy rates after needle injury of the ovary via the vaginal route are unknown. Therefore, this study was performed to determine spontaneous pregnancy rates in anovulatory PCOS women who failed one IVM cycle compared to those that underwent laparoscopic ovarian drilling.

Materials and methods

This study was designed as a prospective cohort study between January 2010 and May 2015 at a referral IVF center in the Province of Trabzon in the northeastern region of Turkey. The primary measured outcome of the study was spontaneous pregnancy resulting in live birth. Secondary outcomes were pregnancy and miscarriage rates, and ovarian reserve parameters. All Patients who failed to ovulate with oral agents (Clomiphene Citrate 150mg daily; Letrozole could not be used in Turkey for this purpose at that time) were offered IVM. Those that refused IVM due to cost or personal convictions were offered LOD. Patients who did ovulate with clomiphene citrate but who failed to conceive were included in the IVM group as well. Sixty-seven women who underwent LOD treatment were invited to participate in the study. Seven patients in the LOD group did not agree to participate in the study group. An additional patient had a spouse with poor sperm quality and was excluded from participation. In the IVM group, 153 patients were contacted to participate. Fifteen patients preferred to undergo an immediate second cycle of IVM. Thirty-six patients refused to participate for personal reasons. Thirteen patients elected to undergo ovulation induction and insemination cycles instead of participating. Nineteen women underwent standard IVF, immediately following the IVM failure. Three couples divorced. The remaining 67 failed IVM patients agreed to undergo 6 months of follow-up without any other medical, surgical or hormonal treatments. No patients were lost to follow-up. None of the subjects had taken clomiphene citrate for at least 90 days before inclusion in this study.

Diagnostic criteria for PCOS included amenorrhea or oligomenorrhea with chronic anovulation, and either (1) clinical and/or biochemical evidence of hyperandrogenism or (2) ultrasonographic appearance of polycystic ovaries. Oligomenorrhea was defined as cycles less frequent than 35 days. All patients with oligomenorrhea had at least two serum progesterone levels negative for ovulation performed 5–10 days before menses occurred. Clinical evidence of hyperandrogenism consisted of a Ferriman–Gallwey score ≥8. The biochemical evidence consisted of serum total testosterone or free testosterone levels greater than female assay maximums. All PCOS subjects had serum total testosterone and DHEAS below the tumor range and am fasting serum 17-hydroxy-progesterone levels less than 2 ng/ml. The polycystic ovary was defined as one of two ovaries having at least 12 follicles of 2–8 mm in diameter.

Exclusion criteria were age less than 20 years or ≥40 years; unilateral or bilateral tubal factor infertility investigated with hysterosalpingography or laparoscopy or male factor infertility per the world health organization 2010 semen analysis guidelines; current 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, or thyroid disease.

Laparoscopic ovarian drilling was performed under general anesthesia and was carried out by a single physician. Three incisions were made in the abdominal wall after blind insufflation. A 10-mm laparoscope was inserted peri-umbilical and two 5-mm lower abdominal incisions were used for the introduction of the instruments. For the procedure, a Wolf video system was used (Richard Wolf Medical Instruments, Germany) and a monopolar electrode needle (Cooper Surgical, USA). Only the right ovary was cauterized. This was performed due to the fact that drilling the left ovary may result in greater formation of adhesions [20]. Six punctures were made in a single ovary at a power setting of 30 W applied for 4–6 s at each point.

Transvaginal ultrasound-guided oocyte collection was performed using a 16G double-lumen aspiration needle (Cook Medical, Sydney Australia), the same as the needle used for standard IVF procedure at the study center. Suction pressure was placed at 110 mm mercury, using a cook suction pump (Cook Medical, Australia). At least 30–40 needle passes through the cortex and stroma were performed, in each ovary. This was performed in the manner described previously [16]. With conscious sedation, this procedure is well tolerated by the patient.

AFC, AMH, body mass index, basal hormonal evaluations, 50-gram oral glucose tolerance tests and baseline transvaginal ultrasonographic ovarian evaluations were all performed on menstrual days 2–3 of a spontaneous menses if regular cycles were occurring. In both groups, baseline, 3 months and 6 months AFC, BMI and AMH values were examined and recorded.

Serum testosterone, prolactin, and progesterone were evaluated with commercially available electrochemiluminescence immunoassay "ECLIA" on the Roche Elecsys E170 (Elecsys module) immunoassay analyzers (Roche Diagnostics, Basel, Switzerland. An Immunoassay for the in vitro quantitative determination of serum follicle-stimulating hormone (FSH) and estradiol was performed with a commercial electrochemiluminescence immunoassay intended for use on the Cobas E immunoassay analyzers (Roche Diagnostics, Basel, Switzerland). Serum AMH was analyzed at a central lab (Düzen laboratory) in Turkey and used an ELISA assay. Serum glucose levels were calculated using the Cobas C Roche Hitachi system (Roche Diagnostics, Basel Switzerland). All intra- and inter-assay coefficients of variability were less than 10%. All results were run in duplicates and averaged. Treatment outcomes were recorded as biochemical pregnancy loss (chemical pregnancy) (a positive pregnancy test without a clinical pregnancy or an ectopic pregnancy), clinical miscarriage before 20 weeks gestational age and live births. Live births were defined as deliveries of at least 24 weeks of gestational age, of a live born child. All patients that were pregnant were contacted one-year later to determine the outcomes of those pregnancies. No subjects had a loss between 20 and 24 weeks of gestation, a fetal demise at any viable gestational age or an ectopic pregnancy.

Statistical analysis

Shapiro–Wilk test was used for assessing whether the variables follow normal distribution or not. Variables were reported as mean ± standard deviation and (minimum: maximum) or median and (minimum: maximum) values, based on the presence or absence of a normal distribution, respectively. According to normality test result, independent samples *T* test or Mann–Whitney *U* test were used for between-group comparisons. For BMI, AMH and AFC measurements obtained from basal, 3rd and 6th month percent change values were computed and between groups, comparisons were performed using Mann–Whitney *U* test. Two-way mixed ANOVA with repeated measurements was performed to examine the main effect of BMI, AMH and AFC measurements and the interaction of these main effects with the LOD and TVOI groups. Pearson chi-square, Fisher's exact test, and Fisher–Freeman–Halton test were used for comparing categorical variables. SPPS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) software was used for performing statistical analysis and $p \leq 0.05$ was set at statistical significance. Medicana International Hospital IRB approval was obtained for this study.

Results

Baseline data are available in Table 1 and was obtained at the time of enrolment.

Median total testosterone levels were found to be higher in the TVOI group when compared to the LOD group ($p = 0.001$). There were no significant differences between the groups in terms of other variables.

Pregnancy outcomes were similar between both groups in Table 2. There was no significant difference between the groups when the cases were evaluated in terms of spontaneous pregnancies resulting in live births, clinical or biochemical miscarriage ($p = 0.53$). There were no multiple pregnancies and no ectopic pregnancies recorded in either group.

Table 3 Provides evidence of the pre-treatment levels and sequential changes at 3 and 6 months of BMI, AMH, and AFC in both groups. BMI values at baseline of both groups were similar (LOD: 29.51 ± 3.0; TVOI: 29.13 ± 3.1 kg/m^2, $p = 0.495$). The mean BMI values of LOD and TVOI groups measured at the 3rd month were 28.28 ± 2.97 kg/m^2 and 27.67 ± 3.23 kg/m^2, and did not differ. Likewise, the mean BMI values of both groups measured at 6th month were similar ($p = 0.591$). Despite trends toward decreased BMI values during the 6-month follow-up, the differences failed to show a statistical significance ($p = 0.07$).

Pre-treatment serum AMH levels of TVOI group were significantly higher than those in the LOD group (7.23 vs. 6.13; $p < 0.001$ nmol/L). AMH levels of LOD vs. TVOI groups measured at 3rd month and 6th month post-procedure were statistically lower as well, respectively. When compared to basal AMH levels there was a 26.4% decrease in the LOD group and a 12.5% decrease in the TVOI group.

When compared to TVOI group, the baseline AFC was significantly higher in the LOD group (medians, range: 25 (22–28) vs. 24(21–30), $p = 0.044$). The number of AFC of the LOD and TVOI groups measured at the 3rd month post-procedure were 19 (16–22) and 21 (12–30), respectively. When compared to basal AFC, the AFC of LOD and TVOI groups measured at 3rd month post-procedure significantly decreased (24% vs. 12%, respectively; $p < 0.001$). Likewise, the AFC of the LOD group vs. the TVOI group measured at 6th month post-procedure significantly decreased (27% vs. 5%, respectively; $p < 0.001$).

The results of the two-way mixed ANOVA demonstrated a significant decrease in BMI over time ($p < 0.001$). However, there was no significant difference of BMI depending on the main effect of group inclusion ($p = 0.387$). There was also no significant interaction between BMI and groups ($p = 0.277$). Therefore, it can be determined that both the LOD and the TVOI groups underwent a similar response to intervention as measured by temporal changes in BMI.

Table 1 Baseline data of the PCOS women who underwent care with laparoscopic ovarian drilling or transvaginal ovarian injury

	LOD ($n=59$)	TVOI ($n=67$)	p value
Female age (years)	29.8 ± 2.9 (23:39)	30.1 ± 3.4 (23:39)	0.666[a]
Duration of infertility (years)	7.0 (3.0:13.0)	6.0 (3.0:11.0)	0.089[b]
Basal serum FSH_(IU/L)	7.70 ± 1.21 (5.36:10.13)	7.81 ± 1.42 (4.65:11.34)	0.652[a]
Basal serum LH (IU/L)	13.23 (8.67:20.71)	13.12 (7.99:23.14)	0.727[b]
Serum progesterone (ng/mL)	0.89 (0.54:1.32)	0.88 (0.66:1.34)	0.585[b]
Serum estradiol (ng/mL)	36.76 (20.66:50.41)	35.21 (23.55:50.03)	0.503[b]
Serum total testosterone (ng/dL)	55.60 (29.76:101.43)	67.54 (34.23:99.32)	**0.001[b]**
Serum prolactin (ng/mL)	27 (17:35)	26 (15:35)	0.455[b]
50_Gr_OGTT			
Normal	27 (45.80%)	39 (58.20%)	0.220[d]
Glucose intolerance	20 (33.90%)	21 (31.30%)	
Diabetes	12 (20.30%)	7 (10.40%)	
Rate of DMII	12 (20.30%)	8 (11.90%)	0.198[c]
Insulin use among diabetics	3 (4.50%)	4 (6.80%)	0.705[e]
Presence of Hirsutism	52 (88.10%)	58 (86.60%)	0.792[c]
Presence of Acanthosis nigricans	3 (4.50%)	2 (3.40%)	1.00[e]

Note DMII; represents type 2 diabetes mellitus. Baseline data on AFC, AMH and BMI are in Table 3

[a]Independent samples *t* test

[b]Mann–Whitney *U* test

[c]Chi-square test

[d]Fisher–Freeman–Halton test

[e]Fisher's exact test

Table 2 A comparison of cumulative pregnancy outcomes obtained at 6 months post-intervention

	LOD ($n=59$)	TVOI ($n=67$)	p value
Total pregnancies	15 (25%)	20 (30%)	0.58
Not pregnant	44 (75%)	47 (70%)	0.53
Biochemical miscarriage	2 (3%)	2 (3%)	
Clinical abortion	4 (6.8%)	2 (3.0%)	
Pregnancy resulting in a live birth	9 (15%)	16 (24%)	

There was a significant decrease in serum AMH levels over time ($p<0.001$). The levels in the LOD group decreased to a more significant level than those in the TVOI group ($p<0.001$).

There was a significant decrease of AFC measurements overall ($p<0.001$). There was also a difference in response to LOD and TVOI over time with the LOD group demonstrating a greater decrease in AFC ($p<0.001$). It should be noted that AFC levels almost returned to baseline at 6 months in the TVOI group which did not occur with the LOD group.

Discussion

This study demonstrated that LOD results in greater change in AFC and serum AMH than does TVOI obtained at the time of an IVM collection. However, pregnancy outcomes were similar between the two groups, as was decrease in BMI. Suggesting that in spite of the milder changes in secondary markers of outcomes obtained with TVOI than LOD, these changes are sufficient to result in a good likelihood of pregnancy. The likelihood of pregnancy at 6 months in this study was consistent with published results of pregnancy after LOD (35%) obtained in the most resent meta-analysis comparing LOD and medications of ovulation induction in PCOS [15] resulting in live birth rates of 15% and 24% in the LOD and the TVOI groups, respectively. Clearly, TVOI offers a new and interesting option for spontaneous ovulation induction in anovulatory women with PCOS. It is relatively low risk and would be done as a day procedure requiring minimal anesthesia. Laparoscopy requires intubation and general anesthesia, and often greater time off work and a prolonged recovery period. Interestingly enough, a recent study by Kandil comparing LOD and transvaginal ovarian needle injury found higher ovulation rates and pregnancy levels with LOD [21]. However, they did not have as many needle passes through the ovary as we did in our study in the TVOI group. However, both studies found that at 3 months, patients in the LOD group experienced a significantly lower

Table 3 Effect of intervention on body mass index, transvaginal follicle count and serum AMH levels

	LOD ($n=59$)	TVOI ($n=67$)	p value
BASAL_BMI (Kg/m^2)	29.51 ± 3.02 (23.55:35.43)	29.13 ± 3.16 (22.31:34.45)	0.495[a]
3-Month BMI	28.28 ± 2.97 (22.13:33.23)	27.67 ± 3.23 (32.09:33.21)	0.274[a]
BMI (3 months→basal)	%− 4.14 ± 2.76 (− 11.49:2.92)	%− 5.05 ± 2.96 (− 11.54:1.46)	0.079[a]
6-Month BMI	28.39 ± 3.03 (21.89:34.44)	27.95 ± 3.21 (21.76:34.24)	0.431[a]
BMI (6 months → basal)	%− 3.76 ± 3.67 (− 13.54:5.44)	%− 4.08 ± 2.8 (− 10.82:2.44)	0.591[a]
Basal AMH	6.13 (4.32:7.54)	7.23 (3.89:12.32)	**< 0.001**[b]
3-Month AMH	4.56 (2.77:6.45)	6.17 (3.47:11.56)	**< 0.001**[b]
AMH (3 months→ basal)	%− 26.42 (− 41.54: − 5.52)	%− 12.50 (− 26.31: − 0.94)	**< 0.001**[b]
6-Month AMH	4.32 (2.01:6.34)	6.13 (3.12:11.78)	**< 0.001**[b]
AMH (6 months → basal)	%− 29.17 (− 55.63: − 3.47)	%− 12.59 (− 28.71:1.86)	**< 0.001**[b]
Basal AFC	25 (22:28)	24 (21:30)	**0.044**[b]
3-Month AFC	19 (16:22)	21 (12:30)	**< 0.001**[b]
AFC (3 months → basal)	%− 24.00 (− 37.04: − 8.33)	%− 11.53 (− 55.56:0)	**< 0.001**[b]
6-month AFC	18 (14:23)	23 (29:30)	**< 0.001**[b]
AFC (6 months → basal)	%− 26.92 (− 44.44: − 4.17)	%− 4.54 (− 28.57:8.70)	**< 0.001**[b]

[a]Independent samples t test

[b]Mann–Whitney U test

[c]Chi-square test

[d]Fisher–Freeman–Halton test

[e]Fisher's exact test

AMH than did the TVOI group in a similar fashion to our study. However, we continued to see improvements in AMH and AFC levels at six months compared to pre-treatment baseline, which was lost at that point in the Kandil study population [21].

IVM collections are either preformed under conscious sedation or propofol and airway support. It is likely that TVOI would have lower anesthesia risk than LOD. Most patients are able to return to normal daily function the day after oocyte retrieval. However, laparoscopy often has a two to four-week convalescence associated with it and resultant lost time from work.

One of the complications associated with LOD has been ovarian failure. Uncontrolled use of cautery has resulted in cases where the ovary was in essence "cooked", and hormonal and ovulation failure resulted. This is unlikely a risk with TVOI. A previous study has investigated outcomes after IVM-induced ovarian injury [14]. This study and that previously published study found slightly different results in terms of duration of outcome. That study demonstrated that two weeks after IVM oocyte retrieval, circulating serum AMH and SHBG levels recovered to pre-puncture values. Three months after oocyte retrieval, all circulating hormone levels had recovered to baseline values. Most likely this is due to differing technique used in oocyte retrieval resulting in different levels of cortical disruption. It is likely that in the Ortega-Hrepich study they did not use the oocyte collection technique which we previously used to collect 125 oocytes at IVM [16], which was the same as the technique used in this study. Future studies should be directed at determining ideal levels of disruption to obtain ideal pregnancy rates using the TVOI approach.

It may be hypothesized that passing a needle 30 to 40 times through the ovary may cause more pain than a standard IVF collection. However, in spite of this technique IVM collections have previously been demonstrated to be less painful than IVF collections [22], possibly because often smaller gage collection needles are used or lower suction pressure.

One weakness of this study was that women with DMII were included. All had received medical clearance for pregnancy. It is possible that including these women may have resulted in some biases in the results. However, rates were similar in both groups as were rates of insulin use and, therefore, any biases were likely minimized. This was not a randomized study and as such undetected bias may exist. *We are unsure of the role played by the higher pre-treatment AFCs and AMH levels in the TVOI group compared to the LOD group.* This may represent more significant pathology in the TVOI group. It is possible outcomes may have been better in terms of pregnancy rates in the TVOI group had the two groups been better matched at the onset. It should be noted that there was a trend toward higher live birth rates with TVOI than with LOD (24% vs. 15%) which may have reached significance if better matched for pathology level. Future prospective randomized studies are needed. Another weakness is the lack of a without treatment arm to determine the spontaneous pregnancy rates among these subjects who

did not receive care. However, recruitment for such an arm would have been impossible since these patients are infertile and desire some intervention to improve outcomes.

Conclusions

These preliminary data suggest that transvaginal ovarian needle injury guided by an ultrasound probe is likely a safe, patient-friendly, low-cost and low-time commitment, treatment option to induce ovulation in women with PCOS. Further studies are needed to determine its success in a large cohort of patients and how many passes are needed to the ovary so that it can be successful. However, it is possible that benefits exist with this treatment option compared to laparoscopic ovarian drilling.

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Compliance with ethical standards

Conflict of interest None of the authors have any conflicts of interest. Authors declare nothing to disclose financially and each author had full control of all primary outcomes and agree to allow the journal to review our data if requested.

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