Clinical consequences of ovarian stimulation in assisted conception and in PCOS
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Chapter 10

Ultrasonographic guided ovarian stroma hydrocoagulation for ovarian stimulation in polycystic ovary syndrome

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Abstract

Objective: to evaluate the safety and effectiveness of transvaginal ultrasound guided injection of hot saline into the ovarian stroma in polycystic ovary syndrome (PCOS) cases in an office based gynecology practice under local anaesthesia.

Setting: outpatient gynecologic office; private and University Hospital based

Study design: case series study

Participants: Sixty anovulatory infertile females diagnosed as PCOS by clinical, chemical and ultrasound criteria were recruited for the study. All cases were resistant to clomiphene citrate for more than 6 months. Fifty two cases completed the follow up period for six cycles.

Intervention: injection of hot sterile saline (75C) into the ovarian stroma under transvaginal monitoring using ovum pickup needle.

Outcome measures: cycle regularity, ovulation rate and safety were primary outcomes. Pregnancy rate and patient convenience were our secondary outcomes

Results: 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 of cases.

Conclusion: Transvaginal ultrasound guided ovarian stroma hydrocoagulation in an office setting seems to be a safe, economic and practical procedure that is acceptable by the patients. If larger studies confirmed its effectiveness it may be an attractive alternative to conventional ovarian drilling.
**Introduction**

Polycystic ovarian syndrome (PCOS) is one of the commonest causes of anovulation. It is estimated that about 25% of PCOS women will not respond to clomiphene citrate and are considered to be clomiphene resistant. Ovarian drilling, is an effective alternative to gonadotrophins in clomiphene resistant PCOS (1-2). Laparoscopic ovarian drilling, using laser or diathermy, needs hospital setting usually with an overnight stay. However, apart from risks of general anaesthesia and laparoscopy, the right dose of diathermy to reliably stimulate the resumption of ovulatory cycles is still not clear in the medical literature. Subsequently, the risk of postoperative adhesions cannot be ignored. Reported adhesion formation rates following laparoscopic ovarian drilling range between 0-100% (3-4).

Current pressures of quality versus cost in an era of managed care has resulted in an emerging trend whereby surgical procedures are gradually migrating to less complex environments. Office gynecologic procedures are now becoming more popular as seen in office microlaparoscopy (5), office hysteroscopy (6), office salpingoscopy (7) and more recently, transvaginal hydrolaparoscopy.(8).

In a previous trial, we reported the validity of thermal aqua puncture (TAP) in induction of ovulation in PCOS cases. The idea is to coagulate areas of the ovarian stroma through conveying thermal energy (hydrocoagulation) using hot saline (9). The ovarian stroma tissue in cases of PCOS is quite echogenic. It can be accurately targeted using the puncture needle. The injected fluid can be identified on the real time ultrasound monitor.

In the present study, we aim at the evaluation of the feasibility of applying transvaginal ultrasound guided ovarian stroma hydrocoagulation (TOSH) as an office procedure.
Material & Methods

The study was conducted between April, 1999 and September, 2000 in an outpatient gynaecologic clinic. Sixty anovulatory infertile females with oligomenorrhoea or amenorrhoea were recruited for the study. All had complete infertility workup. Participants were diagnosed as PCOS based on clinical, ultrasonographic and biochemical investigations. All cases were resistant to clomiphene citrate (CC) for more than 6 cycles. We considered patients to be resistant to ovulation if they fail to ovulate in spite of continuous induction of ovulation using clomiphene citrate for 6 months. The selected cases were younger than 35 years of age and had no history of pelvic surgery. The procedure and its experimental nature were explained to our cases and a written consent was obtained. We got the consent from our local ethical board to carry out the study.

The procedure

The patient was placed in the dorsal lithotomy position and the vagina and perineum were prepared with an antiseptic solution. A preliminary transvaginal sonography was done to scan the pelvis before attempting the procedure and to measure the ovarian volume using the endovaginal probe (model 8561, 6.5 MHz. M.F.I.) of the Ultrasound Machine (Bruel and Kuer 2003 Cheetah, B-K Medical, Sandtofen 9, 2820 Gentofte, Denmark). We recorded the core temperature immediately before and after the procedure through a rectal thermometer.

We used sterile saline (0.9% Sodium Chloride U.S.P XIX) in 500 ml glass bottle (The Nile Company for Pharmaceuticals and Chemical industries, Cairo, Egypt). The bottle was placed in a temperature controlled electric water bath. We used an electronic digital thermometer monitored the water bath temperature: (D2000, Tfa-Germany) as detailed in our original publication (9). An infusion set was fitted to a 500 ml. saline or lactated ringer solution hanged on a 2m stand. A single channel puncture needle (Art. # 8141230 - Swemed Lab, International Ab., 40145-42604 V. Frolunda - Sweden) with 1.4 gauge and 300 mm useable length was used for the procedure. The needle was inserted into the needle guide (B-K UA 1241) followed by the injection of 1-2 ml. of lidocaine into the vaginal puncture site to reduce the pain and heat sensation. The infusion set was then attached to the luer of the needle. Guided by transvaginal ultrasound the site of the ovary was identified in the best accessible location guided by the built in electronic puncture line set by the ultrasound machine. The idea was to design a single vaginal surface puncture nearest to the pouch of Douglas that will make the largest area of the ovarian stroma accessible to injection.
We explained the representation of the image on the ultrasound monitor and the patient was encouraged to follow up the procedure step by step thereafter. We notified the patient before the needle was advanced to puncture the vaginal skin monitoring its course on the ultrasound screen and intermittently monitoring the infusion set drip chamber. Free flow of the saline drip meant that the needle tip is properly located within the pelvic pouch. We usually allowed 150-200 ml of sterile saline at room temperature to accumulate into the Douglas Pouch (hydrofloatation) over a period of about 10 minutes. This amount of fluid is an extra safety measure taken from our side to protect the viscera against any spill of the hot saline injected. We then replaced the infusion set tip a glass syringe filled with 10 ml of hot saline. We notified the patient once more before we started to inject the hot saline (85°C water bath temperature - calculated approximate 75°C injected saline temperature at the needle tip) into the ovarian stroma. The puncture site angle and depth were carefully and minimally changed to allow access to nearby areas of the ovarian stroma from the same puncture site. We allowed a delay of about 30 seconds to pass before changing the site of the injection.

**Follow up**

Our study design was to follow up our patients for 6 months after the procedure. We monitored the ovulation rate (as determined by regular cycles with symptoms suggestive of ovulation and regular transvaginal ultrasound on day 10-14 to detect a mature follicle). We arranged for serum B-hCG assay to diagnose pregnancy whenever the cycle was delayed following a period of ovulatory cycles. Out of the 60 patients, 52 continued our follow up plan and were included in our results. Results were estimated on an intention to treat analysis. The data obtained were represented in terms of means and standard deviation.
Results

The mean age of our patients is 28.8 ± 3.5 years (range 22-34) with a mean period of infertility of 4.9 ± 1.8 years (range 1-8). The mean BMI of our patients is 27.2 ± 2.8 (range 20.8-33.4). The mean ovarian volume for each ovary was 10.6 ± 2.2 ml. We injected a mean of 3.5 ± 1.0 ml of hot saline in each ovary. The mean time for the whole procedure was 11.3 ± 2.2 minutes.

There was no adverse effects recorded in any participant. Twenty three patients (38.3%) experienced pain during the procedure. This was during the ovarian surface puncture and during the injection of the hot saline into the stroma of the ovary (volume related). The pain was tolerable in all cases and all the patients responded negatively when asked if we should abort the procedure. Some patients reported a cool sensation during pelvic hydrofloatation. Some reported it to be a pleasant sensation. Some reported a heat sensation during the injection of the ovary. None reported pain or hot sensation at the vaginal puncture site (anaesthetized). We noticed no change in core temperature before and after the procedure.

Forty-three patients (71.7%) had an episode of bleeding a few days after the procedure. Forty-six patients (76.7%) had three spontaneous successive regular cycles and ovulation was documented by serum progesterone on day 20-22 in at least one cycle. Thirty eight subjects (63.3%) continued to do so for at least six cycles. Fourteen participants (23.3%) became pregnant within the first 6 months of the procedure. Three patients (21.4%) aborted spontaneously within the first trimester. There was no statistically significant difference in the demographic characteristics of all participants, those who ovulate regularly and those who became pregnant (Table I).
Table 1: Demographic characteristics of the study participants

<table>
<thead>
<tr>
<th>Item</th>
<th>All participants</th>
<th>Ovulatory cases</th>
<th>Pregnancy cases</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>28.8 ± 3.5</td>
<td>28.1 ± 1.6</td>
<td>26.9 ± 2.7</td>
<td>NS</td>
</tr>
<tr>
<td>Infertility duration</td>
<td>4.9 ± 1.8</td>
<td>5.0 ± 1.9</td>
<td>4.8 ± 1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Ovarian volume</td>
<td>10.6 ± 2.2</td>
<td>10.6 ± 2.3</td>
<td>10.8 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>27.2 ± 2.8</td>
<td>27.1 ± 2.3</td>
<td>27.2 ± 3.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

Discussion

Patients with clomiphene resistant PCOS are often treated with gonadotrophins. Although effective, it is an expensive, stressful and time-consuming form of treatment requiring intensive monitoring. Besides, patients are exposed to the risks of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy. On the contrary, multiple pregnancy rates are reduced in those women who conceive following laparoscopic drilling and no significant difference in ovulation or pregnancy rates when compared to gonadotrophins therapy as a secondary treatment for clomiphene resistant women (10).

The last decade has witnessed increasing interest in office procedures. The ideal office procedure should be safe, undertaken in a short period of time with minimal morbidity and inconvenience to the patient. In the field of infertility, the scope of transvaginal office procedures is rapidly widening. (11-12). Mio et al, 1999 have tried transvaginal guided follicular aspiration in the midluteal phase for all persistent follicles. None of the participants in this trial conceived in the aspiration cycle (13). However, the response to ovulation induction was improved in subsequent cycles.

Hot saline provides conduction exchange medium through which heat is gently conveyed to the ovarian stroma tissue without tissue substance loss or scarring. Different planes within the ovarian stroma can be accessed without affecting the follicular forming tissues within the ovarian cortex. (9) These findings together with the positive results we obtained in laparoscopic TAP from our previous study (9) has directed our interest to
evaluate and assess the safety and efficacy of transvaginal ultrasonographic guided ovarian stroma hydrocoagulation (TOSH) for ovarian stimulation in polycystic ovary syndrome. We got enough experience in the practice of interventional ultrasonography obtained mainly through oocyte retrieval, cyst aspiration and amniocentesis. Thus, the learning curve for TOSH had been developed rapidly. In contrary to laparoscopic ovarian drilling where immobilisation is done by holding the ovarian ligament. During TOSH the ovary is focused in the view angle and by a jerky needle action the puncture is usually successful in the first attempt.

The success of TOSH depends on the appropriate selection of the patient, the absence of contraindications, adequate instrumentation and meticulous technique. In the present study, we carefully selected our participants as anovulatory infertile females diagnosed on clinical, ultrasonographic and biochemical basis as having PCOS, and proved resistant to clomiphene citrate therapy by follow up for 3-6 month.

The present study demonstrated the effectiveness of TOSH for ovulation induction, resorting cycle regularity and improving the response to clomiphene citrate. These findings match well with those of other investigators who have undergone transvaginal ultrasound guided cyst aspiration in anovulatory PCOS women for research into in vitro maturation and have found so far that ovulatory cycles are resorted without the aid of adjuvant ovulation induction therapy. (14)

Regarding the safety, Injection of fluid within the pelvis through vaginal puncture in the lithotomy position during scanning renders effective hydrofloatation and helps keep the intestine away from the low positioned injection site. TOSH was performed in the office. Allowing the patient to follow up the procedure on the ultrasound monitor reassured the patient and helped her to be distracted from the state of anxiety that may accompany office interventional procedures. Patients almost did not need pain management in the early postoperative period, and the patients were discharged within 1 hour of the completion of the procedure. Another factor in favor of our novel procedure is the cost savings as compared to the hospital charges needed for the conventional laparoscopic ovarian drilling. This is a valuable aspect that has to be considered if the patient is paying for her infertility treatment. The same point may sound valuable to third party medical services.

In the present study we did not carry out hormone assays including LH, FSH or androstenedione before and after the procedure as we have reported in our original study a statistically significant postoperative reduction in the mean basal LH levels and a significant
rise in the mean basal FSH levels. No significant reduction in the mean level of androstenedione was observed. In that same study we recorded no ovarian atrophy or pelvic adhesions following the procedure in those patients who failed to ovulate and were subsequently scheduled for laparoscopic ovarian drilling(9).

We may assume that colour flow mapping (colour Doppler) and 3D technology may be applicable to this novel approach. Colour flow mapping will mark the ovarian stroma vasculature and will represent vivid live imaging during the process of injection. Using 3D-TVS we can portray not only individual image planes, but also store complex tissue volumes which can be digitally manipulated to display a multiplanar view, allowing a systematic tomographic survey of the injected stromal tissue. The same technology can also display surface rendering and transparency views to provide a more realistic 3D portrayal of various structures. (15)

In conclusion, TOSH can be adopted as an outpatient office procedure. The ease of scheduling, reduced costs and rapid recovery suggest it may be the preferred initial procedure for PCO cases resistant to CC. The effectiveness of this procedure depends on the appropriate patient selection. To evaluate the effectiveness of this procedure we need larger sample of PCOS cases to be compared to a control group of PCOS cases managed without surgical intervention.

References

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