Thorough sonographic oocyte retrieval during in vitro fertilization produces results similar to ovarian wedge resection in patients with clomiphene citrate–resistant polycystic ovarian syndrome

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Objective: The purpose of this study was to compare the effectiveness of a thorough sonographic oocyte retrieval to a routine in vitro fertilization retrieval to induce ovulation, pregnancy, and endocrine changes in patients with polycystic ovarian syndrome in their post–in vitro fertilization cycles.

Study design: Sixty-four patients from a tertiary infertility clinic, with clomiphene citrate–resistant polycystic ovarian syndrome and who were undergoing in vitro fertilization, were assigned randomly into 2 groups. Group 1 (n = 34) had a thorough (every possible follicle punctured) sonographic oocyte retrieval, and group 2 (n = 30) had a routine (only follicles that were likely to contain oocytes) in vitro fertilization retrieval. These patients who did not conceive in their in vitro fertilization cycle were monitored with ultrasound scanning for evidence of ovulation, pregnancy, before and after day 3 gonadotropin, and steroid hormone levels. Analysis of variance and the Student t test were used for statistical significance.

Results: Ovulation rates of 53% (18/34) and cumulative pregnancy rate of 44% (8/18) were observed in group 1, with no ovulations in group 2. Significant decreases in luteinizing hormone/FSH ratio (4.1 to 1.7) and testosterone (1.2 to 0.7 ng/mL) occurred after treatment in the thorough sonographic oocyte retrieval group, with no change after routine in vitro fertilization. Operating time was increased significantly in the thorough sonographic oocyte retrieval group (45 vs 24 minutes) in group 2.

Conclusion: Thorough sonographic oocyte retrieval during in vitro fertilization cycle can produce significant improvements in the endocrinologic abnormalities, ovulation, and pregnancies that are comparable with ovarian wedge resection in patients with clomiphene citrate–resistant polycystic ovarian syndrome.

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One of the most common endocrine disorders in women of reproductive age is polycystic ovarian syndrome (PCOS). Although many diagnostic criteria are used to define PCOS, a universally accepted definition is not available. Most definitions rely on the clinical features of menstrual irregularities (amenorrhea/oligomenorrhea), hyperandrogenic effects (hirsutism, acne), the presence of polycystic ovarian morphologic condition, and the exclusion of other known endocrine disorders.

Anovulatory infertility is the most common feature of women with PCOS who are attempting to conceive. The first line of treatment for these women is clomiphene citrate (CC). Although the overall ovulation rate with CC is 75% to 80%, 15% to 20% of the women do not respond to any dose of CC, and pregnancy rates are only 50%. There are multiple adjunctive therapies that include weight loss, metformin, and oral contraceptive pill suppression that can be used either alone or with CC. Those women whose condition does not respond to these therapies usually are moved to gonadotropin therapy. Gonadotropin therapy is expensive, with significant risks of high-order multiple gestations and ovarian hyperstimulation syndrome (OHSS), especially in this type of patient. In vitro fertilization (IVF) is able to control the multiple gestation problem, but at even a higher cost.

The ovarian wedge resection was first used by Stein and Leventhal in 1935 as a treatment for anovulatory infertility in women with PCOS. This surgery involved a laparotomy in which approximately one half of the ovary was removed. The initial study of > 100 patients reported ovulation rates of 95% and pregnancy rates of 85%. This single treatment can lead to sustained physiologic ovulatory cycles over many years. Many other reports have confirmed these benefits but have also documented the severe limitations of periadnexal adhesions that develop as a result of the surgery. However, with the development of successful medical ovulation induction agents, the postoperative adhesion problem caused this surgery to lose favor.

Laparoscopic ovarian drilling (LOD) was the next step in the surgical induction of ovulation. This less invasive modification of the ovarian wedge resection uses a laparoscope and either electrocautery or lasers used in various techniques to drill the ovaries. Numerous studies have confirmed the beneficial effect of these procedures on ovulatory function and pregnancies. Potential risks that are associated with LOD are the laparoscopy itself, general anesthesia, periadnexal adhesions, and ovarian atrophy. These risks and the further success of adjunctive therapies, used alone or with CC, have caused LOD to be performed rarely now.

The idea for this study came from an unexpected finding in a different study. In an attempt to decrease OHSS risk in patients with PCOS, we began to perform a thorough sonographic oocyte retrieval (SER). During a routine IVF SER, only those follicles that are likely to contain oocytes are drained, with the smallest follicles left unaspirated. We theorized that, if we drained these small follicles, it would prevent their growth in the luteal phase and decrease OHSS risk. The thorough SER had no effect on OHSS but produced the unexpected finding of spontaneous menses in these previously amenorrheic patients. This was not something that we had observed after routine IVF procedures.

The objective of the study was to compare the effectiveness of the thorough SER with a routine IVF retrieval to induce ovulation and pregnancy and the resultant endocrine changes in patients with CC-resistant PCOS in their post-IVF cycles.

**Material and methods**

A prospective randomized clinical trial was the study design that was used for this study. Sixty-four patients from a private tertiary infertility clinic who met all the inclusion criteria were assigned randomly into 2 treatment groups. For inclusion into the study, patients had to meet all of the following criteria: (1) amenorrheic or severely oligomenorrheic, (2) hyperandrogenism either clinical (hirsutism, acne) and/or biochemical (elevated testosterone level, > 1.0 ng/mL), (3) unresponsive to CC in any dose either with or without adjuvant therapy (oral contraceptives, metformin, dexamethasone), (4) longstanding infertility of > 18 months and absence of other infertility factors other than anovulation, (5) absence of other androgen excess or ovulation disorders, (6) planning to undergo IVF, (7) did not conceive during the IVF cycle. The study protocol was approved by an independent institutional review board, and all subjects gave their written informed consent.

Initially 95 patients who met the inclusion criteria were assigned randomly to groups, but those women who became pregnant from the IVF cycle were dropped from the study. The patients were recruited over a 7-year time frame because of the restrictive entry requirements for the study. This resulted in 34 patients assigned to group 1, who had the thorough SER, where every possible follicle that could be entered was punctured and drained. Group 2 had 30 patients who had a routine IVF retrieval with only follicles that were likely to contain an oocyte were aspirated.

**IVF ovulation protocol**

All women received monophasic oral contraceptive therapy for 3 weeks from their previous menstrual period. A suppression check ultrasound scan was performed before oral contraceptive therapy was stopped. If no cysts were present, the gonadotropin-releasing hormone–agonist Synarel was started the last 4 days of oral contraceptive use. Ovarian follicular...
development was stimulated with a combination of recombinant human follicle-stimulating hormone (FSH) and human menopausal gonadotropin at doses of 225 to 300 IU/d, which was based on body weight and was adjusted based on ovarian response. Ovulation was triggered when at least 3 follicles were ≥18 mm (mean diameter). Oocyte pickup was performed 34 to 35 hours after the administration of 5000 IU of human chorionic gonadotropin.

**Oocyte retrieval and embryo transfer**

All patients had conscious sedation anesthesia with a combination of propofol-sublimaze and midazolam hydrochloride intravenously administered by an anesthesiologist. The same physician performed all of the oocyte retrievals transvaginally under ultrasound guidance with a standard 16-gauge double lumen aspiration needle. Group 1 (thorough SER) had every possible follicle aspirated, including those follicles in the 4- to 10-mm range. The routine IVF (group 2) had only follicles that were likely to contain oocytes aspirated (all those that were ≥15 mm, most of which were in the 10- to 15-mm range and rarely <10 mm). Embryo transfers were performed on day 3 after SER, and those patients who did not achieve a pregnancy were monitored in the cycles after the IVF.

Day 3 levels of FSH, luteinizing hormone (LH), androstenedione, and testosterone were drawn in both groups before their IVF cycle and in the cycle after their IVF. Transvaginal ultrasound follicular monitoring was started on day 12 of the cycle after the IVF and repeated every 1 to 2 days until ovulation or until the lead follicle failed to grow over 2 consecutive monitoring cycles. Ultrasound ovulation criteria were the disappearance of the preovulatory follicle, the presence of fluid in the cul-de-sac, and/or the formation of an echogenic cyst that was consistent with a corpus luteum. All ovulations were further confirmed by mid-luteal progesterone levels. Follicle growth, endometrial development, and ovulations were followed by ultrasound scans and recorded. Pregnancy was confirmed by serum human chorionic gonadotropin levels and 7-week gestational ultrasound scans. Spontaneous menses were also recorded.

A power calculation that was based on the following assumptions was performed before the study. Most ovarian wedge resection and LOD procedures report ovulation rates from 40% to >90%; we assumed an expected 50% ovulation rate for the thorough SER group and <10% for the routine IVF group. With these assumptions and with 80% power to detect this difference, 21 patients would be needed in each group. Thirty or more patients were enrolled to allow for possibly lower rates. A random permuted block with a block size of 8 was the randomization process that was used to generate the groups. Before the start of the study, 100 consecutive numbered opaque envelopes contained the group assignments, which were opened after the patient enrolled in the study.

Analysis of variance and the Student t test for paired groups were used for statistical significance between the groups and for hormonal comparisons.

**Results**

The patient characteristics of the 2 treatment groups are shown in Table I. No significant differences between the groups were observed in age, weight, body mass index, or baseline hormone levels. Both groups had baseline LH levels of >20, LH/FSH ratios of >4, testosterone levels >1 ng/mL, and androstenedione levels >1.5, which are consistent for this group of patients with CC-resistant PCOS. Initially, 95 patients were assigned randomly to groups, but 31 patients (32.6%) became pregnant during their IVF cycle and were not eligible to be in the study. This resulted in 34 patients in group 1 (thorough SER) and 30 patients in group 2 (routine SER), for a total of 64 patients who completed the study.

The results of the cycle outcomes in terms of ovulations, pregnancies, and spontaneous menses for each group are shown in Table II. The thorough SER group (group 1) had the only ovulatory cycles and pregnancies. The overall ovulation rate was 53% (18/34) for this group. Two of these patients became pregnant in this first cycle; 4 patients became pregnant in their second cycle, and 2 other patients became pregnant in their third cycle, for a cumulative 3-month pregnancy rate of 44% (8/18). Four of the remaining 10 ovulatory patients (who did not become pregnant) were able to be followed for ≥6 months and were continuing to have ovulatory cycles. All of these cycles were monofollicular ovulations by transvaginal ultrasound monitoring, and all of the pregnancies were singletons.

The endocrine profiles for each group before and after treatment are also shown in Table II. Significantly lower LH levels, LH/FSH ratios, and androstenedione and testosterone levels were seen after treatment only after the thorough SER in group 1. After the routine SER, the levels of these same hormones essentially were unchanged. Those in group 1 who ovulated but did not become pregnant had these levels rechecked in their subsequent cycles and remained at posttreatment levels with no significant regression to pretreatment levels. The patients in group 1 who did not ovulate but who had spontaneous menses (10/16) were treated with CC at 100 mg in their next cycle, and 7 of the 10 patients (70%) ovulated with the addition of CC. Examination of the subgroup in the thorough SER group who did not ovulate or show spontaneous menses showed drops
in their LH levels after treatment that were not significant. Operating time was increased significantly in the thorough SER group (45 ± 8 minutes vs 24 ± 7 minutes) in group 2, which reflected the additional time that was required to drain these smaller follicles completely.

**Comment**

There is a wealth of experience in the literature that indicates that various surgical techniques, whose primary purpose is the partial destruction of the ovaries, can produce ovulations in patients with PCOS. These procedures have produced sustained ovulations and pregnancies over many years with a variety of techniques. However, despite their success, they are used rarely now because of the risks of the procedures (adhesions, anesthesia) and the overall success of medical ovulation induction agents. There is a small subgroup of patients with PCOS who do not respond to CC and have noted significant decreases in LH levels, with FSH levels and has less success with these procedures because of poor oocyte quality, decreased fertilization rates, and increased miscarriage rates. Patients with PCOS usually has the most elevated LH levels and has less success with these procedures because of poor oocyte quality, decreased fertilization rates, and are at highest risks for multiple gestations and OHSS.

This study demonstrates that a thorough SER during an IVF cycle can produce significant improvements in the endocrinologic abnormalities, ovulations, and pregnancy rates comparable with the ovarian wedge resection in patients with PCOS in cycles after their IVF cycle. These improvements were not seen in the group that had a standard IVF SER, in which only the larger follicles were aspirated. This extension of the routine IVF procedure represents a little or no cost addition that may improve the ovarian function for years in these patients with severe PCOS.

The mechanisms that are responsible for the ovulation-inducing properties of these procedures remain poorly understood. Early mechanical theories of decreased intraovarian tension in the ovarian capsule, decreased bulk that makes the remaining ovarian tissue more sensitive to gonadotropins, or removal of androgen-producing elements in the ovary largely have been excluded. Most current theories focus on the endocrine changes that were noted after these procedures. Judd et al noted significant but transitory decreases in androstenedione and longer lasting decreases in circulating testosterone after wedge resection. Many authors have noted significant decreases in LH levels, with FSH levels basically unchanged after the procedure, which results in significant decreases in the LH/FSH ratio in these patients. It is thought that this normalization of the LH/FSH ratio allows FSH to recruit new cohorts of follicles and the resumption of ovulatory ovarian function that can be sustained for years. Women with the highest pretreatment levels of LH have been noted to have the best success with LOD procedures. These biochemical changes have been observed to be sustained over years and may help explain the reason that these patients can maintain regular menses over many years without reverting to their previous state.

In our study, we noted similar changes in these same endocrine parameters in the thorough SER group. Significant decreases in testosterone levels, in LH, and in the LH/FSH ratio were noted in our group 1 patients, with no significant changes in the standard SER group. We believe that these changes are responsible for the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Thorough SER</th>
<th>Routine SER</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>31 ± 4.0</td>
<td>29 ± 3.9</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64 ± 5.7</td>
<td>58 ± 7.1</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.5 ± 2.5</td>
<td>23 ± 2.9</td>
<td>NS</td>
</tr>
<tr>
<td>LH (IU)</td>
<td>24.6 ± 6</td>
<td>25.4 ± 3.6</td>
<td>NS</td>
</tr>
<tr>
<td>FSH (IU)</td>
<td>6 ± 0.7</td>
<td>5.4 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>LH/FSH ratio</td>
<td>4.1</td>
<td>4.7</td>
<td>NS</td>
</tr>
<tr>
<td>Testosterone (ng/mL)</td>
<td>1.4</td>
<td>1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Androstenedione (ng/mL)</td>
<td>1.7</td>
<td>2.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

**NS, Not significant.**

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### Table I Baseline parameters in the 2 treatment groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH (IU)</td>
<td>Pretreatment</td>
<td>24.6*</td>
<td>25.4†</td>
</tr>
<tr>
<td>Posttreatment</td>
<td>10.2*</td>
<td>22.7†</td>
<td>NS</td>
</tr>
<tr>
<td>Testosterone (ng/mL)</td>
<td>Pretreatment</td>
<td>6.2†</td>
<td>5.4†</td>
</tr>
<tr>
<td>Posttreatment</td>
<td>6.2†</td>
<td>5.9†</td>
<td>NS</td>
</tr>
<tr>
<td>Androstenedione (ng/mL)</td>
<td>Pretreatment</td>
<td>1.3†</td>
<td>1.2‡</td>
</tr>
<tr>
<td>Posttreatment</td>
<td>1.3†</td>
<td>2.0**</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Pre and posttreatment LH values group 1.
† Pre and posttreatment LH values group 2.
‡ Pre and posttreatment FSH values group 1.
§ Pre and posttreatment FSH values group 2.
¶ Pre and posttreatment testosterone values group 1.
|| Pre and posttreatment testosterone values group 2.
| Pre and posttreatment androstenedione values group 1.
** Pre and posttreatment androstenedione values group 2.

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### Table II Cycle outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovulations (n/N)</td>
<td>18/34 (53%)</td>
<td>0/30 (0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pregnancies (n/N)</td>
<td>8/18 (44%)</td>
<td>0/30 (0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Spontaneous menses (n/N)</td>
<td>25/347 (3.5%)</td>
<td>2/30 (6%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Operating time (min)</td>
<td>48 ± 8</td>
<td>24 ± 7</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>LH Pretreatment (IU)</td>
<td>24.6*</td>
<td>25.4†</td>
<td>&lt;.01*</td>
</tr>
<tr>
<td>Posttreatment (IU)</td>
<td>10.2*</td>
<td>22.7†</td>
<td>NS</td>
</tr>
<tr>
<td>FSH Pretreatment (IU)</td>
<td>6.2†</td>
<td>5.4†</td>
<td>NS</td>
</tr>
<tr>
<td>Posttreatment (IU)</td>
<td>6.2†</td>
<td>5.9†</td>
<td>NS</td>
</tr>
<tr>
<td>Testosterone Pretreatment (ng/mL)</td>
<td>1.3†</td>
<td>1.2‡</td>
<td>&lt;.05‡</td>
</tr>
<tr>
<td>Posttreatment (ng/mL)</td>
<td>1.3†</td>
<td>2.0**</td>
<td>NS</td>
</tr>
<tr>
<td>Androstenedione Pretreatment (ng/mL)</td>
<td>0.9§</td>
<td>2.1**</td>
<td>NS**</td>
</tr>
</tbody>
</table>

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* Pre and posttreatment LH values group 1.
† Pre and posttreatment LH values group 2.
‡ Pre and posttreatment FSH values group 1.
§ Pre and posttreatment FSH values group 2.
¶ Pre and posttreatment testosterone values group 1.
|| Pre and posttreatment testosterone values group 2.
| Pre and posttreatment androstenedione values group 1.
** Pre and posttreatment androstenedione values group 2.
resumption of normal ovarian function in this group. Although transvaginal ultrasound follicular aspiration does less extensive damage to the ovarian surface and is unlikely to affect ovarian stromal tissue, it produces endocrine changes that are similar to the more destructive procedures of ovarian wedge resection or LOD. Therefore, drainage of the follicular contents of these smaller follicles seems to be the important factor in releasing these patients with CC-resistant PCOS from their endocrinologic-mediated disturbance that prevents normal follicular growth and ovulation.

The operating time in the thorough SER group was almost double that of the routine IVF retrieval. This significant difference must be anticipated because of the compulsiveness that is necessary to drain all the small follicles. We also used conscious sedation given intravenously by anesthesiologists for all our cases. It is important to minimize patient discomfort to allow the best opportunity to do the thorough job that is needed. The experience of the person who performs the retrieval is important to allow drainage of the smallest follicles. Finally, we found that the ovarian stimulation during the IVF cycle makes it technically easier to drain smaller follicles because the larger-sized ovary moves less than

Stein, in his initial study of a group of women with amenorrhea, noted that they had bilateral polycystic ovaries at the time of laparotomy. He originally performed ovarian wedge biopsies in the hope of discovering the cause of their amenorrhea. The surgery failed to determine the cause of the amenorrhea but produced the unexpected results of regular menses and pregnancies. This finding lead to his study of the wedge resection as a fertility procedure. We began using the thorough SER potentially to reduce OHSS in these patients by draining secondary follicles and preventing their continued growth in the luteal phase. However like Stein, we did not reduce OHSS but noted that several of these patients who did not become pregnant in the IVF cycle began to have regular menses after the procedure. We had not seen this after routine IVF, and this observation lead to the idea for this study.

In summary, this study demonstrated that a thorough SER during IVF in which all the follicles in the ovary are drained in patients with CC-resistant PCOS can produce endocrinologic changes that are similar to those seen after ovarian wedge resection or LOD. These changes most likely explain the regular menses, ovulations, and pregnancies in previously anovulatory and mostly amenorrheic patients. This extension of a normal ovaries at the time of laparotomy. He originally per- form an ovarian wedge biopsy. Endoscopy 1984;16:143-5.

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Discussion

DAVID ADAMSON, MD. This paper compared the effectiveness of thorough SER to a routine IVF retrieval to induce ovulation, pregnancy, and endocrine changes in patients with PCOS. A prospective randomized