Characteristics of baseline ovarian cysts in clomiphene citrate ovulation cycles

To evaluate the incidence and factors associated with ovarian cysts in infertile patients receiving clomiphene citrate (CC), we performed a retrospective cohort study involving 466 CC treatment cycles. Ovarian cysts are a common finding in patients presenting for CC, with approximately one in five patients having a baseline ovarian cyst >10 mm. (Fertil Steril® 2004;82:979–81. ©2004 by American Society for Reproductive Medicine.)

Women are using assisted reproductive technologies now more than ever. Despite the increasing availability of gonadotropin ovulation induction and IVF, the use of clomiphene citrate (CC) ovulation induction continues to be the first-line therapy for most etiologies of female infertility (1). In contrast to gonadotropin ovulation induction and IVF cycles, there are no studies in the literature designed to assess the incidence or effect of pretreatment ovarian cysts during CC ovulation induction cycles (2–8).

There is no agreement regarding how and when to monitor for ovarian cysts during CC cycles. Protocols for ovulation induction vary among institutions. Some physicians routinely perform baseline ultrasound examinations before starting therapy and then on a monthly basis, whereas others perform ultrasound examinations less routinely. Extrapolating from IVF data, ovarian cysts are often considered a contraindication to CC therapy (2–8). An ovarian cyst theoretically might increase in size, twist, or mechanically interfere with ovulation. We could find only one study that commented on the effects of ovarian cysts in patients receiving CC therapy. In the study by Opsahl et al. (9), only eight patients had ovarian cysts. Although their study was not designed to evaluate ovarian cysts, seven of the eight patients had regression of their ovarian cyst.

To investigate the incidence and factors associated with ovarian cysts in CC cycles, we performed a retrospective cohort study, examining demographic data, serum hormone levels, and cyst characteristics. We evaluated the data for correlations that might streamline or change the way cysts are monitored during CC cycles.

This study was approved by the institutional review board at Tripler Army Medical Center. The patients included in the study were undergoing infertility evaluation and treatment with CC (Teva Pharmaceuticals, Sellersville, PA) ovulation induction. All patients eligible for CC ovulation induction were included, regardless of their diagnosis. All patients had simple-appearing cysts <6 cm in size. Patients were excluded for severe tubal disease, cyst size ≥6 cm, a complex-appearing cyst, inability to visualize both ovaries, history of ovarian surgery, history of ovarian cysts, and severe male factor infertility requiring IVF or intracytoplasmic sperm injection.

Data were collected via retrospective database review of all patients presenting for CC ultrasound examinations. These data were placed into a database recording age, diagnosis, dose, previous cycles with CC, the presence or absence of cysts, and serum day 3 hormone levels (FSH, LH, and E2) for each patient before CC administration. If a patient had a baseline ovarian cyst, data on the size and persistence of the cyst were included. A baseline ovarian cyst was defined as an anechoic structure ≥10 mm in mean diameter. This size threshold is justified in the IVF literature as being detrimental to pregnancy success (3–6). Cyst persistence was defined as the continued presence of the cyst at repeat ultrasound 4 weeks after the initial ultrasound.

During the study period, 213 patients underwent 466 CC ovulation induction cycles and pretreatment transvaginal ultrasound examinations. Patients underwent a transvaginal ultrasound examination monthly between days 2 and 4 of the patient’s menstrual cycle before receiving CC. All patients received CC for 5 days, starting on cycle days 2, 3, 4, or 5 as previously described (10). Ovulation was assessed with a LH-ovulation predictor kit. No patients received hCG for ovulation induction. Timed intercourse or intra-uterine insemination was recommended as appropriate for the patient’s diagnosis.

The cyst was measured at the largest cross-section, and the two perpendicular diameter measurements were averaged ([(D1 + D2)/2]. Only cysts ≥10 mm were recorded. No patient was given CC if a cyst ≥10 mm was noted on transvaginal ultrasound. Instead, patients were followed expectantly and seen after their subsequent menstrual cycle. All data were collected and recorded onto a CC evaluation sheet. The data were placed into a computerized database by the infertility nurse who was blinded as to the study’s hypothesis.
Comparison of baseline data for all clomiphene citrate cycles.

<table>
<thead>
<tr>
<th></th>
<th>All cycles (n = 466)</th>
<th>Cycles with ovarian cysts ≥10 mm (n = 83)</th>
<th>Cycles without ovarian cysts (n = 383)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cycles with persistent cysts (n = 40)</th>
<th>Cycles with nonpersistent cysts (n = 43)</th>
<th>P value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>30.5 ± 4.9</td>
<td>31.1 ± 4.3</td>
<td>30.4 ± 4.9</td>
<td>.19</td>
<td>31.4 ± 3.6</td>
<td>30.8 ± 5.1</td>
<td>.58</td>
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<tr>
<td>Cycle no.</td>
<td>1.4 ± 1.5</td>
<td>1.5 ± 1.5</td>
<td>1.4 ± 1.4</td>
<td>.49</td>
<td>1.7 ± 1.4</td>
<td>1.3 ± 1.4</td>
<td>.13</td>
</tr>
<tr>
<td>Dose (mg/d × 5 d)</td>
<td>81.8 ± 33.7</td>
<td>76.9 ± 32.0</td>
<td>82.7 ± 34.0</td>
<td>.24</td>
<td>77.3 ± 25.3</td>
<td>76.6 ± 38.1</td>
<td>.54</td>
</tr>
<tr>
<td>Cyst size (mm)</td>
<td>20.6 ± 9.9</td>
<td>20.6 ± 9.9</td>
<td>N/A</td>
<td></td>
<td>22.7 ± 10.7</td>
<td>18.5 ± 8.8</td>
<td>.03&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*Note: Comparison data were subdivided into those cycles with and without ovarian cysts ≥10 mm and also subdivided for those cycles in which the cysts persisted vs. those in which the cysts did not persist. Values are depicted as mean ± SD.

<sup>a</sup> P value comparing patients with cysts with those patients without cysts.

<sup>b</sup> P value comparing patients with persistent cysts with patients with nonpersistent cysts.

<sup>c</sup> Significance is represented by P<.05.


Statistical analysis was performed with a Kruskal-Wallis one-way analysis of variance for nonparametric data, t-test for parametric data, and a χ² test for trends. All data are reported as means with their associated standard deviation. An α error of .05 was considered significant. Relative risks and 95% confidence intervals are used where appropriate.

Baseline data are shown in Table 1. In our patient population, the mean age was 30.5 ± 4.9 years (range, 19–43 years). The mean ovarian cyst size was 20.6 ± 9.9 mm (range, 10–53 mm). When comparing the patients with cysts to those without baseline cysts and the patients with persistent ovarian cysts to those in whom the cyst did not persist, there were no significant differences in age, day-3 FSH, day-3 LH, or day-3 E₂ concentrations, number of cycles, diagnosis, or dose of CC (Table 1).

The overall cyst incidence was 17.8%. Of the 466 transvaginal ultrasound examinations, 83 revealed baseline ovarian cysts. Twenty patients who had never received CC had a baseline ovarian cyst on transvaginal ultrasound evaluation, for an incidence of 13.8%, with a mean cyst size of 21.7 ± 10.1 mm (range, 10–49 mm). Fifty-five patients who had received CC in the preceding cycle had an ovarian cyst, for an incidence of 17.7% and a mean cyst size of 16.7 ± 9.0 mm (range, 10–53 mm). Of note, all of the patients had an ultrason examination in the previous month, with CC given in the absence of a persistent cyst. There was no significant difference between the incidence of cysts (P= .29), but there was a significant difference between the mean cyst size when comparing the two groups (P<.05) (Table 1).

Of the 83 baseline ovarian cysts, 40 persisted for an overall incidence of 48.2%. We evaluated cyst persistence in relation to cyst size and use of CC in the preceding cycle. For cysts between 1.0 and 2.0 cm in size, the incidence of cyst persistence was 42.5%. If the cyst was ≥2 cm, the incidence of persistence was 63%; these values were not significantly different (P=.19) (power = 10%). In patients receiving CC previously, the incidence of having a persistent cyst was 56.4% vs. 30.0% in the patients who had never received CC. These data were significant, demonstrating that ovarian cysts were more likely to persist if a patient had received CC in the preceding cycle (P=.04, relative risk = 1.9, 95% confidence interval 0.92–3.82).

Our data found the incidence of baseline ovarian cysts in CC ovulation induction cycles to be significant. A review of the literature revealed no studies in which the main objective was to characterize the incidence of baseline ovarian cyst in CC ovulation induction cycles (9). Our data demonstrate that approximately one in every five patients (17.8%) presenting for CC therapy will have an ovarian cyst ≥10 mm.

The incidence of baseline cysts was not predictable according to any of the parameters chosen in our study, including age, diagnosis, medication dose, cycle number, or serum hormone concentrations. However, in the patients who had not previously received CC, cysts were noted to be significantly larger than in those who had taken CC in a prior cycle. This finding could indicate a difference in cyst etiology between the groups. The smaller cysts in the patients with history of previous CC might represent early functional or rapidly maturing follicles, and the larger cysts in the patients without previous CC might represent a pathologic process (11). Unfortunately, given the nature of this retrospective study, we were unable to determine the functionality of the ovarian cysts in our cohort.

The size of the cyst was not predictive of cyst persistence. However, the power of our study for this prediction was 10%. A post hoc power analysis revealed that we would need 1,128 patients with baseline cysts to determine significance between cyst size and persistence. A prior CC ovulation induction cycle was the only parameter that was predictive of persistent cysts. Cysts were more common after ovulation induction therapy (17.7%) and more likely to persist (56.4%). However, cysts were still present in 13.8% of patients who presented for their first CC cycle.

We attempted to limit bias in this study in many ways. Ascertainment bias was minimized by having the data collection performed by a nurse blinded to the study hypothesis. We attempted to limit selection bias by thoroughly assessing the clinic records for patients presenting for CC evaluation. Recall bias was limited by using the data collected prospectively on our clinic Clomid evaluation forms.

In summary, baseline ovarian cysts are difficult to predict and are a common finding in patients presenting for ovulation induction. Based on the overall incidence of 17.8%, we recom-
mend the use of transvaginal ultrasound to detect baseline ovarian cysts before CC ovulation induction cycles. Further prospective studies involving CC ovulation induction cycles are essential in determining how baseline ovarian cysts actually affect pregnancy rates and in defining the etiology of these baseline cysts.

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References