COMPARISON BETWEEN LETROZOLE ALONE VERSUS LETROZOLE-GONADOTROPHINS COMBINATION IN VERSUS CLOMIPHENE CITRATE – GONADOTROPHINS COMBINATION IN OVARIAN INDUCTION FOR PCOS PATIENT UNDERGOING INTRAUTERINE INSEMINATION

By

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ABSTRACT

Background: Ovulatory dysfunction is a common cause of infertility and polycystic ovary syndrome (PCOS) is the main reason of this dysfunction. PCOS is the most common endocrinopathy in women of childbearing age. A combination of ovarian stimulation or superovulation with intrauterine insemination (IUI) remains an important option available to an infertility specialist and is a widely used treatment modality for a broad range of indications.

Objective: To compare between Letrozole-Gonadotrophins combination in and Clomiphene Citrate – Gonadotrophins combination in ovarian induction for PCOS Patient undergoing Intrauterine Insemination.

Patients and methods: prospective cohort study was conducted in International Islamic Center for Population Study and Research, Al-Azhar University including 300 infertile women who already diagnosed as PCOS by Rotterdam 2003 Criteria. Women had been divided randomly into three equal groups: Group (A) were given clomiphene citrate 100 mg daily starting on day 3 till 7 day of cycle plus gonadotrophins (75 IU) once daily starting from 6th day of the cycle till growing follicle reach 18 mm, Group (B) were given letrozole (5mg/ day) starting on day 3 till 7 day of cycle plus gonadotrophins 75 IU once daily starting from 6th day of the cycle till growing follicle reach 18 mm and Group (C) were given letrozole (5mg/ day) starting on day 3 till 7 day of cycle.

Results: Women’s ovulation rate in Group (A) was 78% had ovulation while in Group (B) 80% had ovulation and 68% in group (C). There were statistically significant differences between groups. Women’s pregnancy rate in Group (A) was 8% in Group (B) was 7% in group (C) was 4%. There were no statistically significant differences between groups. Group A showed more multiple follicles, more OHSS and then group B and C. more cancellation rate than group B. Group B showed less in multiple follicles and less OHSS than group A and less in cancellation rate than group A and C better in endometrial thickness. Group C Letrozole alone more monofollicular growth, less multiple follicles, less multiple pregnancy, less OHSS and less coast. Than group A and B but had less ovulation rate and more in cancellation rate than group A and B.

Conclusion: We can offer ovulation induction and intrauterine insemination (IUI) for PCOS if first lines (lifestyle changes, pharmacotherapy (metformin, clomiphene citrate, letrozole, gonadotrophins) failed.

Keywords: Letrozole, Letrozole-Gonadotrophins Combination, Clomiphene, Gonadotrophins Combination, PCOS, Intrauterine Insemination
INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous condition affecting 5–10% of women at reproductive age. It is the most common cause of anovulatory infertility, characterized by hyperandrogenism and arrested follicle development, and is frequently associated with metabolic features such as insulin resistance and obesity. The diagnosis of PCOS, based on the Rotterdam criteria, can be made when at least two of the following three main features are met: oligo-ovulation and/or anovulation, hyperandrogenism (clinical and/or biochemical), and polycystic ovarian morphology at ultrasound examination. Several approaches to ovulation induction have been proposed in women with PCOS. These approaches vary in efficacy, treatment duration, cost, and patient compliance. Management includes lifestyle changes, pharmacotherapy (metformin, clomiphene citrate, letrozole, gonadotropins, inositol), laparoscopic surgery (ovarian drilling), and assisted reproductive techniques, usually in vitro fertilization. Clinical decisions in PCOS anovulatory patients are currently supported by a recently published international evidence-based guideline provides recommendations to help clinicians in the diagnosis and management of PCOS and to guide clinical practice (Giulia and Jose, 2018).

Ovarian stimulation and IVF are considered the third-line treatment for infertile women with PCOS. IVF is especially recommended if there are additional infertility factors, such as tubal damage, advanced woman age, severe endometriosis, and male subfertility. A single embryo-transfer procedure markedly reduces the risk for multiple pregnancies, which is one of the main drawbacks of using gonadotropins (Teede et al., 2018).

IUI with or without ovarian stimulation (OS) has become a first-line treatment option for many infertile couples, worldwide. The appropriate treatment modality for couples and their clinical management through IUI or IUI/OS cycles must consider maternal and perinatal outcomes (Cohlen, et al., 2018).

Intrauterine insemination (IUI) is widely used to treat moderate male infertility and unexplained infertility. However, studies on the use of IUI in women with PCOS are limited. In addition, PCOS were included with other types of infertility (Bordewijk et al., 2017).

In PCO, when first lines failed, there is no consensus as to the optimal approach. IVF is more effective but more costly and not always available or acceptable to the patient, while ovulation induction and intrauterine insemination (IUI) is less expensive, but when ineffective delays conception. While the selection of infertility treatment is based on medical indications, factors such as patient age, patient preference, procedure risk, birth rate, insurance coverage, and cost must also be considered. As an example, we would typically offer a woman younger than age 35 ovulation induction and IUI because of the low risk of the treatment, low cost, and reasonable chance of conception. However, an identical woman may prefer to go directly to IVF to maximize her chance of a live birth despite the higher cost and invasive
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A combination of ovarian stimulation or superovulation with intrauterine insemination (IUI) remains an important option available to an infertility specialist and is a widely used treatment modality for a broad range of indications. Common indications include cervical factor, mild endometriosis, mild to moderate male factor, ovulatory dysfunction and unexplained infertility (Kamath et al., 2010).

The aim of this work was to study the effect of induction of ovulation with Letrozole alone or Letrozole and gonadotrophins or Clomiphene Citrate and gonadotrophins in patients with PCOS undergoing intrauterine insemination (IUI).

PATIENTS AND METHODS

Randomized control trial was conducted in International Islamic Center for Population Study and Research, Al-Azhar University. The study was conducted on 300 infertile women who already diagnosed as PCOS by the Rotterdam Criteria (2003). At least, twelve small follicles 2-9 mm in at least one ovary; Symptoms or biochemical evidence of hyperandrogenism; (Hirsutism/acne or elevated serum total testosterone) and Anovulation or oligo-ovulation with fewer than nine menstrual periods every 12 months.

Inclusion Criteria:

Age 18-35 year, normal semen analysis, normal hysterosalpingography, infertility more than two year and body mass index less than 30.

Exclusion Criteria:

Tubal factor infertility, abnormal semen analysis, abnormal serum TSH, elevated serum PRL and history of medical disorders e.g hypertension or diabetes.

• Sampling Method: Convenience sampling method.

• Sample Size:

This sample size was calculated with confidence interval (CI) 95% Alpha (α error) 0.05 and power of the study 80%.

\[
 n = \left(\frac{Z_{\alpha/2}}{E}\right)^2 \times P(1-P)
\]

(Dawson and Trapp, 2004).

Where:

\( n \) = sample size

\( Z_{\alpha/2} = 1.96 \) (The critical value that divides the central 95% of the Z distribution from the 5% in the tail)

\( p = \) the Prevalence of polycystic ovary syndrome among infertile women in Egypt = 13% (Sanad, 2014).

\( E = \) the margin of error (=width of confidence interval).

Sample size had been at least 300 patients.

All women in the study were subjected to the following:

1. Informed consent was obtained before their inclusion in the study.

2. Full History Taking: Personal history, menstrual history, obstetric history which included gravidity, parity, abortions, sexual history which included coital frequency and

Women had been divided randomly into three equal groups: Group (A) were given clomiphene citrate (100 mg daily) starting on day 3 till 7 day of cycle, plus gonadotrophins (75 IU once daily) starting from 6th day of the cycle till growing follicle reach 18 mm, group (B) were given letrozole (5mg/ day) starting on day 3 till 7 day of cycle, plus gonadotrophins (75 IU once daily) starting from 6th day of the cycle till growing follicle reach 18 mm and group (C) were given letrozole (5mg/ day) starting on day 3 till 7 day of cycle. Regular follow up of ovulation with folliculometry by transvaginal ultrasound starting from cycle day 9 for growing of follicle until reach 18 mm or more. The endometrial thickness in (mm) was measured at this time. HCG was administered when the leading follicle reached 18 mm. or more. All groups were subjected to intrauterine insemination (IUI) 36-40 hours after hCG administration. In IUI semen was obtained by masturbation after three to five days of abstinence then preparation carried out by swim up technique then IUI was done. The patient was asked to rest for 10-15 minutes following insemination. Luteal phase support for the two groups by use of progesterone (100- 200 mg.) twice daily for two weeks. Serum pregnancy test was done 2 weeks after hCG administration and if positive trans-vaginal ultrasound was done 2 weeks later to confirm clinical pregnancy.

Statistical analysis of the data:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean and standard deviation. Significance of the obtained results was judged at the 5% level. Chi-square test: for categorical variables, to compare between different groups. ANOVA test: For normally quantitative variables, to compare between more than two studied groups. Kruskal-Wallis H test was used for abnormally quantitative variables to compare between two studied groups.

RESULTS

Endometrial thickness at day of HCG in Group A ranged between 5-12 with mean±S.D. 8.37±1.359, while in Group B ranged between 4-12 with mean±S.D. 8.64±1.474 and in Group C ranged between 4-11 with mean±S.D. 7.83±1.640. There was statistically significant differences between all groups and between Group C and each of group A and group B. Number of mature follicle in Group A ranged between 0-12 with mean±S.D. 3.26±2.538 while in Group B ranged between 0-7 with mean±S.D. 2.10±1.168 and in Group C ranged
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...differences between all groups and between group each other (Table 1).

Table (1): Comparison between three groups as regard endometrial thickness at day of HCG and patient’s Number of mature follicle

<table>
<thead>
<tr>
<th>Groups Parameters</th>
<th>Group (A) (n=100)</th>
<th>Group (B) (n=100)</th>
<th>Group (C) (n=100)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial Thickness at day of HCG:</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Min.-Max.</td>
<td>5-12</td>
<td>4-12</td>
<td>4-11</td>
<td></td>
</tr>
<tr>
<td>Mean± S.D</td>
<td>8.37±1.359</td>
<td>8.64±1.474</td>
<td>7.83±1.640</td>
<td></td>
</tr>
<tr>
<td>P&lt;1</td>
<td>0.203</td>
<td>0.011</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>P&lt;2</td>
<td>0.001*</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Number of mature follicle:</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Min.-Max.</td>
<td>0-12</td>
<td>0-7</td>
<td>0-2</td>
<td></td>
</tr>
<tr>
<td>Mean± S.D</td>
<td>3.26±2.538</td>
<td>2.10±1.168</td>
<td>0.85±0.687</td>
<td></td>
</tr>
<tr>
<td>P&lt;1</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>P&lt;2</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P: p value for comparing between the three studied groups
P<1: p value for comparing between group (A) and other groups
P<2: p value for comparing between group (B) and group (C)

Women’s pregnancy rate in Group (A) showed that 8(8%) were pregnant and 92(92%) were non-pregnant while in Group (B) 7(7%) were pregnant and 93(93%) were non-pregnant and in group (C) 4(4%) were pregnant and 96(96%) were non-pregnant. There were no statistically significant differences between groups. Women’s Ovarian hyperstimulation syndrome in Group (A) showed that 5 (5%) Ovarian hyperstimulation syndrome while in Group (B) 1(1%) Ovarian hyperstimulation syndrome and group (C) NO Ovarian hyperstimulation syndrome. There were statistically significant differences between groups. Women’s ovulation rate in Group (A) showed that 22(22%) had no ovulation and 78(78%) had ovulation while in Group (B) 20(20%) had no ovulation and 80(80%) had ovulation and in group (C) 32(32%) had no ovulation and 68(68%) had ovulation. There were statistically significant differences between groups (Table 2).
Table (2): Comparison between three groups as regard to patient’s pregnancy rate by both serum pregnancy test and confirmed by ultrasound, ovarian hyperstimulation syndrome (OHSS), number of follicle and ovulation rate

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group (A) (n=100)</th>
<th>Group (B) (n=100)</th>
<th>Group (C) (n=100)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Pregnancy Rate:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnant</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Non-Pregnant</td>
<td>92</td>
<td>92</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>Ovarian hyperstimulation syndrome:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>95</td>
<td>95</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Number of Follicle:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One follicle</td>
<td>16</td>
<td>16</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Two follicles</td>
<td>35</td>
<td>35</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>&gt;2 follicles</td>
<td>49</td>
<td>49</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Ovulation rate:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>22</td>
<td>22</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Yes</td>
<td>78</td>
<td>78</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Women’s Cancellation rate due to anovulation in Group (A) show that 78(78%) had ovulation and 22(22%) had cancellation due to anovulation while in Group (B) 80(80%) had ovulation and 20(20%) had cancellation due to anovulation and in group (C) 68(68%) had ovulation and 32(32%) had cancellation due to anovulation. There were statistically significant differences between groups. Women’s cancellation rate due to anovulation in Group (A) showed that 73(73%) had no cancellation, 22(22%) had cancellation due to anovulation and 5(5%) had cancellation due to OHSS, while in Group (B) 79(79%) had no cancellation and 20(20%) had Cancellation due to anovulation and1(1%) had Cancellation due to OHSS, while in group (C) 68(68%) had no cancellation and 32(32%) had cancellation due to anovulation. There were statistically significant differences between groups (Table 3).

Table (3): Comparison between three groups as regard to patient’s Cancellation rate due to ovulation and cancellation rate

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group (A) (n=100)</th>
<th>Group (B) (n=100)</th>
<th>Group (C) (n=100)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Cancellation rate due to anovulation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovulation</td>
<td>78</td>
<td>78</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Anovulation</td>
<td>22</td>
<td>22</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Cancellation rate:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>73</td>
<td>73</td>
<td>79</td>
<td>79</td>
</tr>
<tr>
<td>Cancellation due to anovulation</td>
<td>22</td>
<td>22</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Cancellation due to OHS</td>
<td>5</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
DISCUSSION

Group (A) show that (8%) were pregnant while in Group (B) (7%) were pregnant and in group (C) (4%) were pregnant There was no significant difference between groups as regard pregnancy test (clinical and chemical).

Group A had similar ovulation rate with group B with more multiple follicles, more OHSS than group B and C. more cancellation rate than group B.

Group B had similar ovulation rate with group A less in multiple follicles, less OHSS than group A, and less in cancellation rate than group A and C better in endometrial thickness.

Group C more monofollicular growth, less multiple follicles, less multiple pregnancy less OHSS and less coast than group A and B But had less ovulation rate and more in cancellation rate than group A and B.

Huang et al. (2018) concluded that women with PCOS undergoing stimulated IUI, CC, letrozole and gonadotropins were equally effective and safe. Since multifollicular growth increased the multiple pregnancy rates without increasing the overall live birth rate, ovulation induction would strictly aim for mono-follicular growth. Since letrozole had the highest mono-follicular growth rate, they recommend this drug as the treatment of first.

A randomized trial Clomiphene citrate versus letrozole with gonadotropins in intrauterine insemination cycles Pourali et al. (2017) concluded that the number of matured follicles, cycle cancellation, and abortion were the same in both groups. Endometrial thickness was higher at the time of human menopausal gonadotropin administration in letrozole group. Chemical and clinical pregnancy rates were much higher in letrozole group. Ovarian hyperstimulation was significantly higher in clomiphene group. Conclusion: Letrozole appears to be a good alternative to clomiphene citrate with fewer side effects which are consistent with our study.

In the study of Yu et al. (2019) endometrial thickness on the day of hCG injection in the letrozole + HMG group (8.8±2.1 mm) was significantly higher than that in the letrozole group (7.3±1.6 mm). These results were consistent with our study also the number of follicles with diameters greater than 18 mm was higher in the letrozole + HMG (1.21±0.56) and letrozole (1.14±0.48) groups than that in the CC group (0.85±0.36) (P<0.010). These results come in disagreement with our study.

In the study of Abu Hashim et al. (2012) the total number of follicles ≥18mm during stimulation was statistically significantly greater in the CC group which is consistent with our study.

In the study of Fouda and Sayed et al. (2011) the pregnancy rate per cycle and the cumulative pregnancy rate were significantly higher in extended letrozole group compared with clomiphene citrate group (18.96% Vs 11.43% and 37.73% Vs 22.86%, respectively) which is in disagreement with our study.

In the study of Yu et al. (2019) regarding the clinical pregnancy rate, the letrozole group and CC group had a lower rate than the letrozole + HMG group, but
the statistical results showed no significant difference (P=0.052) which is consistent with our study.

Choice in infertile women undergoing ovulation induction and IUI.

CONCLUSION

Ovulation induction and intrauterine insemination (IUI) for PCOS if first lines (lifestyle changes, pharmacotherapy (metformin, clomiphene citrate, letrozole, gonadotropins,) failed. But after complete explanation of the procedure and the success rate and also discuss the alternatives (laparoscopic surgery (ovarian drilling), and in vitro fertilization) with their risks, coast and success rate and totally respect the patient decision.

There was a successful use of Letrozole plus gonadotrophins in induction of ovulation for PCOS patients undergoing IUI with similar benefits and fewer risks than clomiphene plus gonadotrophins

Also Letrozole plus gonadotrophins had better benefits (more ovulation rate and less cancellation rate and better endometrial thickness) than letrozole alone .but less in monofollicular growth .and more in multiple pregnancy and more coast.

REFERENCES


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مقارنة بين عقار الليتروزرول منفردا أو الليتروزرول مصحوبا بالجنودوتروفين مع الكلوسيفين سترات مصحوبا بالجنودوتروفين لتحفيز التبويض في حالات تكيس المبيضين المجهزة للتلفيق الصناعي

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قسم أمراض النساء والتوليد, كلية الطب, جامعة الأزهر

خلفية البحث: ملاحظة تكيس المبيضين من أهم أسباب العقم لدى السيدات. وتعاني السيدات الأثناويّات بسبب نقص المبيضين بغير أو نقص ​​ال世界经济 والتربية وزن الجسم، وظهور التهابات المبيضين بدرجة إفراز الهرمونات المذكورة. ويعتبر ضرع الكولوميغين فعال في العلاج مع التسوسة وتنصير عمليَّة التبويض لدى السيدات اللاتي تعاني من العقم نتيجة مرش ثكيس المبيض وتتراوح فاعلية الدواء في نسبة حدوث التبويض ما بين 75-80٪. وقد وضع عقار الليتروزرول كوسيلة أمن لعلاج الكولوميغين لتجنب التأثير السلبي لعقار الكلوسيفين على بطاقة الرحم ومخطط عنق الرحم مع تجنب احتمالية حدوث الحمل بالتوأم والاستجابة الزائدة للعقم بعد تنشيط التبويض.

الهدف من البحث: مقارنة فاعلية عقار الليتروزرول أو الليتروزرول مصحوبا بالجنودوتروفين أو سترات الكلوسيفين مصحوبة بالجنودوتروفين في حالات تكيس المبيض المحضرة للتلفيق الصناعي.

المراجعات وطرق البحث: أجريت الدراسة على 300 امرأة من اللاتي تعاني من متلازمة تكيس المبيض. وتم تقسيمهم إلى ثلاث مجموعات متساوية: المجموعة الأولى: أجريت عقار سترات كولوميغين (100 مجم يوميًا)حتى 7 أيام ثم الجنودوتروفين (75 جم وحدة دولية) مرة واحدة يوميًا من اليوم 6 من الدورة حتى تصل الالتباضة إلى 18 مم أو أكثر. والمجموعة الثانية: أجريت عقار ليتروزرول (5 مجم) من اليوم 3حتى 7 أيام من الدورة ثم الجنودوتروفين (75 جم وحدة دولية) مرة واحدة يوميًا من اليوم 6 من الدورة حتى تصل الالتباضة إلى 18 مم أو أكثر.
المجموعة الثالثة: أعطيت عقار ليتروزول (5مجم) من اليوم 3 حتى 7 أيام من الدورة.

نتائج البحث: حدوث التبويض لدى النساء بنسبة 78% في المجموعة (أ)، و80% في المجموعة (ب) و68% في المجموعة (ج). وكانت هناك فروقًا ذات دلالات إحصائية بين المجموعات، وبلغ معدل حمل النساء 8% في المجموعة (أ)، و7% في المجموعة (ب) و4% في المجموعة (ج) ولم تكن هناك فروق ذات دلالات إحصائية بين المجموعات. وكانت المجموعة (أ) أكثر حدوثاً للتزاحمية افراط التشتيت من المجموعة (ب) والمجموعة (ج). وكانت المجموعة (ج) ذات معدل إلغاء أكبر من المجموعة (أ) والمجموعة (ب). وكانت المجموعة (ب) أقل في معدل الإلغاء من المجموعة (أ) والمجموعة (ج). وكانت المجموعة (ج) أكثر نموًا أحادي للبيويضات.

الإستنتاج: من الممكن إختبار اجراء التلقائي الصناعي مع تشتيت التبويض مع حالات تكيسات البيويض بعد موافقة الحالة.