Effect of Sildenafil Citrate on Success Rate of Ovulation Induction by using Clomiphene Citrate

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Abstract

Background: Infertility is defined as the inability to conceive after one year of unprotected intercourse. This study aimed to investigate whether sildenafil vaginal tablet plus clomiphene citrate would improve endometrial thickness, ovulation rates and pregnancy rates compared with clomiphene citrate alone. Methods: The present study is a prospective randomized controlled clinical trial on 58 infertile patients with Polycystic ovary syndrome (PCO) who were divided into two groups; each group included 29 patients, group one was given Clomophene, and group two was given Clomophine citrate and Sildenafil. A transvaginal Scan for imaging the uterus and adnexa for any pathology and measuring the basic Endometrial Thickness was also one on Day 3. Results: our study showed that there was increase in endometrial thickness in sildenafil group (13.4±1.814 mm) comparable with clomiphene citrate group only (8.52±2.081 mm) (P=0.01). The result was statistically significant with increase threshold regard for implantation with statistically significant in group B (P=0.018). Conclusions: Addition of sildenafil citrate to clomiphene citrate therapy for induction of ovulation in patients with PCOS resulted in significant increase of endometrial thickness and non-significant increase of pregnancy Rates.

Key words: Sildenafil, Clomiphene, PCO

INTRODUCTION

Disorders of ovulation are common causes of infertility, and polycystic ovary syndrome (PCOS) is by far the most frequent condition. In the general population(1), there are different lines for ovulation induction in ladies with PCOS including lifestyle adjustment and utilization of clomiphene citrate (CC), exogenous gonadotropins, laparoscopic ovarian surgery(2).

Although CC is easy to use and results in ovulation in most patients (57-91%), the pregnancy rates are disappointing (27-40%)(3). It is because of the adverse effects of CC mainly on quality of the cervical mucus and the endometrial development during the stimulation (4).

Inappropriate development of the endometrium is associated with low implantation rate and early pregnancy loss owing to luteal phase defect. Overall, 20–25% of patients do not respond to CC despite high doses (5).

No consensus has been reached with regard to the minimum endometrial thickness
required for successful pregnancy. Pregnancies did not occur when the endometrial thickness was less than 7 mm.\(^6\)

Sildenafil may have an effect on vasoactive cytokines that regulate endometrial development or implantation. Sildenafil increases uterine receptivity by the development of spiral arteries and by increasing the uterine arterial blood flow.\(^7\)

A good correlation has been found between endometrial thickness and the prevalence of conception. An endometrial thickness of \(\geq 9\) mm in the late proliferative phase, as determined by vaginal ultrasound, correlates well with the chance of pregnancy after IVF, whereas a thinner endometrium is associated with poorer prognosis for success.\(^8\)

**Aim of the work:**

This study aimed to investigate whether sildenafil vaginal tablet plus clomiphene citrate would improve endometrial thickness, ovulation rates and pregnancy rates compared with clomiphene citrate alone.

**Materials and Methods:**

A Prospective Comparative Study was carried out at Obstetrics and Gynecology Department, Zagazig University Hospitals. Attending the outpatient Clinics of the department over a period from May 2019 to September 2020. The study included 58 patients with primary and secondary infertility aged between 18 years to 35 years. The patients were included in the study after giving written from the couple. They were distributed into two equal sized groups by Closed envelope technique. In group A, 29 patients were prescribed Clomiphene citrate (CC) alone. In group B, 29 patients were prescribed Clomiphene citrate (CC) and Sildenafil tab. The study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work was carried out for studies involving humans in accordance with the World Medical Association's Code of Ethics (Helsinki Declaration).

**Inclusion criteria:** Age less than 35 years and more than 18 years, Primary or Secondary infertility, with regular menstrual cycles, and normal semen parameters of the husband, BMI less than \(35\) kg/m\(^2\). PCO diagnosed According Rotterdam, ESHR, ASRM consensus workshop 2004. Exclusion criteria: Pathology of uterus and ovaries, endocrine and thyroid disorders, tubal infertility as detected by Hysterosalpingogram (HSG), and cardiovascular, renal or hepatic disorders.

All the couples with infertility were initially taken up for detailed history taking and then subjected to general and local medical examination. A basic semen analysis was done and read according WHO 2010 criteria, to rule out male factor infertility and limit confounding. This was then followed by investigating the female partner by basal hormonal profile on Day 3 (Follicle Stimulating hormone, Luteinizing hormone and Prolactin). A Transvaginal Scan (TVS) for imaging the uterus and adnexa for any pathology and measuring the basic Endometrial Thickness was also one on Day 3. The patients who met the criteria were then taken for ovulation induction in the next cycle.

Ovulation induction in group A and B was done with 50mg CC (Clomide) orally 2times/day from Day 3 to Day 7 of the cycle. In group B additionally vaginal Sildenafil tablets 25mg/12h daily was given from Day 8 up to ovulation trigger. TVS scan as performed
for Follicular study and measurement of endometrial thickness (ET). Basicaly at day 3, then day 9 and there after daily till leading follicle reach 18-20mm in diameter. 5000 IU of Human Chorionic Gonadotrophin - hCG was administered intramuscularly as an ovulation trigger if the follicular size was 18mm – 20mm. Pregnancy was detected by testing for the β subunit hCG in urine on Day 30. Patients were closely monitored during this period for side effects as Ovarian Hyperstimulation Syndrome (OHSS). The patients were followed thereafter for a period of 8 weeks for spontaneous miscarriages, tubal ectopics and multiple gestation.

RESULTS:

Table (1): Demographic characteristics in studied groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A clomiphene citrate only group (N=29)</th>
<th>Group B Sildenafil group (N=29)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean± S.D Range (20-35)</td>
<td>30.45±6.522</td>
<td>28.28±6.216</td>
<td>P =0.56</td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean± S.D Range (0-5)</td>
<td>0.3±0.021</td>
<td>0.29±0.081</td>
<td>P =0.61</td>
</tr>
<tr>
<td><strong>Types of infertility</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Primary</td>
<td>N=18(62.1 %)</td>
<td>15(51.7)</td>
<td>P = 0.56</td>
</tr>
<tr>
<td>• Secondary</td>
<td>N=11(37.9 %)</td>
<td>14(48.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of infertility(years)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean± S.D Range;2-7</td>
<td>5.3±1.7</td>
<td>5.7±1.6</td>
<td>P =0.60</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td></td>
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</tr>
<tr>
<td>Mean ±S.D</td>
<td>21.7 ± 1.93</td>
<td>22.3 ± 1.76</td>
<td>P = 0.8</td>
</tr>
</tbody>
</table>

Both groups were comparable with non- significant differences table 1.
Both groups were comparable with no statistically significant differences between both groups regarding TSH, LH, FSH and prolactin serum levels figure (1).

Figure (1): Hormonal profile of studied groups

Endometrial Thickness was significantly high (P=0.001) in Sildenafil group (13.4±1.814 mm) compared to control group with clomiphene citrate only (8.52±2.081 mm). However, number of dominant follicles > 18 mm was comparable in both groups with no statistically significant difference figure 2,3.

Figure (2): Pre-Ovulatory mean Endometrial Thickness (mm) of studied groups.
Table (2): Stratification of studied groups according to Endometrial thickness threshold (7mm)

<table>
<thead>
<tr>
<th>Endometrial thickness</th>
<th>Group A clomiphene citrate only group (N =29)</th>
<th>Group B Sildenafil group (N =29)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases &gt; 7mm</td>
<td>15(51.7%)</td>
<td>18(62.1%)</td>
<td>0.019*</td>
</tr>
<tr>
<td>Cases &lt; 7mm</td>
<td>14(48.2%)</td>
<td>11(37.9%)</td>
<td>0.813</td>
</tr>
</tbody>
</table>

Proportion of patient with Endometrial thickness above (7mm) was significantly high in sildenafil group (P=0.019) *table 2.*

Pregnancy Test in both groups by serum B.HCG done 3-5 days after expected menses. Shows a non-significant higher pregnancy rate in sildenafil group (14/29- 48.3%) compared to clomiphene citrate only group (8/29- 27.6%) Figure 4.
DISCUSSION

The demographic data show no significant different between two studied group regarding to age, parity, BMI, type and duration of infertility. Regarding to hormonal profile of studied groups. Both groups were comparable with no statistically significant differences between TSH, LH, FSH and prolactin serum levels.

This study shows that Endometrial was significantly Thick more in Sildenafil group (13.4±1.814 mm) compared to control group with clomiphene citrate only (8.52±2.081 mm) (P=0.01). with Endometrial thickness above 7mm, a level below which receptivity of endometrium is improved was statistically significant in group B (P=0.019). Improved endometrial thickness in the study group compared with the control group might be attributed to the vasodilator effect of sildenafil citrate, which leads to an increase in uterine blood flow. Improved endometrial thickness when adding Sildenafil to Clomiphene citrate during ovulation induction has been reported in other studies (9).

A systematic review and meta-analysis, on effect of sildenafil citrate on treatment of infertility in women with a thin endometrium, reported that Sildenafil citrate is effective in improving endometrial thickness, the clinical pregnancy rate, and the biochemical pregnancy rate in women who have a thin endometrium (10).

Some studies have reported that Sildenafil citrate improves the uterine artery blood flow and the sonographic endometrial thickening in patients with a prior assisted reproductive cycle failing due to poor endometrial response with a comparable higher pregnancy rates (11).

On the other hand some authors reported a non-significant increase of endometrial thickness when adding sildenafil to conventional gonadotropin-releasing hormone (GnRH) protocol during ovarian stimulation (12).

We reported a comparable numbers of preovulatory dominant follicles (> 18 mm) in
both groups. So, sildenafil does not appear to affect follicular growth or numbers. Similarly, which according with other studies which reported that adjuvant sildenafil does not enhance ovarian responsiveness in cases of previous low ovarian response to controlled ovarian hyperstimulation\(^{(13)}\).

Also, in a randomized clinical trial of sildenafil plus clomiphene citrate to improve the success rate of ovulation induction in patients with unexplained infertility, similar to result of this study, the number of mature follicles didn't differ significantly among the studied groups with a significant increase of endometrial thickness in sildenafil group. However, a significantly higher pregnancy rate was reported in sildenafil group which is not similar to our study. But, this study was carried out on patients with unexplained infertility and not on patients with PCOS as in our study\(^{(14)}\).

The result of the study reported, only, a non-significant higher pregnancy rate in sildenafil group (8 patients = 27.6\%) compared to clomiphene citrate only group (14 patients = 48.3\%).

Similar to Vardhan and contrary to This study treatment with sildenafil citrate suppositories enhances endometrial blood flow by decreasing the mean resistance index (RI) values of endometrial spiral artery (SA) and consequently improves endometrial growth and receptivity in cases of unexplained infertility, thus yielding a better conception rate \(^{(15)}\). However, this study was carried out on patients with unexplained infertility and abnormal uterine perfusion may be a contributing factor to etiopathology of infertility in this category of infertility\(^{(16)}\). Additionally, clomiphene citrate, that may adversely affect the endometrium, was not used in this study\(^{(17)}\).

Contrary to result of this study, a meta-analysis evaluating the effect of sildenafil citrate in women undergoing assisted reproduction reported that the probability of clinical pregnancy was significantly higher in women who received the combination of sildenafil citrate and clomiphene citrate compared with clomiphene citrate alone. Furthermore, clinical pregnancy was reported to be significantly increased in women who received combination of estradiol valerate and sildenafil citrate compared to estradiol valerate\(^{(17)}\).

Our study, compared to a meta-analysis included a small number of cases. So, non-significant pregnancy rate reported in our study could be explained on the light of this fact. Consequently, a larger study including more patients may prove significant pregnancy rates\(^{(17)}\).

**CONCLUSIONS**

Addition of sildenafil citrate to clomiphene citrate therapy for induction of ovulation in patients with PCOS resulted in significant increase of endometrial thickness and non-significant increase of pregnancy Rates. The increase in endometrial thickness may prove beneficially due to improving receptivity of large scale study is performed.

Sildenafil citrate could be added to clomiphene citrate during induction of ovulation in patients with PCOS to increase of endometrial thickness in patient with slim endometrium.
Larger studies, including large number of patients, are still required to better evaluate the effect of adding Sildenafil citrate to clomiphene citrate during induction of ovulation in patients with PCOS pregnancy rates.

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