Conception Rate in Polycystic Ovary Syndrome

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Polycystic ovary syndrome is characterized by enlarged ovaries, multiple peripherally arranged cysts and increased stromal density(1). Polycystic ovary syndrome is responsible for approximately 25-30% of infertility in women, which is mainly anovulatory(2). Ovulation can be induced with antiestrogens in many women but a proportion fail to respond and even in those who ovulate, the pregnancy rate is often low and the miscarriage rate is high.

Abstract
**Objective:** To compare pregnancy rate in women with polycystic ovary syndrome (PCOS) resistant to clomiphene citrate, using different methods of treatment.

**Design:** Prospective randomized study

**Subjects:** One hundred infertile women known to have PCOS and failed to conceive with one-year clomiphene citrate treatment.

**Intervention:** Women randomly classified into 5 groups, each comprised 20 cases. Group (I) received clomiphene citrate plus human menopausal gonadotrophines (HMG) plus human chorionic gonadotrophins (HCG). Group (II) received HMG + HCG. Group (III) received pure FSH plus HCG. Group (IV) received LHRHa plus HMG. Group (V) subjected to laparoscopic ovarian drilling using diathermy.

**Main Outcome Measure:** Pregnancy rate.

**Results:** In group (I) four out of 20 women (20%) responded to treatment and became pregnant in 60 treatment cycles (6.66%). In Group (II) six women (30%) had pregnancy in 60 cycles of treatment (10%). In the third group pregnancy occurred in 3 women (15%) with 60 treatment cycles (5%). In the fourth group eleven women became pregnant (55%) during the same treatment cycles (18%), this was statistically significant when compared to group I and III. In the laparoscopic group 9 (45%) women had pregnancy during three months after ovarian drilling.

**Conclusion:** Several alternative ovulation induction methods are available, the use of LHRH analogue combined with HMG/HCG had better results and laparoscopic diathermy can be the second in rank in the selection of treatment.

**Introduction**
Polycystic ovary syndrome is characterized by enlarged ovaries, multiple peripherally arranged cysts and increased stromal density(1). Polycystic ovary syndrome is responsible for approximately 25-30% of infertility in women, which is mainly anovulatory(2). Ovulation can be induced with antiestrogens in many women but a proportion fail to respond and even in those who ovulate, the pregnancy rate is often low and the miscarriage rate is high. However, treatment with human menopausal gonadotrophins may be successful but extremely demanding for women and for the clinic, and there is a significant risk of hyperstimulation and multiple pregnancy even with intensive monitoring(3). Pulsatile luteinizing hormone releasing hormone (LHRH) therapy has been used but the results have been disappointing and miscarriage rate is high(4). However, the use of LHRHα in down regulation mechanism (pituitary desensitization) gave a rather good results with entire elimination of premature luteinization and higher pregnancy rate(5).

Wedge resection of the ovaries was used successfully in the management of women with PCOS prior to the availability of anti-estrogens in the 1960, this treatment resulted in a high rate of ovulation.
but was followed by significant formation of adhesions that prevented pregnancy from a few months after the procedure was performed(6). Recently laparoscopic diathermy has been introduced as an alternative to wedge resection(7-10). The advantages of this form of treatment are that it entails laparoscopy rather than laparotomy and the scars are small. Ovulation has been found to occur post operatively in more than 80% of women(7).

These alternative methods of management of PCOS cases resistant to clomiphene citrate provoked us to study pregnancy rate with different methods of treatment.

**Subjects and Methods**

One hundred women with primary infertility and ultrasonic features of polycystic ovaries(1) were selected for this prospective study. All had oligomenorrhoea with or without hirsutism. Biochemically, all had an Lh/FSH ratio >3.

All patients failed to conceive after one year of treatment with clomid. In all, fallopian tubes were patent, proved by HSG and laparoscopy, their husbands had normal semen analysis and no obvious cause of infertility apart from anovulation was found.

All patients signed a consent to be involved in the study and they were randomly classified into 5 groups.

Group I comprised 20 patients, received Clomid in a dose of 150 mg/day from day 3 through day 7 of the menstrual cycle, human menopausal gonadotrophins (Pergonal, serono) started with an initial dose of 150 IU given I.M at day 5 of the menstrual cycle and the dose was adjusted according to ovarian response with the intention to obtain one or more mature follicles with follicular diameter greater than 17 mm and estradiol (E2) level >800 pg/ml. Treatment was monitored by ultrasound and serum assay for estradiol. Ultrasound was performed twice usually at day 10 and day 13, E2 estimation was performed at days 11,12, and 13. HCG injection (Profasi, serono) was given in a dose of 10,000 IU IM when we reached our criteria of ovulation and timed intercourse was requested post HCG by 24-36 hours.

Group II comprised 20 patients who received Pergonal initially in 2 amps dose (300IU) and adjusted according to the ovarian response. Treatment started on day 3 of the menstrual cycle and the criteria and monitoring of ovulation followed the same protocol as in group I. Timed intercourse was requested 24-36 hours after HCG (10,000IU) injection.

Group III also comprised 20 patients, received pure FSH (metrodin, 75 IU) started on day 3 of the menstrual cycle in dose of 2 amps which was increased or decreased according to the ovarian response. The same criteria and monitoring of ovulation were used in this group as previous groups. Timed intercourse was requested 24-36 hours after 10,000 IU injection of HCG.

Group IV included 20 patients, received LHRH agonist (superfact, Hoechst hounslow, uk). Nasal spray started on day 24 of the preceding cycle with one puff per nostril every 6 hours to deliver 100 ug. The drug was continued till day 0 (day of HCG administration). Pergonal was given on day 3 of the menstrual cycle with initial dose of 2 amps and the dose was adjusted according to the ovarian response. The same criteria and monitoring of ovulation was as previous and timed intercourse advised 24-36 hours post HCG injection (10,000IU).

Group V Twenty patients had laparoscopic ovarian drilling using diathermy during the proliferative phase of the menstrual period. Diathermy was applied to each ovary for 4-6 seconds at a time in 4-8 separate places according to the ovarian size. All patients were followed for 3 months with no further treatment.

**Pregnancy Test**

A semi quantitative urinary test was performed 10 days after the expected date of next period or 24 days post HCG injection.

**Hormonal Assay**

Blood samples were collected in a dry plastic disposable syringe on heparinized tubes and then
centrifuged. Plasma was taken for determination of E2, FSH and LH.

E2 was measured by RIA using the method of Schmidt et al(11). LH was determined by the heterologous ovine double antibody radioimmunoassay according to the method used by loudon et al(12). FSH was measured in duplicate in single assay using an ovine radioimmunoassay method described by McNatty et al(13).

Results
All patients had primary infertility, where the duration of infertility is shown in table (1), in terms of mean and standard deviation, group V had a longer duration of infertility (10.2 ±5.3 years).

The mean age and SD of the studied groups was also compared in table (1), group IV had the oldest patient with mean age and SD (36.4 ±1.9). None of these are statistically significant.

The pretreatment hormonal levels of both the LH and FSH showed the characteristic feature of PCO, where as seen in table (1) the LH is higher than the FSH by two or three times.

In group I four out of the 20 cases (20%) responded to the treatment and became pregnant in a total of 60 treatment cycles (6.66%). In group II six women (30%) had pregnancy out of 20 women in 60 treatment cycles (10%). In the third group pregnancy was achieved in 3 out of 20 cases (15%) over 60 treatment cycles (5%). In group IV, 11 women became pregnant (55%) out of 20 women over 60 treatment cycles (18%), this was statistically significant (p<0.05) when compared to group I and also when compared with group II (p<0.02).

In the fifth group nine women became pregnant (45%) over 3 months (60 cycles, 15%).

Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of patients</th>
<th>Age(SD) years</th>
<th>Treatment cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>20</td>
<td>31± 2.3</td>
<td>60</td>
</tr>
<tr>
<td>Group II</td>
<td>20</td>
<td>29.9± 4.2</td>
<td>60</td>
</tr>
<tr>
<td>Group III</td>
<td>20</td>
<td>28.9± 4.2</td>
<td>60</td>
</tr>
<tr>
<td>Group IV</td>
<td>20</td>
<td>36.4 ±1.9</td>
<td>60</td>
</tr>
<tr>
<td>Group V</td>
<td>20</td>
<td>32.4± 4.2</td>
<td>60</td>
</tr>
</tbody>
</table>

Pretreatment hormonal level

<table>
<thead>
<tr>
<th>Group</th>
<th>LH (IU/ml)</th>
<th>FSH (IU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>14.5</td>
<td>5.3</td>
</tr>
<tr>
<td>Group II</td>
<td>13.3</td>
<td>5.1</td>
</tr>
<tr>
<td>Group III</td>
<td>16.2</td>
<td>6.3</td>
</tr>
<tr>
<td>Group IV</td>
<td>14.2</td>
<td>6.2</td>
</tr>
<tr>
<td>Group V</td>
<td>16.3</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Table 2 Pregnancy rate in studied group

<table>
<thead>
<tr>
<th>Group</th>
<th>Pregnancy per patient</th>
<th>Pregnancy per treatment cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>4/20* (20%)</td>
<td>6/20 (6.6%)</td>
</tr>
<tr>
<td>Group II</td>
<td>6/20</td>
<td>30%</td>
</tr>
<tr>
<td>Group III</td>
<td>3/20</td>
<td>15%**</td>
</tr>
<tr>
<td>Group IV</td>
<td>11/20* (55%)</td>
<td>55%**</td>
</tr>
<tr>
<td>Group V</td>
<td>9/20</td>
<td>45%</td>
</tr>
</tbody>
</table>

Statistically significant, p<0.05
Statistically significant, p<0.02

Discussion
Several alternative ovulation induction methods are available to women with clomiphene resistant anovulation associated with polycystic ovary syndrome (PCOS) but there are no accepted guide lines on the choice of treatment.

The use of HMG with clomiphene citrate to enhance follicular growth and increase its efficacy as in group I of this study is a known method. It is less expensive than the others but the pregnancy rate...
per cycle is and the use of LHRHa combined with HMG is statistically significant \( p < 0.05 \) when both regimes were compared.

The pregnancy rate in the second group (HMG+HCG) regime was 10% (pregnancy per treatment cycle) these results are less than the result of Farhi et al. 1993. When the pregnancy in this group compared with the other groups no statistically significance was found.

The third group received FSH, there results as a pregnancy per treatment cycle was 5%, which is less than the pregnancy rate obtained by the Farhi et al, 1993, where they reported pregnancy rate 23%. However, this group results were significant when compared to group IV, \( p < 0.02 \).

The fourth group LHRHa combined with HMG/HCG, gave a better results regarding pregnancy rate which might be explained because of the elimination of premature luteinization and prevention of the interference and interplay of the high LH which is a dominant feature in PCOS. Our results were similar to Farhi et al, 1993; and Wada et al, 1993. The results of the LHRHa group had a statistical significance when compared with group I and group III.

The last group, where the laparoscopic drill was offered as a surgical line of treatment the current study results were less in terms of pregnancy per treatment cycles than the results of Armard and Lachalin, 1993 and Gjonneses, 1994.

The laparoscopy group when compared to other groups no statistical significance was found but apparently the laparoscopy carries advantages over the other lines of treatment as the chance of recurrent spontaneous ovulation and repeated pregnancy allowing the women to lead a normal life with the stress of frequent hospital visits and no risk of hyperstimulation.

**Conclusion**

In conclusion we have shown that women with PCOS resistant to clomiphene citrate have had several alternative ovulation induction. The use of LHRHa combined with HMG/HCG has better results and laparoscopic diathermy can be the second in rank in the selection of the treatment.

**References:**

10- Schmidt AM, Nadal Schmidt MJ, and Beamer NB. Serum concentration of oestradiol and progesterone during the normal oestrous cycle and early pregnancy in the loin. Journal of

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