

## The Effect of Metformin Therapy on Clomiphene Citrate-resistant Polycystic Ovarian Syndrome Women

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**Objective:** This study was performed to investigate the effect of metformin therapy on ovulation induction & pregnancy rate in clomiphene citrate-resistant PCOS women.

**Method:** This study used a randomized, single-blinded, case-controlled methods. Total study group consisted of 21 women who showed clomiphene citrate-resistant pattern on previous ovulation induction cycles. Patients of metformin group received metformin 500 mg three times daily, for 7 weeks. Control group received none. Metformin group was consisted of 10 women and control group was consisted of 11 women. Then clomiphene was administered at daily 50 mg for 5 days to both groups. Clomiphene dosage was increased to daily 150 mg until ovulation was occurred. Before and After metformin treatment, blood samples for measurement of insulin, glucose, steroids were obtained.

**Results:** In the metformin and control groups, 6 of 10 women (60%) and 2 of 11 women (18%) ovulated. And 4 of 10 women (40%) and 0 of 11 women (0%) conceived. Comparisons between the groups were significant.

**Conclusion:** In PCOS women who are resistant to CC, metformin use increased the ovulation rate and pregnancy rate from CC treatment, significantly.

**Key Words:** Metformin, Insulin resistance, Polycystic ovarian syndrome

PCOS) (Polycystic ovarian syndrome, tance) (Compensa-  
(chronic anovulation) tory hyperinsulinemia)  
(hyperandrogenism) 1 2-9

(Insulin resis-

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<sup>10</sup>  
 가 가 , 가  
 (Insulin-like Growth Factor, IGF)  
 (folliculogenesis)  
<sup>11</sup>  
<sup>12</sup> (insulin sensitizing drug) troglitazone (metformin)  
 (Clomiphene citrate, GnRH-agonist), troglitazone  
 hMG, pure-FSH, GnRH-agonist, troglitazone  
<sup>13</sup> 70% 50 mg 100 mg . 1994 Velazquez  
 250 mg 150 mg <sup>17</sup> bigua-  
<sup>14</sup> 가 <sup>19,20</sup>  
<sup>15</sup> 가  
 (Ovarian hyperstimulation syndrome, OHSS)  
 가  
 hMG FSH

1.

2000 10 2001 6

9 75 g  
60 , 120 ,  
10 ,  
21 11 7  
18~35 75~98 kg 가  
가  
500 mg 3  
(Progesterone  
LH/FSH free or total testosterone, androstenedione, DHEA-sulfate 가 level > 4 ng/mL) 10, 20,  
30, 40  
7  
가,  
가 (hypercortisolism) 5 50 mg  
(congenital adrenal hyperplasia, CAH) 21 28 progesterone  
50 mg 가 150 mg  
가 6  
50 mg 가 150 mg  
150 mg 5  
5  
가 progesterone  
1  
TSH, Prolactin, 17-hydroxyprogesterone (< 200 ng/dL)  
lactic acidosis 가  
(serum creatinine concentration < 1.4 mg/dL) 가  
가

randomized, single-blinded, case-controlled

2.

3.

12 8  
(Body Mass Index, BMI), Waist-hip ratio 8:30,  
8:45, 9:00 insulin, glucose,  
17-hydroxyprogesterone, total and free T, androstenedione, DHEA-sulfate, E<sub>2</sub>, estrone, LH, FSH, SHBG

Student's t-test Fisher exact test  
, p 0.05  
가

**Table 1.** Characteristics and biochemical markers of Clomiphene Citrate-resistant PCOS women before and after 7 weeks of treatment with metformin or placebo

| Characteristics                      | Metformin Group (n=10) |           | Control Group (n=11) |           | P-value |
|--------------------------------------|------------------------|-----------|----------------------|-----------|---------|
|                                      | Baseline               | After Tx  | Baseline             | After Tx  |         |
| Age (years)                          | 28.2 ±1.4              |           | 29.3 ±1.3            |           |         |
| Weight (kg)                          | 64.3 ±5.4              | 65.3 ±7.2 | 65.4 ±5.4            | 66.3 ±6.3 | NS      |
| BMI (kg/m <sup>2</sup> )             | 35.4 ±3.8              | 34.2 ±4.3 | 37.2 ±4.3            | 37.5 ±5.2 | NS      |
| Fasting plasma insulin level (mU/ml) | 7.8 ±1.4               | 8.4 ±2.1  | 8.2 ±1.5             | 8.5 ±1.7  | NS      |
| Fasting glucose level (mg/dL)        | 83.2 ±2.4              | 81.2 ±1.8 | 84.2 ±2.6            | 85.3 ±2.2 | NS      |
| Serum free T level (pmol/L)          | 6.6 ±0.4               | 6.2 ±0.6  | 6.8 ±0.7             | 6.5 ±0.4  | NS      |
| Serum androstenedione level (ng/mL)  | 2.3 ±0.25              | 2.1 ±0.18 | 2.0 ±0.17            | 2.1 ±0.16 | NS      |
| Serum E <sub>2</sub> level (pg/mL)   | 25.3 ±3.5              | 24.3 ±4.7 | 24.7 ±3.2            | 26.4 ±4.1 | NS      |
| Serum DHEAS level (ug/dL)            | 12.4 ±1.5              | 13.1 ±2.1 | 13.2 ±2.2            | 14.2 ±1.8 | NS      |
| Serum LH level (mIU/mL)              | 4.5 ±0.25              | 4.8 ±0.17 | 5.3 ±0.45            | 5.6 ±0.38 | NS      |
| Serum FSH level (mIU/mL)             | 198 ±24.6              | 204 ±18.7 | 203 ±21.3            | 187 ±34.2 | NS      |
| Serum progesterone level (ng/mL)     | 1.2 ±0.89              | 2.0 ±0.67 | 0.98 ±0.07           | 1.6 ±0.12 | NS      |

NS: not significant

**Table 2.** Ovulatory and pregnancy outcomes in response to clomiphene citrate in both groups

| Outcome                                       | Metformin Group (n=10) | Control Group (n=11) | P value |
|---|------------------------|----------------------|---------|
| No. of women who ovulated/total no. of women  | 6/10                   | 2/11                 | <0.05   |
| No. of women who ovulated (%)                 | 60%                    | 18.1%                | <0.05   |
| No. of women who conceived/total no. of women | 4/10                   | 0/11                 | <0.05   |
| No. of women who conceived (%)                | 40%                    | 0%                   | <0.05   |

testosterone, androstenedione, E<sub>2</sub>, LH, FSH, DHEA-S

28.2 29.3  
64.3 kg, 65.3 kg, 66.3 kg (Table 1).  
65.4 kg 가  
35.4 kg/ 37.2 kg/m<sup>2</sup> 34.2 kg/m<sup>2</sup>, 37.5 kg/m<sup>2</sup> 18%  
34.2 kg/m<sup>2</sup>, 37.5 kg/m<sup>2</sup> 18%  
10 6 60%  
4 40%  
11 2  
0%  
가 (Table 2).

**Table 3.** Ovulatory response to treatment with metformin and clomiphene citrate in Metformin group (n=10)

| Patients | No. of ovulatory cycles | Pregnancy achieved |
|----------|-------------------------|--------------------|
| 1        | 3                       | Yes                |
| 2        | 0                       | No                 |
| 3        | 1                       | No                 |
| 4        | 2                       | Yes                |
| 5        | 0                       | No                 |
| 6        | 2                       | Yes                |
| 7        | 0                       | No                 |
| 8        | 5                       | Yes                |
| 9        | 3                       | Yes                |
| 10       | 2                       | Yes                |

1980 Burghen

25

가

가

가

6 가 2 1  
 5 가 3 2  
 1 3  
 (Table 3).  
 21

(central obesity)

10

가

가

26

가

가

가

27

rum)

(spect-  
subset  
(non-

obese, non-obese)

가

non-obese

가

가

21,22

-I (insulin-like growth factor-I, IGF-I) 가,  
(insulin-like

growth factor binding protein, IGFBP)

가

28 IGF (IGF system) IGF

23,24

IGF

(IGF-bin-

ding protein, IGFBP) IGF  
 (intraovarian regulating growth factor)  
 가 .<sup>27</sup> IGF  
 IGF-I IGF-II 가 ,  
 .<sup>11</sup>  
 가  
 (insulin receptor dis- , hMG, pFSH 가 <sup>31</sup>  
 order) GnRH-agonist  
 . 1961 Greenblatt  
 (peripheral insulin re-  
 sistance)  
 가  
 가  
 IGF-I dexamethasone  
 .<sup>29,30</sup>  
 IGF-I .<sup>32</sup> 5  
 (CC failure)  
 IGF-I  
 가 .  
 가  
 가 IGF-I  
 가 OHSS  
 ,<sup>16</sup>  
 disul-  
 fide bond α-β dimer heter 가 OHSS  
 rotetramer α-subunit ligand-  
 binding domain β-subunit 가,  
 가 protein tyro-  
 sine kinase ligand-medi-  
 ated autophosphorylation .  
 IGF-I protein tyrosine  
 kinase IGF-I 15 ,  
 substantial sequence (ho-  
 mology) 가 cross-over  
 .<sup>11</sup> (sensitizer) 가  
 가  
 가

troglitazone metformin  
 Troglitazone  
 가 .35-39  
 5 1 가 Ma-  
 1957 biguanide  
 (antihyperglycemic) 2 .12  
 가  
 postre-  
 ceptor level (insulin sensitivity) (masking)  
 가 insulin-mediated glucose disposal  
 (stimulation) .33  
 1.7~4.5 가 David  
 lactate PCOS  
 3 8 32  
 lactic acidosis가 3  
 가 .34  
 testosterone , kg/m<sup>2</sup>  
 가 OHSS non-obese  
 500 mg 3 가  
 tolerance 500 mg 가  
 1 1 1 2 2  
 3  
 가 850 mg 가  
 2 가 7 1  
 .34  
 500 mg 3 7 가  
 가

가 .

가

David  
32

가

가

(IVF-ET)

가

OHSS 가

non-obese

가

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