Metformin in polycystic ovary syndrome

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Chapter 4

Does adding metformin to clomifene citrate lead to higher pregnancy rates in a subset of women with polycystic ovary syndrome?

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Abstract

Background
An RCT among newly diagnosed, therapy naive women with polycystic ovary syndrome (PCOS) showed no significant differences in ovulation rate, ongoing pregnancy rate or spontaneous abortion rate in favour of clomifene citrate plus metformin compared with clomifene citrate. We wanted to assess whether there are specific subgroups of women with PCOS in whom clomifene citrate plus metformin leads to higher pregnancy rates.

Methods
Subgroup analysis based on clinical and biochemical parameters of 111 women randomised to clomifene citrate plus metformin compared with 114 women randomized to clomifene citrate plus placebo. The data for age, BMI, waist-hip ratio (WHR) and plasma testosterone were available in all women, 2 h glucose in 80% of women and homeostatic model assessment for assessing insulin sensitivity (HOMA) in 50% of women.

Results
Of the women that were allocated to the metformin group, 44 women (40%) reached an ongoing pregnancy. In the placebo group 52 women (46%) reached an ongoing pregnancy. There was a significantly different chance of an ongoing pregnancy for metformin versus placebo between subgroups based on age and WHR (p= 0.014). There was a positive effect of metformin versus placebo on pregnancy rate in older women (≥ 28 years) with a high WHR, a negative effect of metformin versus placebo in young women (< 28 years) regardless of their WHR and no effect in older, not viscerally obese women. No significant differences in effect of treatment were found for groups based on BMI, 2 h glucose, HOMA or plasma testosterone.

Conclusions
Metformin may be an effective addition to clomifene citrate in infertile women with PCOS, especially in older and viscerally obese patients.
Introduction

Polycystic ovary syndrome (PCOS) is characterised by oligo-anovulation, clinical or biochemical hyperandrogenism and/or polycystic ovaries. Insulin resistance (IR) accompanied by compensatory hyperinsulinemia constitutes another major biochemical feature of PCOS. The syndrome affects 5% to 10% of women during reproductive age.

Because of the link between IR and PCOS, metformin has been put forward as a drug to induce ovulation in women with PCOS. In fact, metformin either alone or in combination with clomifene citrate, is now the most widely used insulin-sensitizer for ovulation induction in women with PCOS. The rationale of this treatment was based on only a few small studies with conflicting results.

Recently, we demonstrated in a RCT among newly diagnosed, therapy naive women with PCOS that there were no significant differences in either ovulation rate, ongoing pregnancy rate or spontaneous abortion rate in women using clomifene citrate plus metformin compared with women using clomifene citrate. Since then, our results considering ongoing pregnancy rates have been confirmed in another large RCT.

However, PCOS is a heterogeneous condition and thus both studies included a heterogeneous group of women. Surprisingly, there is only one small study involving 32 patients with PCOS that has investigated the effect of metformin in specific subgroups. This study showed in a multivariable analysis that higher insulin, lower androstenedione and less severe cycle abnormalities appeared to be independent significant parameters for better response to metformin.

Increasing age and high waist hip ratio (WHR) are known risk factors in developing IR and, as such, these factors may also affect clinical response to metformin. Apart from these parameters, some authors suggest that metformin would most likely be beneficial in women with high BMI.

Thus, although many investigators claim a beneficial effect of metformin in specific subgroups of women, the evidence is limited.

We therefore wanted to determine whether co-treatment with metformin improves pregnancy rates compared with the standard treatment of clomifene citrate alone in subgroups of women based on clinical and biochemical variables. For this purpose we reanalyzed the data from a previously published randomised trial.
Materials and Methods

The data used in this study were collected in a RCT that has been reported elsewhere. This double blinded trial took place from June 2001 to May 2004 in 20 Dutch hospitals. All patients with chronic anovulation (a menstrual cycle ≥ 35 days), World Health Organization type II criteria (normogonadotropic normoestrogenic oligo- or anovulation), polycystic ovaries diagnosed by transvaginal ultrasonography and a desire to conceive were randomly allocated to clomifene citrate (50-150 mg a day for five consecutive days in the beginning of a menstrual cycle, per os) plus metformin (500 mg 4/day) or to clomifene citrate plus placebo. Primary exclusion criteria were other causes of anovulation, age over 40 years and liver-, kidney or heart disease/failure (i.e. abnormal results on liver function tests, serum creatinine concentration > 95 umol/l or a history of heart disease/failure) and sperm quality indicating male subfertility (Total Motile Count < 10 x 10⁶).

Randomisation was carried out in the coordinating centre (AMC, Amsterdam), using computer generated blocks of four. The containers with study medication were prepared by Merck Santé, France. The randomisation was stratified per centre, and the centres received blinded, numbered containers with medication. Each included patient received the container with the next number in their own hospital.

Patients continued to take the study medication until a positive pregnancy test (four weeks after the first day of menstruation), six ovulatory cycles or clomifene citrate resistance occurred, whichever came first. Women had to discontinue their medication as soon as they had a positive pregnancy test as the safety and benefit of using metformin during pregnancy have not yet been proven.

Ongoing pregnancy was defined as a viable pregnancy at 12 weeks of gestation. The study was approved by the Institutional Review Boards of all hospitals. Written informed consent was obtained from all participants.

At the start of the study we measured height, weight, WHR and plasma testosterone. Testosterone was measured in several laboratories. Total plasma testosterone concentrations were determined using an in-house radioimmunoassay, without extraction and chromatography and with tritiated testosterone as label. Intra-assay and inter-assay coefficients of variation were 4-7% and 509% respectively. An oral glucose tolerance test was also performed. Subgroup analysis was performed on age, BMI, WHR, testosterone, 2 h glucose and HOMA (homeostatic model assessment for assessing insulin sensitivity) as a measure of
Since not all data were available for all women, in some analyses only a proportion of the women could be included.

The subgroup analysis which we present here was planned in the original protocol. The parameters to be analysed were chosen, after completion of the trial, according to the most recent literature.17-23

Data analysis

For this subgroup analysis, we explored differences in treatment effect on ongoing pregnancy rate in subgroups defined on age, BMI, WHR, plasma testosterone, 2 h glucose level and IR evaluated by HOMA-IR. For this purpose, we performed logistic regression analysis including treatment, the subgroup indicator and the interaction between treatment and subgroup.

We assessed the linearity of the association between the continuous variables age, BMI, WHR, testosterone, 2 h glucose level and HOMA and the ongoing pregnancy rate using spline functions.28 Non-linear associations were accommodated by redefining the corresponding variables.

By testing the interaction in logistic regression, we compared directly the effect sizes of treatment for the subgroups. If the interaction is statistically significant, this is a clear indication that the effect of treatment differs between subgroups.29

Next, to explore potential interesting subgroup features, we combined subgroups for which the interaction with treatment was $P<0.20$. In all analyses, p-values $<0.05$ were considered significant. Data were analyzed using the Statistical Package for the Social Sciences 11.5.1.

Results

Baseline characteristics are presented in Table I. Out of the 111 women in the clomifene citrate plus metformin group, 44 (40%) reached an ongoing pregnancy versus 52 (46%) of the 114 women in the clomifene citrate group, a difference which was not significant (relative risk (RR) 0.87; 95% confidence interval (CI) 0.64 to 1.2). A significantly larger proportion of patients in the metformin group discontinued treatment because of side-effects (18/111 versus 6/114; RR 2.9; 95% CI 1.2 to 7.1). The total drop out rate in both treatment arms was not statistically different (28/111 versus 21/114; RR 1.3; 95% CI 0.82 to 2.2).
The data for age, BMI, WHR and testosterone levels were complete. The data for 2 h glucose level were available in 80% of patients, and for HOMA, in 50% of patients.

In women ≥28 years of age the effect of metformin versus placebo showed a small trend towards a different effect compared with the effect of metformin versus placebo in women <28 years (P-value of interaction 0.11)(Table II). In women with a WHR ≥ 0.85 the effect of metformin versus placebo was significantly different from the effect of metformin versus placebo in women with a WHR <0.85 (P-value of interaction 0.012)(Table II).

We did not find significant differences in effect of treatment for groups based on BMI, plasma testosterone, 2 h glucose values or HOMA.

On the basis of these findings, we combined age and WHR and created four subgroups. We found a significantly different chance of reaching an ongoing pregnancy of metformin versus placebo between these subgroups (P-value of interaction 0.014) (Table III). A positive effect of metformin versus placebo on pregnancy rate was found in older women (≥28 years) with a WHR ≥0.85, a negative effect of metformin versus placebo in young women regardless of their WHR, and no effect in the older, not viscerally obese women (Fig. I).

Discussion

In the present analysis, there was a significantly different chance of an ongoing pregnancy of metformin versus placebo between subgroups, based on age and WHR. A positive effect of metformin versus placebo on pregnancy rate was found in older women with a high WHR, a negative effect of metformin versus placebo in young women regardless of their WHR and no effect in older, not viscerally obese women.

We have included women with PCOS, who had never used clomifene citrate and were seeking treatment for their fertility problems for the first time. We evaluated eligibility irrespective of their BMI. By using these criteria our study group reflects the largest group of women with PCOS a fertility clinic will see and treat.

Our results contradict those from the only other subgroup analysis, where no differential effect of metformin was shown in subgroups of women based on age and WHR\textsuperscript{17}: this study did show that in multivariable analysis higher insulin, lower androstenedione and less severe cycle abnormalities appeared to be significant
parameters for better response to metformin, variables we did not assess in our study. However, our data may be more valid, because we analyzed over 200 patients, 10 times more than in the subanalysis by Moghetti\textsuperscript{17} and because our study was based on a double blinded RCT as opposed to the open protocol used in the previous subanalysis.

The most likely reason why metformin has a beneficial effect on pregnancy rates in older and viscerally obese women is that IR is common in these women.\textsuperscript{30,31} However, we did not find a significant interaction between pregnancy rates and the outcome of other surrogate markers of IR, including BMI, plasma testosterone, 2 h glucose value and HOMA. This is probably due to the fact that WHR is the most powerful predictor of IR of all surrogate markers.\textsuperscript{23,31-33} We did not measure IR directly by means of the gold standard, the glucose clamp technique, since this is considered to be too invasive and burdensome to be part of a large clinical trial in outpatients.\textsuperscript{27,34,35}

The lack of effect of metformin in patients with high BMI, increased plasma testosterone, higher 2 h glucose levels and HOMA may be real, if confirmed by further studies. However, another possibility is that the present study did not have enough power to show a difference. This might especially hold true for HOMA, since we only had data on half of the patients.

A limitation of the study is that we did not collect all parameters in all patients. In particular, fasting insulin is missing in 49% of the patients. When comparing baseline characteristics of the patients for whom data on insulin were available with those for whom data were not available, we found no significant differences (data not shown). The lack of data appears, therefore, to be due to a random effect of not executing the complete study protocol rather than a deliberate omission of patients with certain clinical or biochemical characteristics.

An additional limitation of the study relates to the testosterone analysis. After our study protocol was written (1999) and our study performed (2001-2004), it became clear that testosterone assays show a wide inter-laboratory variability.\textsuperscript{36,37} When we had finished the trial, it was impossible to adjust for this. The calculations performed in this trial were therefore performed without correcting for this inter-laboratory imprecision, as is the case in all previous literature. It is possible that the variation is sufficiently high to render the result not significant. This relatively new understanding
of the variability of testosterone assays variability may have great impact, not only on existing but also on future literature on PCOS, especially in multicentre studies.

Our RCT was not powered for these subgroup analyses; therefore the data need to be interpreted with great caution. Nonetheless, we feel that our data argue for performing a trial comparing metformin and clomifene citrate with clomifene citrate alone in older visceral obese women with PCOS.

**Conclusion**

Although our initial randomised trial showed no benefit for metformin, our current findings suggest that metformin may be an effective addition to clomifene citrate in infertile, older and visceral obese women with PCOS. Randomized studies should be performed specifically for this subgroup, or data from other existing trials should be re-analyzed before we can consider implementing these findings in clinical practice.
References


(31) Lord J, Thomas R, Fox B, Acharya U, Wilkin T. The central issue? Visceral fat mass is a good marker of insulin resistance and metabolic disturbance in women with polycystic ovary syndrome. BJOG 2006; 113(10):1203-1209.


Table I. Baseline characteristics of patients with polycystic ovary syndrome (PCOS) who were treated with clomifene citrate plus metformin or clomifene citrate alone. Figures are mean (SD) unless stated otherwise.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (metformin versus placebo)</th>
<th>clomifene citrate and metformin</th>
<th>clomifene citrate and placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>111 versus 114</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>111 versus 114</td>
<td>27.9 (3.7)</td>
<td>28.4 (4.7)</td>
</tr>
<tr>
<td>Parity N(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>89 versus 95</td>
<td>89 (80%)</td>
<td>95 (84%)</td>
</tr>
<tr>
<td>Multiparous</td>
<td>22 versus 18</td>
<td>22 (20%)</td>
<td>18 (16%)</td>
</tr>
<tr>
<td>Duration of desire to conceive</td>
<td>100 versus 107</td>
<td>1.6 (1.2)</td>
<td>1.3 (1.1)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>104 versus 109</td>
<td>28 (7.1)</td>
<td>27 (6.7)</td>
</tr>
<tr>
<td>Waist hip ratio</td>
<td>102 versus 103</td>
<td>0.82 (0.1)</td>
<td>0.83 (0.1)</td>
</tr>
<tr>
<td>LH/FSH ratio</td>
<td>106 versus 109</td>
<td>1.9 (1.3)</td>
<td>2.1 (1.4)</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>104 versus 108</td>
<td>3.5 (3.7)</td>
<td>3.6 (3.5)</td>
</tr>
<tr>
<td>Free androgen index</td>
<td>70 versus 69</td>
<td>12 (18)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Volume ovaries (ml)</td>
<td>71 versus 65</td>
<td>9.1 (6.1)</td>
<td>10.1 (4.9)</td>
</tr>
<tr>
<td>Total motile sperm count</td>
<td>102 versus 105</td>
<td>134 (223)</td>
<td>222 (370)</td>
</tr>
<tr>
<td>Glucose, fasting (mmol/l)</td>
<td>101 versus 99</td>
<td>4.9 (0.7)</td>
<td>4.9 (0.6)</td>
</tr>
<tr>
<td>Glucose, 2 hours (mmol/l)</td>
<td>91 versus 90</td>
<td>5.0 (1.4)</td>
<td>5.1 (1.3)</td>
</tr>
<tr>
<td>Insulin, fasting (pmol/l)</td>
<td>56 versus 59</td>
<td>85 (169)</td>
<td>60 (131)</td>
</tr>
<tr>
<td>Insulin, 2 hours (pmol/l)</td>
<td>58 versus 57</td>
<td>233 (274)</td>
<td>270 (386)</td>
</tr>
<tr>
<td>HOMA</td>
<td>56 versus 57</td>
<td>11 (12)</td>
<td>10 (11)</td>
</tr>
</tbody>
</table>

HOMA: homeostatic model assessment for assessing insulin sensitivity
Table II. Pregnancy rates for subgroups of women with PCOS treated with clomifene citrate plus metformin or clomifene citrate alone.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>metformin n/N (%)</th>
<th>placebo n/N (%)</th>
<th>RR (95% CI)</th>
<th>p-value of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>225</td>
<td>44/111</td>
<td>52/114</td>
<td>0.87 (0.64 to 1.2)</td>
<td>-</td>
</tr>
<tr>
<td>Age (years) &lt; 28 years</td>
<td>91</td>
<td>13/48 (27)</td>
<td>19/43 (44)</td>
<td>0.61 (0.35 to 1.1)</td>
<td>0.11</td>
</tr>
<tr>
<td>Age (years) ≥ 28 years</td>
<td>134</td>
<td>31/63 (49)</td>
<td>33/71 (47)</td>
<td>1.1 (0.74 to 1.5)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²) &lt; 28</td>
<td>118</td>
<td>27/56 (48)</td>
<td>32/62 (52)</td>
<td>0.93 (0.65 to 1.3)</td>
<td>0.23</td>
</tr>
<tr>
<td>BMI (kg/m²) ≥ 28</td>
<td>95</td>
<td>16/48 (30)</td>
<td>19/47 (40)</td>
<td>0.82 (0.49 to 1.4)</td>
<td></td>
</tr>
<tr>
<td>WHR &lt; 0.85</td>
<td>134</td>
<td>33/70 (47)</td>
<td>37/64 (58)</td>
<td>0.82 (0.59 to 1.1)</td>
<td>0.012</td>
</tr>
<tr>
<td>WHR ≥ 0.85</td>
<td>71</td>
<td>10/32 (31)</td>
<td>11/39 (28)</td>
<td>1.1 (0.54 to 2.3)</td>
<td></td>
</tr>
<tr>
<td>Testosterone (nmol/l) ≤ 3.5</td>
<td>143</td>
<td>30/71 (42)</td>
<td>34/72 (47)</td>
<td>0.89 (0.62 to 1.3)</td>
<td>0.87</td>
</tr>
<tr>
<td>Testosterone (nmol/l) &gt; 3.5</td>
<td>69</td>
<td>13/33 (39)</td>
<td>15/36 (42)</td>
<td>0.95 (0.53 to 1.7)</td>
<td></td>
</tr>
<tr>
<td>Glucose 2 hours (mmol/l) ≤ 5</td>
<td>101</td>
<td>22/48 (46)</td>
<td>28/53 (53)</td>
<td>0.87 (0.58 to 1.3)</td>
<td>0.22</td>
</tr>
<tr>
<td>Glucose 2 hours (mmol/l) &gt; 5</td>
<td>80</td>
<td>16/43 (37)</td>
<td>12/37 (32)</td>
<td>1.1 (0.63 to 2.1)</td>
<td></td>
</tr>
<tr>
<td>HOMA &lt; 3.8</td>
<td>42</td>
<td>10/23 (44)</td>
<td>6/19 (32)</td>
<td>1.4 (0.61 to 3.1)</td>
<td>0.88</td>
</tr>
<tr>
<td>HOMA ≥ 3.8</td>
<td>71</td>
<td>13/33 (39)</td>
<td>14/38 (37)</td>
<td>1.1 (0.59 to 1.9)</td>
<td></td>
</tr>
</tbody>
</table>

RR: relative risk, CI: confidence interval, WHR: waist hip ratio
**Table III.** Pregnancy rates for combined subgroups in women with PCOS treated with clomifene citrate plus metformin or clomifene citrate alone.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Metformin n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>RR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) &lt; 28, WHR &lt; 0.85</td>
<td>54</td>
<td>10/32 (31)</td>
<td>13/22 (59)</td>
<td>0.53 (0.28-0.98)</td>
<td>0.014</td>
</tr>
<tr>
<td>Age (years) ≥ 28, WHR &lt; 0.85</td>
<td>80</td>
<td>23/38 (61)</td>
<td>24/42 (57)</td>
<td>1.1 (0.73-1.5)</td>
<td></td>
</tr>
<tr>
<td>Age (years) &lt; 28, WHR ≥ 0.85</td>
<td>29</td>
<td>3/14 (21)</td>
<td>5/15 (33)</td>
<td>0.64 (0.19-2.2)</td>
<td></td>
</tr>
<tr>
<td>Age (years) ≥ 28, WHR ≥ 0.85</td>
<td>42</td>
<td>7/18 (39)</td>
<td>6/24 (25)</td>
<td>1.6 (0.98-3.8)</td>
<td></td>
</tr>
</tbody>
</table>