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Medication Adherence and Treatment Success in the NICHD-Reproductive Medicine Network's "Pregnancy in Polycystic Ovary Syndrome" (PPCOS) Trial

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Abstract

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Capsule: Failure of adherence with study medications was not the cause of poor success in the metformin-containing arms of the PPCOS Trial.

We investigated whether poor adherence with metformin tablets may have contributed to the poor success rates seen in the metformin-containing arms of the PPCOS Trial. Median adherence for both metformin and clomiphene citrate tablets were within acceptable limits and unrelated to ovulation: thus, failure to comply with physician recommendations for metformin dosing was not the reason for low ovulation and pregnancy rates in the PPCOS Trial.

Keywords

PCOS; medication adherence; metformin

The recently-published NICHD-sponsored multicenter trial of the Reproductive Medicine Network (Pregnancy in Polycystic Ovary Syndrome or PPCOS) determined that clomiphene citrate alone (as compared to metformin XR alone), or the combination was the safest and most efficient way to achieve livebirth pregnancy in women with PCOS (1). A very mild synergy was found in the combination arm, but it only appeared useful in the most extremely obese women (BMI ≥ 35). These results were opposite to a number of previous smaller randomized trials, which had seemed to show much better ovulation and clinical pregnancy rates with metformin therapy as compared to clomiphene citrate. One suggested explanation for this observed difference was that poor adherence with metformin tablets (presumably secondary to increased GI side effects) may have led to the poor rates of ovulation and pregnancy discovered in PPCOS (2). The purpose of this study was to examine medication adherence in the metformin-containing arms of PPCOS in greater detail (3), to determine whether they fell within the expected range for similar trials.

The PPCOS Trial randomly assigned 626 infertile women with PCOS to clomiphene citrate alone (“C”; n=209), metformin alone (“M”; n=208) or the combination (“B”; n=209) in a double blind fashion. Entry criteria included elevated serum testosterone or free testosterone and irregular menstrual cycles, along with the exclusion of hyperprolactinemia, diabetes, menopause, thyroid, adrenal, renal or liver disease. The “M” tablets contained either placebo or metformin extended release (XR) 500 mg; subjects were instructed to take one per day for 5 days, then one tablet BID for 5 days, then one tablet TID for 5 days and thereafter two tablets twice daily. Subjects who could not tolerate 4 pills (2,000 mg) daily were allowed to take only 3 and remain in the study. All subjects were strongly encouraged to take at least 3 pills per day. The “C” pills contained either placebo or clomiphene citrate 50 mg; subjects were instructed to take one per day for 5 days. The main PPCOS study results were that livebirth pregnancy was over 3 times more likely in the clomiphene citrate containing arms than in the metformin alone group (“C” 22.5% livebirths per subject versus “B” 26.8% livebirths per subject versus “M” 7.2% livebirths per subject). A letter (2) to the editor of the New England Journal of Medicine submitted promptly in response to this study’s publication suggested that poor adherence with metformin medication (possibly secondary to a high incidence of diarrhea) was the reason for the lower pregnancy rate in the “M” arm. We therefore wanted to more carefully investigate this issue, to determine whether poor adherence with metformin tablets may have contributed to the poor success rates seen in the metformin-containing arms of the PPCOS Trial (3). As our subjects returned their bottles of study medication with each monthly visit, we were able to track adherence with metformin tablets through pill counts.

Medication adherence results for metformin and clomiphene tablets are listed in Table 1. We calculated adherence as the percentage of the recommended tablets that were not in the returned bottle when we counted the remaining tablets (4); e.g. every 30 days, 120 “M” pills were prescribed, so if a bottle containing 150 tablets was given and 30 days later the bottle which was returned contained 50 pills, then only 100 tablets were removed from the bottle, yielding an adherence rate of 100/120 or 83.3%. We found that there was no difference in adherence

rates between the “M” and “B” groups (P=0.80). The median adherence was 81.6 % in the “M” group and 81.7 % in the “B” group, with similar proportions in both groups having less than 60% adherence (13.3% for the “M” group vs 11.7% for the “B” group). We also compared the relationship of adherence to the incidence of ovulation by using linear regression when they are treated as continuous variables and by chi-square test when they are categorized as categorical variables (Table 1) within each group. Ovulatory rates were low in the “M” group across all levels of adherence, and there was no evidence of a trend for increasing ovulation as adherence increased within each group (slope parameters of 0.10 (P=0.48) and 0.04 (P=0.79) from linear regressions for the “M” and “B” groups respectively, or P=0.22 and P=0.18 from the chi-square tests in Table 1 for the “M” and “B” groups, respectively).

We anticipated much better compliance using the clomiphene citrate tablets, due to the prescription of a smaller number of tablets for only 5 days per cycle. We did not directly compare adherence with “C” vs. “M” pills, because of the inherent difficulty in comparing a regimen consisting of 1-3 pills per day for 5 days once per month (the “C” regimen) with 3-4 pills per day every day for several months. However, as an internal control, we did examine medication adherence results for clomiphene citrate tablets (Table 1). Median adherence was better with the smaller number of clomiphene citrate tablets prescribed: median adherence for clomiphene citrate tablets was 100% in both the clomiphene citrate only and the combined clomiphene citrate and metformin XR groups. We found that there was no difference in adherence rates between the “C” and “B” groups (P=0.80). We also compared the relationship of adherence to the incidence of ovulation by using linear regression when they are treated as continuous variables and by chi-square test when they are categorized as categorical variables (Table 1) within each group. There was no evidence of a trend for increasing ovulation as adherence increased within each group (slope parameters of 0.18 (P=0.18) and 0.16 (P=0.15) from linear regressions for the “C” and “B” groups respectively, or P=0.10 and P=0.17 from the chi-square tests for the “C” and “B” groups, respectively).

Reported levels of patient adherence with recommended medications are extremely varied and depend upon a variety of parameters. For example, Deyo et al. (5) evaluated adherence using medication refills and found that > 50% of patients using prednisone as chronic therapy for arthritis used < 80% of the refills which would be needed to take their medication as prescribed. Using pill counts, Rudd et al. (4) looked at hypertensive patients given extra tablets of either hydralazine or pinacidil: while median compliance approached 100%, they noted that 8-15% of the subjects had either < 80% or > 120% adherence. They ascribed the excessive adherence to “pill-dumping” and judged that many of those probably were not taking a large percentage of their tablets. Pullar et al. (6) showed that increasing the number of daily doses from one to two to three adversely affected adherence – as measured by pill counts- in a progressive and significant fashion (P<0.05). The same investigators used trace amounts of Phenobarbital in tablets containing arthritis medication and found that 48% of subjects had serum Phenobarbital levels < 90% of the lowest level seen after short-term use by paid volunteers of the same age, yet only 16% had pill counts less than 90% (7). They concluded that return tablet counts overestimate compliance.

In contrast to studies of chronic disease, we could only identify scattered articles which explicitly measured patient adherence to medications in trials of infertility treatments (8). Our median adherence of 81% overall compares favorably to one trial, which noted a median adherence of 76% in subjects given ethinyl estradiol 2 or 4 times daily for only 7 days (BID compliance was 85% vs. 67% for QID). Given the relatively short-term treatment and the high degree of motivation of most patients presenting for infertility care, we would predict that adherence rates would be as good or better than those observed for therapies for chronic conditions. Positive feedback in the form of ovulation and menses may play a bigger role—although adverse events and adherence to medication were similar in both metformin-

containing arms in PPCOS, the drop-out rate was highest in the "M" arm, which we, and the study coordinators in contact with subjects, attribute largely to frustration at lack of ovulation.

Limitations of this analysis are that the study was not designed to assess adherence in a systematic manner and that this is a post-hoc analysis of data derived for other purposes. The use of pill counts alone has been questioned as a less-than reliable method of assessing adherence, when compared to methods such as adding trace levels of phenobarbital and documenting serum levels (5,7). The dramatic paucity of data regarding medication adherence which we discovered through search of the infertility literature, however, supports both the publication of our data and the need for more careful study of this issue in future trials.

We conclude that adherence in both metformin-only and combined metformin and clomiphene citrate arms was within reported norms for similar clinical trials and further that there was clearly no relationship between adherence and ovulation. Failure to comply with physician recommendations for metformin dosing was not the reason for low ovulation and pregnancy rates in the metformin arms of the PPCOS Trial.

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Table 1

Adherence vs ovulation by treatment group : Metformin XR and Clomiphene tablets.

Metformin Pills	**Metformin Only (N=195)**				**Metformin + Clomiphene (N=195)**			
Adherence to treatment (% of prescribed pills used)		**Ovulatory Cycles (P=0.22)**				**Ovulatory Cycles (P=0.18)**		
		<30%	**30-59%**	**≥60%**		**<30%**	**30-59%**	**≥60%**
<60%	n=26	57.7%	19.2%	23.1%	n=23	34.8%	4.4%	60.9%
60-80%	n=62	61.3%	25.8%	12.9%	n=65	21.5%	23.1%	55.4%
>80%	n=107	57.0%	15.9%	27.1%	n=107	18.7%	16.8%	64.5%
Clomiphene Pills	Clomiphene Only (N=209)				Metformin + Clomiphene (N=209)			
Adherence to treatment (% of prescribed pills used)		**Ovulatory Cycles (P=0.10)**				**Ovulatory Cycles (P=0.17)**		
		<30%	**30-59%**	**≥60%**		**<30%**	**30-59%**	**≥60%**
<100%	n=84	40.5%	20.2%	39.3%	n=80	31.3%	17.5%	51.2%
100%	n=125	26.4%	24.8%	48.8%	n=129	20.9%	15.5%	63.6%

Percentages in each cell represent the proportion of subjects in each treatment group falling within the respective ovulation category given an adherence category.