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Intercourse Compliance, Ovulation and Treatment Success in the NICHD-Reproductive Medicine Network's "Pregnancy in Polycystic Ovary Syndrome" (PPCOS) Trial

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Abstract

Objective—To investigate the relationship between intercourse compliance, ovulation and the occurrence of pregnancy in the PPCOS Trial.

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Design—Post ad hoc data analysis of subjects in the RMN PPCOS Trial

Setting—Academic medical centers

Intervention(s)—None

Patients—Six hundred twenty-six infertile women with PCOS with a mean age of 28.1 ± 4 years and mean body mass index of $35.2 \text{ kg/m}^2 \pm 8.7$.

Main Outcome Measure(s)—Intercourse compliance, ovulation and pregnancy

Result(s)—Data on 2925 cycles were included in the analysis, of which 1340 were ovulatory cycles and 1585 were non ovulatory cycles. The rates of intercourse compliance in the PPCOS trial were similar across all treatment groups at all cycles except cycle number four ($P < 0.04$). Among cycles with known ovulation status, 81.2% of patients were compliant with intercourse instructions. Patients were more intercourse-compliant in those cycles where ovulation occurred (83.2% vs. 79.4%, $P = 0.02$). With regard to ovulatory cycles, there was no difference in the occurrence of pregnancy when comparing intercourse compliant vs. intercourse non-compliant cycles ($P = 0.59$).

Conclusion(s)—Intercourse compliance was not associated with the occurrence of pregnancy in ovulatory cycles in the PPCOS Trial. The occurrence of ovulation still remains a critical predictor in the occurrence of pregnancy.

Keywords

intercourse timing; ovulation; intercourse frequency; polycystic ovary syndrome

The NICHD-sponsored multicenter trial of the Reproductive Medicine Network (Pregnancy in Polycystic Ovary Syndrome or PPCOS) reported a higher live birth delivery in women with PCOS treated with clomiphene citrate alone or the combination compared to metformin XR alone, (1). Live birth delivery was over 3 times more likely in the clomiphene citrate containing arms than in the metformin alone group. The live birth rate was 22.5% (47 of 209) in the clomiphene group, 26.8% (56 of 209) in the combination therapy group and 7.2% (15 of 208) in the metformin group ($P < 0.001$ for the metformin vs., both clomiphene and combination therapy; $P = 0.31$ for clomiphene vs. combination therapy. live births per subject). These results were contrary to those of prior reports. One difference may related to body mass index (BMI); at least one trial with opposite results excluded all women with a BMI greater than 30 (2)

Further, the rate of ovulation was significantly higher in the combination group than in either of the single-agent groups. Over the course of the trial the mean ($\pm$ SD) number of ovulations per subject was 2.22 ± 1.87 in the clomiphene group, 1.43 ± 1.72 in the metformin group, and 2.80 ± 2.04 in the combination group ($P < 0.001$ for the comparisons of the clomiphene and combination therapy groups with the metformin group). Yet the differences in the ovulation rates did not translate into a significant increase in the live-birth rate. Ovulation is the key event in the menstrual cycle that determines the timing of the fertile interval during which intercourse can result in a pregnancy. Hence, a critical predictor, is the timing of non contraceptive intercourse during the menstrual cycle. Intercourse compliance is a potential confounding variable as behavior differences between exposure groups may exist while also having a large impact on conception probabilities. Patients were considered intercourse compliant if intercourse frequency was ≥ 2 times per week. Although the rates of intercourse compliance in the PPCOS trial were similar across all treatment groups at all cycles except cycle number four, the possible effect of intercourse compliance on the occurrence of pregnancy was not further explored.

Based on the above observations,. We chose to evaluate the effect of intercourse compliance as a secondary outcome measure on the occurrence of pregnancy from the original cohort of

women involved in the multicenter, randomized controlled trial, of the RMN-PPCOS trial. In brief, the RCT evaluated the effectiveness of treatment with extended release metformin, alone or in combination with clomiphene citrate compared to clomiphene citrate alone on live birth rate.

The study is a post hoc secondary analysis of the interaction between intercourse compliance, ovulation and pregnancy occurrence in the RMN PPCOS trial. The purpose of this study was to examine: 1) the correlation between intercourse compliance and ovulation; and 2) to assess the effects of intercourse compliance in ovulatory cycles upon pregnancy occurrence.

MATERIALS AND METHODS

In the PPCOS Trial, 626 women with PCOS were randomly treated with clomiphene citrate alone ("C"; n=209), metformin alone ("M"; n=208) or the combination ("B"; n=209). Medication was blinded to investigators and subjects. Subjects were instructed to have regular intercourse every 2 to 3 days and to keep a diary recording intercourse, vaginal bleeding and symptoms. Ovulation was confirmed by a serum progesterone concentration above 5 ng/ml measured weekly or every other week. If two consecutive measurements showed elevated progesterone, a weekly pregnancy test was administered until positive or menses occurred. All subjects were required to maintain a handwritten daily prospective diary, in which symptoms such as vaginal bleeding, GI upset, etc., medications taken, and the occurrence of intercourse were recorded. These diaries were brought in by subjects for the weekly visits with study staff, and reviewed to make sure that medications were taken as prescribed, intercourse was occurring at a 2–3 times weekly interval, and to discuss any symptoms or medication side effects. In this study we examined intercourse compliance in both ovulatory and non-ovulatory cycles. As there was no chance of pregnancy in non-ovulatory cycles, the association between intercourse compliance and pregnancy was examined only in those cycles with documented ovulation.

Compliance status was based on patients' written prospective diaries, as reviewed weekly by study staff. Intercourse frequency of two-three times per week, as recommended for all subjects in the study, was considered compliant. Patients who had intercourse ≤ 1 per week were considered non-compliant. If the compliance status was missing from the data base, subjects were considered as non-compliant.

Statistical Analysis

Data management and analysis were performed at the Data Coordinating Center at the Duke Clinical Research Institute. Frequency and percentage are used to describe the data. Generalized estimating equations approach was used for computing the P-value to account for correlation of multiple cycles for each subject. Odds ratios point estimates and 95% Wald confidence limits are also reported to determine the effects. All analyses were performed with SAS software, version 8.2 (SAS Institute)). A P-value of ≤ 2 was considered statistically significant to account for the post hoc analysis of the data set.

RESULTS

In brief, 626 infertile women with PCOS with a mean age of 28.1 ± 4 years and mean body mass index of $35.2 \text{ kg/m}^2 \pm 8.7$, representing a total of 2925 cycles were evaluated. Of the 2925 cycles included in the study, 1340 were characterized as ovulatory and 1585 were non ovulatory. The rates of intercourse compliance with the recommended frequency of sexual intercourse ranged from 74 to 76% at the first visit and declined to 54 to 56% at the visit at 6 months (1). The compliance rates were similar across treatment groups at all cycles except cycle 4, during which the rates were 71% in the clomiphene group, 66% in the metformin

group, and 76% in the combination-therapy group. For cycle 4 an absolute difference was seen between the combination-therapy group versus the metformin group ($P=.04$) (1).

Among the cycles with known ovulatory status, 81.2% were intercourse compliant. In those ovulatory cycles, intercourse compliance was more likely to occur than in non-ovulatory cycles (83.2% vs. 79.4%, Table 1, $P = 0.02$, Odd Ratio=1.28, 95% CI 1.04–1.58). With regard to ovulatory cycles, there was not a significant difference in the occurrence of pregnancy when comparing intercourse compliant vs. intercourse non-compliant cycles (9.5% vs. 12.0%, Table 2, $P=0.59$).

DISCUSSION

It was beyond the scope of this study to determine the reasons for the association between intercourse and ovulation. However, teleologically, efficiency of reproduction would suggest a system in which the occurrence of ovulation would be associated with factors that increase the coincident occurrence of intercourse. An increase in female-initiated sexual intercourse at midcycle has previously been attributed to an increase in androstenedione 2 hours prior to ovulation and an increase in free testosterone resulting from the effect of the estrogen increase on SHBG 48 hours prior ovulation (3–4). Further, there is the intriguing hypothesis that intercourse itself may provoke an ovulatory response in certain susceptible subjects. In other words, that some women may be reflex ovulators, the norm for certain other mammals (5). We also acknowledge that given the post hoc nature of our study, the observed difference in intercourse compliance with regard to ovulation compared to no ovulation although statistically significant may not necessarily imply a causal relationship. Regardless of the explanation, it was ovulation itself, and not intercourse compliance that was the strongest predictor of pregnancy occurrence.

This is a post-hoc analysis of a study not designed to assess adherence to instructions for intercourse frequency, and is thus subject to the general limitations of all post-hoc analyses. Hence, extrapolation of the above observations beyond this study population should be guarded. A significant strength of this study is its reliance upon prospective, written diaries checked by study staff on a weekly basis throughout the trial, which would limit the ability of a non-recording subject to “fill in” what she thought we wanted to see after the trial was completed. As intercourse was a self-reported phenomenon, it may well be that subjects were reluctant or embarrassed to admit non-compliance or even more-than recorded intercourse, leading to under- or over-reporting of intercourse frequency.

Conclusion

In conclusion, we have confirmed the previous observations that sexual behavior increases during the ovulatory phase of the menstrual cycle in committed relationships. However, intercourse timing alone has less impact on the occurrence of pregnancy than ovulation itself.

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TABLE 1

Intercourse compliance in all cycles with known ovulation status.

	Ovulatory Cycles n=1340	Non-ovulatory Cycles n=1585
Intercourse Compliant	1115/1340 (83.2%)	1259/1585 (79.4%)
Intercourse Non-compliant	225/1340 (16.8%)	326/1585 (20.6%)

P=0.02

TABLE 2

Intercourse compliance only in cycles with documented ovulation.

	Intercourse Compliant n=1115	Intercourse Non-compliant n=225
Not Pregnant	1009/1115 (90.5%)	198/225 (88.0%)
Pregnant	106/1115 (9.5%)	27/225 (12.0%)

P=0.59