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# Tear Osmolarity and Dry Eye Symptoms in Women Using Oral Contraception and Contact Lenses

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## Abstract

**Purpose—**To examine the relationship between oral contraceptive pill (OCP) use, contact lens wear, and dry eye signs and symptoms in healthy young females.

**Methods—**Fifty-two women using OCPs and forty-five women not using any form of hormonal contraception were enrolled. Medical, menstrual, and contact lens histories were obtained and dry eye symptoms were assessed using the Ocular Surface Disease Index (OSDI) and Symptom Assessment iN Dry Eye (SANDE) questionnaires. Tear osmolarity testing was performed using the TearLab™ Osmolarity System.

**Results—**Mean age of all subjects was 26.0 ± 3.7 years. There were no significant differences in any of the measurements between the follicular and luteal phases. While SANDE scores were significantly higher in subjects with OCP and recent contact lens use ($p<0.01$), there were no significant differences in OSDI and tear osmolarity amongst the same subject groups. Subjects who reported both OCP and recent contact lens use had significantly higher OSDI and SANDE scores ($p=0.015$ and $p<0.001$, respectively).

**Conclusions—**There were no differences between the phases of the menstrual cycle. Tear osmolarity was not affected by OCP or contact lens use in young females. However, the combination of OCP use and contact lens wear may increase the severity of dry eye symptoms.

### Keywords

Dry eye; oral contraceptives; tear osmolarity; contact lenses

## INTRODUCTION

Dry eye disease (DED or keratoconjunctivitis sicca) is a common multifactorial disease of the tears and the ocular surface that can significantly diminish visual function and quality of life. It is one of the leading causes of patient visits to ophthalmologists and optometrists in the United States and is estimated to affect 5-35% of the population.[1,2] DED predominantly affects women, raising the question regarding estrogen's role in DED.[1,2] However, the relationship between DED and estrogen is complex as it is associated with both low and

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Conflicts of Interest
For the remaining authors none were declared.

high estrogen states, leading investigators to consider the influence of not only estrogen but also of androgen and other sex hormones in the pathophysiology of DED.[3,4]

While the influence of androgens may account for most of the sex-related differences found in the lacrimal tissue, the effects of estrogen are still unclear and the evidence regarding its role is often conflicting.[3] Estrogen is known to cause a decrease in lipid production and size of sebaceous glands in general.[5] Thus, one could speculate that dry eye symptoms would be more severe during states of increased estrogen, such as in pregnancy or hormonal contraceptive use. Yet, despite the widely held clinical perception that the use of hormonal contraceptives may be associated with dry eye symptoms, there are surprisingly few studies examining this relationship.[6-8]

In addition to the complex influence of hormones on DED, contact lens wear is another common cause of DED. Of the more than 125 million contact lens wearers worldwide, as many as 80% report occasional to frequent dry eye symptoms.[9,10] In an era of increasing contact lens and hormonal contraceptive use, some clinicians have noted increased contact lens intolerance in women using OCPs.[11-14] However, very few studies have attempted to elucidate the relationship between hormonal contraceptive use, contact lens wear and dry eye.[13,15]

In recent years, evidence has emerged supporting the use of tear osmolarity testing as a potentially useful global marker for DED that is elevated in both evaporative and aqueous tear-deficient subtypes of DED.[16-18] The 2007 amended definition for dry eyes states that tear film instability and hyperosmolarity are core mechanisms of dry eye pathology.[2] The purpose of this study was to examine the relationships among tear osmolarity, dry eye symptoms, contact lens wear, and oral contraceptive pill use in young women.

## METHODS

### Subjects

Subjects enrolled were students, employees, and patients at the University of Pennsylvania. The study was approved by the University's Institutional Review Board and conducted in accordance with the University's guidelines for experimental investigation with human subjects. Informed consent was obtained from each participant prior to starting study procedures.

Eligible subjects were females between the ages of 18 and 40 years. Eligible subjects were required to be either using oral contraceptive pills currently and during the previous three months (OCP+ group) or not having used any form of hormonal birth control for at least one week (OCP- group). Subjects in the OCP- group needed to have reported regular menstrual cycles lasting between 21 and 35 days. Subjects were excluded if they were currently pregnant, used ophthalmic drops within two hours of the study visit, or had a history of ocular inflammation in the past three months, ocular surgery in the past six months, or an autoimmune disease (i.e., Rheumatoid arthritis, Lupus, sarcoidosis, or Sjögren's syndrome).

All subjects completed a study visit to provide a medical history, complete questionnaires on DED symptoms, and have measurements of tear osmolarity. Subjects in the OCP- group completed a second visit. The two visits were approximately two weeks apart, depending on the reported length of the subject's menstrual cycle, to capture measurements from both the follicular and luteal phase of the cycle.

### History

Demographic information, contact lens wear, ocular history, past medical and surgical history, current systemic and ophthalmic medications, and menstrual cycle information were obtained by patient self-report. Day of ovulation was calculated by subtracting 14 days from the reported menstrual cycle length. The follicular phase was defined as the days before ovulation and the luteal phase as those following ovulation. Contact lens history was recorded as contact lens use in the past 30 days (CL30+/-), contact lens wear during the study visit ($CL_{visit}$+/-), and any history of contact lens use. The frequency of contact lens use in the past 30 days and the time since first contact lens use were also recorded.

### Assessments of Dry Eye Disease

Dry eye symptoms were assessed using the Ocular Surface Disease Index (OSDI; Allergan, Inc, Irvine, CA) and the Symptom Assessment iN Dry Eye (SANDE; Daiichi Pharmaceutical Corporation, Montvale, NJ) questionnaires.[19,20] The OSDI consists of 12 questions on symptoms within the past week and yields scores ranging from 0 (least severe) to 100 (most severe). The SANDE consists of two questions, one on average frequency and the other on average severity of symptoms, with responses recorded on a visual analogue scale ranging from 0 to 100 millimeters. Tear osmolarity measurements were obtained from each eye using the TearLab™ Osmolarity System (TearLab, San Diego, CA). Subjects were instructed not to rub their eyes for at least 10 minutes. Tear samples were collected by placing the tip of the TearLab device gently at the inferior lateral tear meniscus with care being taken not to induce reflex tearing. At the beginning of each day of patient testing, the TearLab™ Osmolarity System was calibrated in accordance with the manufacturer's instructions. All measurements were performed by the same investigator. Since inter-eye variability has been found to be associated with an increased severity of DED, the measurement from the eye with the higher osmolarity was used for data analysis.[17]

### Statistical Analysis

Differences in demographics were analyzed using Student t-test for continuous measures and Fisher's exact test for categorical factors. Differences in outcome measures between the follicular and luteal menstrual phases were assessed by paired t-tests using data only from the 29 patients who had measurements taken during both phases. Only the values from the first visit were used for all other analyses. Differences in measurements between two groups were assessed with t-tests for tear osmolarity and with Wilcoxon rank sums tests for the questionnaire scores. Bootstrapping with 2000 repetitions and using bias-corrected percentiles was used to generate 95% confidence intervals for the median differences between questionnaire scores. Differences among the four groups were assessed with one-way analysis of variance (ANOVA) for the tear osmolarity measurement and the Kruskal-Wallis test for the OSDI, SANDE severity, and SANDE frequency scores. Additionally, using the recently published cut-off point of 308 mOsm/L, differences in high versus low tear osmolarity between groups were assessed using Fisher's exact tests.[17] Spearman rank-order correlation coefficients were used to examine the pairwise relationships.

## RESULTS

### All subjects

One hundred female subjects were enrolled in the study. Three subjects were excluded due to a menstrual cycle length greater than 35 days for the cycle observed, resulting in 52 subjects in the OCP+ group and 45 in the OCP- group. Among the 97 subjects, 48 (49%) wore contact lenses in the past 30 days (CL30+). One subject carried a DED diagnosis and fifteen (15%) reported suffering from "dry eye symptoms" in the ocular history. Overall,

self-reported histories revealed a healthy study population; 95% and 86% of all subjects had no ocular and medical history, respectively, and 67% of subjects had not taken any medication (e.g., nasal or inhaled steroids, antihistamines, or antidepressants) in the past 30 days. The distribution of age and race, stratified by oral contraceptive pill use and by contact lens wear, is summarized in Table 1.

Women in the OCP+ group were on average 2.1 years older ($p<0.005$) than women in the OCP- group. There were significant differences in the race distribution between the OCP+ and OCP- groups. ($p=0.03$). Notably, there were more Caucasians and less African-American women in the OCP+ group. However, upon further stratified sub-analysis, race did not appear to be responsible for differences in scores between the OCP groups. The women in the OCP+ groups were taking nineteen different brands of OCP; eighteen were combined estrogen-progesterone pills and one was progesterone-only. The six forms of progesterone were desogestrel, levonorgestrel, norethindrone acetate, drospirenone, norgestimate and ethynodiol diacetate. The average menstrual cycle length in the OCP- group was 29.1 ± 2.6 days.

There were no significant age differences between women who had worn contact lenses in the past 30 days (CL30+) and those who had not (CL30-). However, there were significantly more Caucasian and Asian women and less Black women in the CL30+ group ($p=0.002$). Upon further analysis, race did not appear to be responsible for differences in the CL30 groups. Sixty percent of the CL30+ subjects and 45% of the CL30- subjects were taking OCPs.

Overall, OSDI correlated well with both SANDE severity (data not shown; $\rho=0.53$, $p<0.0001$) and frequency (data not shown; $\rho=0.63$, $p>0.0001$). However, OSDI and tear osmolarity were not correlated ($\rho=-0.03$, $p=0.80$).

### Oral contraceptive pill use

Among the 29 $OCP^-$ subjects with measurements taken from both the follicular and luteal phase, the mean values for the assessments of dry eye disease were slightly worse during the follicular phase, but none of the differences were statistically significant (Table 2). Therefore, only measurements from the initial study visit were used for all other analyses. Table 3 summarizes the results for each group. Between the OCP+ and OCP- subjects, the SANDE severity and frequency scores were significantly worse in the OCP+ subjects ($p=0.01$ and 0.007, respectively).

However, there were no significant differences in tear osmolarity and OSDI ($p>0.25$ for both). Similarly, the proportion of subjects with tear osmolarity >308 mOsm/L was similar in the OCP+ (27%) and OCP- (24%) groups (data not shown; $p=0.78$). The amount of estrogen in the OCPs (ranging from 0.020 mg to 0.035 mg) was analyzed as a continuous variable using Spearman correlations. Estrogen dose did not correlate with tear osmolarity ($\rho=-0.09$ $p=0.52$) or symptom scores (OSDI $\rho=0.04$, $p=0.78$; SANDE severity $\rho=0.09$, $p=0.50$; SANDE frequency $\rho=-0.03$, $p=0.82$).

### Contact lens wear

Within the CL30+ group, nearly all (98%) wore soft contact lenses. Thirty-eight (79%) had “consistent” (>50 hours per week) or “moderate” (30-50 hours per week) contact lens wear on average and the mean time since first contact lens wear was 10.83 ± 3.97 years for these 38 subjects. Thirty-four (89%) of the 38 subjects in this group were wearing contact lenses during the study visit ($CL_{visit+}$). Table 3 provides a summary of the measurements of dry eye for the different contact lens groups. Among CL30+, SANDE scores for severity and frequency were significantly higher ($p=0.002$ and $p<0.0001$, respectively) but tear

osmolarity and OSDI score were not. Among $CL_{visit}$+ subjects, the mean tear osmolarity and SANDE scores were significantly higher than among $CL_{visit}$- subjects

### Oral contraceptive pill use and contact lens wear

When women were classified simultaneously by OCP use and contact lenses wear within the past 30 days, women with both factors had the highest median score on the SANDE severity and frequency questions, those with neither had the lowest and those with one factor had intermediate values (Table 4; $p<0.001$ for both SANDE scores). Subjects with both OCP and contact lens wear within the past 30 days had the highest median OSDI score of all groups ($p=0.015$). Tear osmolarity did not differ among the groups ($p=0.403$ by ANOVA; $p=0.592$ by Kruskal-Wallis test).

## DISCUSSION

### Sex hormones and dry eye

Sex hormones appear to influence structural and functional aspects of the eye and contribute to ocular surface disorders such as DED and Sjögren's syndrome.[3,5] The female menstrual cycle provides an opportunity to study changes resulting from the ebb and flow of sex hormones such as estrogen and progesterone. Typically, in a normal menstrual cycle, the follicular phase (day 1-14) is marked by low levels of progesterone and a gradual rise in estrogen, ovulation occurs mid-cycle (day 13-16) after the estrogen peak, and the luteal phase is marked by rising progesterone levels and a less steep rise in estrogen levels. Hormonal contraceptives, most commonly combined synthetic estrogen and progesterone, work by inhibiting ovulation.[21]

Studies evaluating ocular changes over the menstrual cycle are few in number and most draw findings from a limited number of subjects. [6,22-25] A recent study analyzing dry eye symptoms over the normal menstrual cycle reported worsening of ocular surface parameters related to eye dryness and inflammation during the follicular phase, especially in dry eye patients; however, subjective dry eye symptoms increased during the luteal phase, which they attributed to the 'premenstrual syndrome' (PMS).[23] Central corneal thickness appears to increase around ovulation and the end of the menstrual cycle, both of which occur after estrogen peaks.[6,24]

While some authors have found subjective dry eye symptoms and tear production and stability to be significantly related to hormonal fluctuations in the menstrual cycle, our study found no significant differences between the follicular and luteal phases of the menstrual cycle.[23] Tomlinson et al likewise found no significant differences in tear film parameters and dry eye symptoms between the follicular and luteal phases in their small study population.[8] The follicular and luteal study visits for control subjects occurred at different points across the respective phases and hence, data may have been captured from a continuum of hormonal fluctuations as opposed to hormonal peaks and troughs. Furthermore, the normal menstrual cycle exhibits variations in cycle length.[26] Relative estrogen and progesterone levels were based on normal menstrual cycle physiology; we did not perform serum hormone testing to confirm levels.

### Effect of oral contraceptive pill use on dry eye

In this study, neither OCP use nor estrogen dose of OCPs appeared to have a meaningful effect on tear osmolarity and dry eye symptoms as measured by OSDI. However, OCP use was associated with significantly higher SANDE scores as well as a greater number of subjects reporting dry eye symptoms in the ocular history. Though the OCP+ group was significantly older than the OCP- group, the age difference is unlikely to account for

differences in the SANDE scores. For the most part, dry eye prevalence increases with age, but most large population-based studies of dry eye have been in the over 50 population and few have examined prevalence in individuals under 40 years of age.[2] Race differences also do not appear to be responsible for differences in scores. Though the effect of race or ethnicity on DED is unclear, limited data in the literature suggests that the prevalence of dry eye symptoms among women is higher in Hispanics and Asians when compared to Caucasians.[27]

Our finding that OCPs did not significantly affect tear osmolarity is consistent with other reports in the literature. For example, other authors have reported no difference in Schirmer I and tear break-up time (TBUT) results between women using OCP and controls.[7] In addition, Tomlinson et al found no significant differences in tear osmolality, pre-rupture phase time, evaporation rate, turnover rate, or volume between OCP users and controls or between the follicular and luteal phases.[8]

### Effect of contact lens wear on dry eye

While the exact mechanism of contact lens-associated dry eye is unclear, contact lenses have been proposed to cause inflammation, meibomian gland dysfunction, corneal hyposensitivity, or a combination which results in decreased tear production, increased evaporation, and subsequent tear film hyperosmolarity.[15,28-33]

Although 48% of CL30+ subjects compared to 22% of CL30- subjects reported experiencing dry eyes in the past 30 days (data not shown; p=0.01) and CL30+ subjects reported significantly higher SANDE scores, the OSDI and tear osmolarity measurements did not detect a significant difference. Only 25% of the CL30+ subjects and 29% of $CL_{visit}$+ subjects had dry eye symptoms characterized by an OSDI score >13, the cutoff for mild dry eye.[44] This rate of dry eye is much lower than the 50-80% reported by studies using self-reported dry eye surveys such as the Contact Lens Dry Eye Questionnaire.[9,10,15,34] However, in two of these survey studies, the mean age of contact lens wearers was approximately 13 years older than subjects in our study.[9,10] Since dry eye prevalence increases with age, this could partially explain the difference in dry eye rates between the current study and earlier studies.[2] Designed as a disease specific questionnaire, the OSDI would be expected to capture complaints of dry eye (i.e., eyes that feel gritty, painful or sore) associated with contact lens wear. [19]

Earlier studies characterizing tear osmolarity require contact lenses to be removed prior to the measurement; we chose to capture real-time tear osmolarity measurements during contact lens wear and did not ask subjects to remove their contact lenses at testing.[15,17,18,28,29,35] Tear sampling was performed at the lateral meniscus and care was taken not to perturb the contact lens or induce reflex tearing. We found that the mean tear osmolarity was the same for all subjects not wearing contact lenses during the study visit, regardless of their history of contact lens wear in the past 30 days. Subjects who were wearing contact lenses during the study visit had a mean tear osmolarity 5.8 mOsm/L higher than either the CL30- or CL30+/$CL_{visit}$- groups (p=0.054), thus supporting the notion that the presence of contact lenses alters tear film physiology.

### Effect of oral contraceptive pill use and contact lens wear on dry eye

Though median OSDI scores were not significantly higher for subjects with OCP use or contact lens wear within the past 30 days, OSDI was significantly higher in subjects with both factors. This is consistent with the belief that oral contraceptives may increase contact lens intolerance, an idea supported by an early paper demonstrating that contact lens wearing females with OCP use are almost twice as likely to report dry eye symptoms as

contact lens wearing females without OCP use.[11] However, previous studies examining this relationship were conducted more than three decades ago and therefore, do not reflect the effects of modern contact lenses and OCPs.[11-14] The overall lack of correlation between OSDI and tear osmolarity in this study adds further evidence supporting the poor relationship between dry eye signs and symptoms.[36]

### Limitations

Potential limitations of the study include the fact that we did not control for different OCP types, contact lens materials, contact lens wear patterns and duration, diurnal variations, climate, and environmental stress. In addition, findings from a recent study indicate that TearLab osmolarity measurements have wide variation and recommended averaging three consecutive measurements to obtain a more reliable value.[37] In our study, tear osmolarity was checked only once in each eye at each study visit. Future studies, which use three consecutive measurements per eye, may yield results different from ours.[38] Finally, this study was designed to assess subjective symptoms and one objective dry eye marker—tear osmolarity, which has been reported to exhibit better sensitivity and/or specificity as well as less variability than common dry eye tests such as corneal staining, meibomian gland grading, TBUT, and Schirmer's.[17,38] As such, we did not perform a comprehensive clinical exam to assess DED status or sub-type during the study visits.

### Conclusions

The evidence surrounding the role of sex hormones in dry eye disease is unclear and at times, contradictory. In this study, we hoped to better elucidate the effect of sex hormones in dry eye disease by studying differences in 1) the normal menstrual cycle phases of healthy young women and 2) women using and not using OCPs. We did not find significant differences in tear osmolarity among any of our comparison groups. Interestingly, by not excluding contact lens wear, our results demonstrated a possible synergistic effect of OCP use and contact lens wear in exacerbating dry eye symptoms. Further studies need to be performed to better characterize this relationship and to study the utility of tear osmolarity measurements in clinical practice.

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**Table 1**

Characteristics of subjects

| | | Current OCP* Use | | | Contact Lens Use (within the last 30 days) | | |
|---|---|---|---|---|---|---|---|
| | **All** | **Yes** | **No** | **p-value** | **Yes** | **No** | **p-value** |
| **N** | **97** | **52** | **45** | | **48** | **49** | |
| **Age, years (mean±SD)** | 26.0 ± 3.7 | 25.1 ± 3.1 | 27.2 ± 4.1 | 0.005 | 25.6 ± 2.9 | 26.5 ± 4.4 | 0.21 |
| **Race, (%)** | | | | | | | |
| **Caucasian** | 56.7 | 67.3 | 44.4 | | 60.4 | 53.1 | |
| **Asian** | 16.5 | 17.3 | 15.6 | 0.03 | 25.0 | 8.2 | 0.002 |
| **Black** | 22.7 | 11.5 | 35.6 | | 8.3 | 36.7 | |
| **Hispanic** | 4.1 | 3.9 | 4.4 | | 6.3 | 2.0 | |
| **OCP ethinyl estradiol, (%)** | | | | | | | |
| **≤0.025 mg** | 29.9 | 55.8 | -- | NA | 33.3 | 24.5 | |
| **0.030 mg to 0.035 mg** | 23.7 | 44.2 | -- | | 27.1 | 20.4 | 0.33 |
| **Not applicable** | 46.4 | -- | 100.0 | | 39.6 | 55.1 | |

*OCP denotes oral contraceptive pill

## Table 2

Differences, follicular minus luteal phase measurements, in dry eye assessments among subjects not taking oral contraceptives

| | Difference Mean ± SD | p-value |
|---|---|---|
| Tear osmolarity (mOsm/L) | 2.3 ± 15.9 | 0.43 |
| Ocular Surface Disease Index score | 0.4 ± 5.8 | 0.74 |
| Symptom Assessment iN Dry Eye severity score | 0.7 ± 8.8 | 0.69 |
| Symptom Assessment iN Dry Eye frequency score | 1.2 ± 8.7 | 0.48 |

**Table 3**

Dry eye assessment scores by oral contraceptive pill use and by contact lens wear

| | | | | Symptom Assessment iN Dry Eye | |
|---|---|---|---|---|---|
| | | Tear Osmolarity (mOsm/L) | Ocular Surface Disease Index | Severity | Frequency |
| | N | Mean± SD | Median (25%, 75%) | Median (25%, 75%) | Median (25%, 75%) |
| **All** | 97 | 301.6 ± 14.2 | 4.5 (0.0, 10.4) | 7.0 (1.0,19.0) | 12.0 (3.0, 27.0) |
| **OCP use** | | | | | |
| Yes | 52 | 302.8 ± 14.4 | 5.3 (1.0, 14.6) | 11.0 (2.0, 28.0) | 17.5 (7.0, 29.0) |
| No | 45 | 300.2 ± 13.9 | 4.2 (0.0, 7.5) | 3.0 (0.0, 12.0) | 6.0 (1.0, 23.0) |
| Difference 95% CI* | | 2.6 [-3.0, 8.3] | 1.1 [-2.1, 5.2] | 8.0 [2.5, 19] | 11.5 [2.5, 19] |
| p-value** | | 0.37 | 0.26 | 0.01 | 0.007 |
| **Contact lens wear (last 30 days)** | | | | | |
| Yes | 48 | 303.7 ± 16.6 | 4.6 (1, 13.5) | 12.5 (6.5, 32.5) | 21.0 (9.5, 33.0) |
| No | 49 | 299.6 ± 11.2 | 4.5 (0.0, 8.3) | 2.0 (0.0, 11.0) | 6.0 (1.0, 15.0) |
| Difference 95% CI* | | 4.2 [-1.5, 9.8] | 0.04 [-2.1, 4.2] | 10.5 [6, 17] | 15.0 [9, 22] |
| p-value** | | 0.15 | 0.52 | 0.0002 | <0.0001 |
| **Contact lens wear (today)** | | | | | |
| Yes | 34 | 305.4 ± 17.5 | 5.3 (2.1, 14.6) | 14.0 (7.0, 33.0) | 22.5 (10.0, 40.0) |
| No | 63 | 299.6 ± 11.7 | 4.2 (0.0, 10.4) | 2.0 (0.0, 13.0) | 7.0 (1.0, 21.0) |
| Difference 95% CI* | | 5.8 [-0.03, 11.7] | 1.1 [-1.5,7.3] | 12.0 [8, 30] | 15.5 [8.5, 26.5] |
| p-value** | | 0.054 | 0.38 | 0.0002 | 0.0002 |

*95% confidence intervals (CI) calculated from the standard error of the difference for tear osmolarity, and from the 2000-times bootstrapped bias-corrected percentiles for others

**p-values calculated by t-test for tear osmolarity and by Wilcoxon rank sums tests for others

**Table 4**

Dry eye assessment scores by oral contraceptive pill use and contact lens wear

| OCP Use/Contact Lens Wear | N | Tear osmolarity (mOsm/L) Mean± SD | Ocular Surface Disease Index Median(25%, 75%) | Symptom Assessment iN Dry Eye | |
|---|---|---|---|---|---|
| | | | | Severity Median(25%,75%) | Frequency Median(25%,75%) |
| **Yes/Yes** | 29 | 303.8 ± 17.1 | 8.3 (4.2, 14.6) | 18.0 (7.0, 36.0) | 27.0 (20.0, 53.0) |
| **No/Yes** | 19 | 303.5 ± 16.1 | 4.2 (0.0, 6.3) | 9.0 (1.0, 15.0) | 10.0 (2.0, 25.0) |
| **Yes/No** | 23 | 301.6 ± 10.3 | 2.1 (1.0, 10.4) | 4.0 (1.0, 12.0) | 7.0 (2.0, 14.0) |
| **No/No** | 26 | 297.8 ± 11.8 | 5.4 (2.1, 8.3) | 1.0 (0.0, 10.0) | 4.0 (1.0, 18.0) |
| **p-value** | | 0.403 | 0.015 | <0.001 | <0.001 |