## ORIGINAL ARTICLE

# TEAR VOLUME AND STABILITY ACROSS THE PHASES OF THE MENSTRUAL CYCLE AMONG WOMEN IN BENIN CITY, NIGERIA.

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## ABSTRACT

**Background:** The menstrual cycle has been reported to affect many physiological processes. While the effects of the menstrual cycle on ocular parameters have been studied extensively in Caucasian women, not much is known about its effect on tear volume and stability in Nigerian women. **Objective:** To investigate the changes in tear volume and stability during the different phases of the menstrual cycle in Nigerian women. **Methods:** A longitudinal study of one hundred healthy women with a regular cycle of 26 to 29 days was carried out. The women were between 20 to 35 years old with mean age of 30 ± 2.1 years. Tear volume was measured by the Schirmer's tear test, while tear stability was measured by the non invasive tear break up time (NITBUT**). Results:** The difference in mean tear volume across the phases of menstrual cycle was statistically significant (p = 0.001). Tear volume reduced during ovulation and rose again during the luteal phase. This difference was statistically significant (p=0.04). The difference in tear volume between the follicular phase and the luteal phase was not significant (p=0.3). Increase in mean tear stability between the follicular and ovulatory phases was marginally statistically significant (p=0.046). However, there was no statistically significant difference between the ovulatory and luteal phases (p=0.44). **Conclusions:** The findings of this study suggest that hormonal variation during the different phases of the menstrual cycle influence tear volume and tear stability in healthy young women of reproductive age. These changes may be clinically significant particularly in contact lens wearers where fluctuations in ocular parameter may alter the contact lens fit, leading to a possible change in comfort and reduced visual acuity.

**KEYWORDS:** Tears, menstrual cycle, hormones, follicular, luteal.

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## INTRODUCTION

For most women, the menstrual cycle is an integral part of their lives and tends to affect many physiological processes, and exert a significant influence on variation in ocular functions[1,2]. Various authors[3-5] have investigated the influence of the menstrual cycle on various ocular and visual parameters. While some[5-8] had identified a protective role of the female sex hormones during the menstrual cycle on some ocular conditions such as dry eyes, others[9-11] had reported no effects on ocular or visual parameters.

Tears lubricate, nourish and protect the eyes from dust, irritants and infections[12]. Tears also keep the surface of the eye optically clear and smooth. The imbalances in the composition of tears, may either decrease tear production or encourage excessive tear evaporation. This situation can lead to tear film dysfunction, usually diagnosed as "dry eye"[13-15]. The tear film is a complex structure composed of tears, mucin and lipids. When the tear film becomes insufficient to support the surface of the eyes due to a lack of production of tears or a decrease in stability of tears, dry eye syndrome occurs[16,17]**.** The tear film coating the eye, known as the pre corneal film, has three distinct layers, from the most outer surface lipid layer to the middle aqueous layer and the innermost mucous layer[18].

Deficiency of any of the three layers of the tear film can lead to a 'dry eye' condition, causing anything from mild eye irritation to severe pain[19]. Interestingly, in some cases excessive tearing or watering of the eyes can be a symptom of a dry eye condition. This is because when, for whatever reason, there is an inadequate normal tear layer on the eye, irritation results[20,21]. This causes an overproduction of the lacrimal gland and a flooding of lacrimal fluid into the eye[22,23].

Dry eye is a very common condition among women. Women are said to be twice more likely to have dry eyes than men[23]. There are no readily accessible prevalence studies done in Nigeria, however, the prevalence of Dry eye syndrome (DES) has been reported to increase with age from 5.7% among women less than 40 years old to 9.8% der among women greater or equal to 75 years old [24]. Moss et al[25] reported a prevalence of 8.4% in postmenopausal subjects younger than 60 years to 19% in those older than 80 years. Research[8-11,21] suggests that dry eyes may be related to women's monthly cyclical changes in hormone levels, in particular, related to estrogen levels. Studies[26-28] suggest that the estrogen peak which occurs during the follicular phase is associated with impairment of tear production resulting in ocular dryness and inflammation.

The endocrine system exerts significant influences on the physiology and pathophysiology of the lacrimal gland[3, 4]. Androgens, estrogens and progestin have been identified in the tear film and their levels in the tears appear to correlate with those of the serum[9, 22]. Receptors for androgens, estrogens, progesterone and prolactin have been found in several ocular tissues of rats, rabbits and humans. These hormones regulate the immune system, secretary functions of lacrimal and the meibomian glands[3, 4, 23]. Thus the eye is a target organ for sex hormones. Rocha et al[24] reported that androgen, estrogen and progesterone receptors mRNAs were present in the epithelial cells of the lacrimal gland, meibomian gland, lid, palpebral and bulbar conjunctivae, cornea, uveal body, lens, and retina of humans. These observations demonstrate that sex steroid receptors mRNAs exist in a variety of ocular tissues. It has been suggested that these receptors in the eye might be target sites for androgens, estrogen and progestin; and also be susceptible to administered topical and systemic hormonal contraceptives[22]. Several authors[3, 4, 9] reported that these sex steroids (i.e. androgens, estrogens and progestin)

modulate the structural characteristics, functional attributes and pathological features of ocular tissues. These observations account for the gender-related differences in dry eyes[3].

Meibomian gland function is critically important in maintaining the health and integrity of the ocular surface[29]. This gland through its production and secretion of lipids, promotes the stability, and prevents the evaporation, of the tear film. The lacrimal gland promotes spreading of the tear film, the control of infectious agents and promotes osmotic regulation. This layer coats the aqueous layer, provides a hydrophobic barrier that evaporates and prevents tears spilling onto the cheek[24, 30]. Sex steroid hormones have been implicated in the structural and functional activities of this gland[31].

The purpose of this work was to determine if the cyclical variation in hormone levels in the different phases of the menstrual cycle has any influence on tear volume and tear stability in young Nigerian women of reproductive age.

## MATERIALS AND METHODS

This study was part of a research thesis done in the Department of Physiology, University of Benin for the award of the Doctor of Philosophy (PH.D) degree. The thesis was on ocular changes in pregnant, premenopausal and postmenopausal women with participants recruited from the outpatient clinics of the University of Benin Optometry Clinic and the Department of Obstetrics and Gynaecology, University of Benin Teaching Hospital, Benin City. This present study explored the effects of the different phases of the menstrual cycle on tear volume and stability among the premenopausal women and was independent of the other aspects of the thesis. This was a longitudinal study of one hundred menstruating women, aged 20-35 years, who visited the University of Benin Optometry Clinic as outpatients.

The women were selected by systematic random sampling using the list of patients attending the clinic as a sample frame. To be included, the women had to have regular menstrual cycles of 26-29 days. Excluded from the study were women who had irregular menstrual cycles, lid-gland dysfunction (blepharitis) ocular surface abnormalities and any other obvious ocular pathology. Women with history of systemic disease, ocular surgery, laser therapy and on any medications were also excluded as were contact lenses wearers, pregnant women, smokers, women under topical eye drops, and post-menopausal women. Exclusion criteria also included use of oral contraceptive pills, history of hypertension, cardiovascular abnormalities, diabetes mellitus and any ocular infections that could affect tear volume or stability. Ethical approval was obtained from the University of Benin Teaching Hospital Research Ethics Committee and informed consent from the women. Confidentiality was ensured by avoiding the use of identifiers of patients during data collection, using codes instead.

The women were screened for systemic and ocular diseases. Monocular direct ophthalmoscopy was done to rule out any diseases of the posterior segment. The women were examined for changes in tear volume and tear stability during the first

five days of the cycle (follicular phase), on the 13th to 15th day (ovulatory phase) and during the last five days (luteal phase) of their menstrual cycle. Only women having a regular 26 to 29 day cycle length were examined. The women were examined for 3 consecutive cycles and the mean value was recorded.

The findings of the various tests carried out and their implications were explained to the participants and they were counselled on appropriate measures or treatment necessary, where anomalies were found and on general eye care habits. All participants in this study had a free comprehensive ocular examination, besides that needed for their presenting complaints.

**Measurement of tear secretion**

Schirmer's tear test, which measures tear volume and the non invasive tear break up time (NITBUT) which measures tear stability were carried out on the women. The Schirmer's test strip was used for this test. This is a 35mm by 5mm filter paper that is calibrated in mm and is used to measure the amount of tears produced over a period of 5 minutes. The patient was comfortably seated on a chair in a room with ambient illumination. The fan and/or air conditioning system was turned off to avoid environmental interference with the Schirmer's tear test values. With the subject looking up, the lower eyelid of the right eye was pulled down and the tip of the Schirmer's test strip was inserted at the junction of the middle and lateral third of the lower eyelid of right eye with care so as not to touch the cornea and elicit a tearing response. With the Schirmer's test strip in place in the right eye, the stop watch was set. After five minutes, the Schirmer's test strip was carefully removed from the eye and the amount of wetting read off. Values less than 10mm in 5 minutes are indicative of poor tear production or volume.

**Measurement of tear stability**

The noninvasive tear break up time was done with a hand held keratoscope. It is noninvasive because the eye is not touched. Measurement is achieved by observing the breakup of keratometer mire (the reflected image of keratometer grid). The clinician focuses and views the crisp mires, and then records the time taken for the mire image to break up (NITBUT). NITBUT measurements are longer than fluorescein break up time. NITBUT values of < 10 seconds are consistent with dry eyes. NITBUT are considered to be more patient-friendly, repeatable and precise.

**Sample size calculation**

This was done using the formula[32]

$$n = \frac{Z^2 P(1-P)}{d^2}$$

n= sample size

Z=Z statistic for a level of Confidence of 95% (1.96)

P= maximum reported prevalence or proportion of dry eyes (5.7%)[25] =0.057

d= Precision desired (5%, d=0.05)

Therefore:

$$n = \frac{1.96^2 \times 0.057 (1-0.057)}{0.05^2} = 82$$

This implied that a minimum sample size of 82 was required; hence the decision was taken to recruit 100 women to enhance the power of the study.

**Statistical Analysis**

Data was analyzed with GraphPad InStat (Statistical graphics incorporation, USA). Comparison of data among the different

phases was performed with one-way analysis of variance (ANOVA), and test between phases with the student's t-test.

## RESULTS

Difference in mean tear volume across the phases of menstrual cycle was statistically significant, p = 0.001. Tear volume reduced during ovulation and rose again during the luteal phase. This difference was statistically significant, (p=0.04). The difference in tear volume between the follicular phase and the luteal phase was however not significant, p=0.3 (Table 1).

Increase in mean tear stability during the follicular and ovulatory phases of the menstrual cycle was statistically significant, p=0.046. However, there was no statistically significant difference between the ovulatory and luteal phases, p=0.44. This is shown in Table 2 and Figure 2.

**Table 1: Changes in Tear Volume during the Menstrual Cycle**

| Statistics | Follicular | Ovulation | Luteal |
|---|---|---|---|
| MTV(mm) | 24.76 | 17. 54 | 21.14 |
| SD | 8.91 | 9.42 | 10.60 |
| SEM | 1.26 | 1.33 | 1.50 |
| Minimum | 12.00 | 11.00 | 12.00 |
| Median | 35.00 | 14.50 | 20.00 |
| Maximum | 35.00 | 35.00 | 35.00 |
| **N** | **100.00** | **100.00** | **100.00** |

MTV=Mean tear volume, SD=Standard deviation, SEM=Standard error of mean, N=Sample size

**Table 2: Changes in Tear Stability during the Menstrual Cycle**

| Statistics | Follicular | Ovulation | Luteal |
|---|---|---|---|
| MTS (sec) | 13.70 | 16.32 | 17.44 |
| SD | 7.76 | 10.03 | 10.79 |
| SEM | 1.10 | 1.42 | 1.53 |
| Minimum | 5.00 | 7.00 | 7.00 |
| Median | 13.00 | 13.00 | 17.00 |
| Maximum | 59.00 | 60.00 | 68.00 |
| **N** | **100.00** | **100.00** | **100.00** |

MTS=Mean tear stability

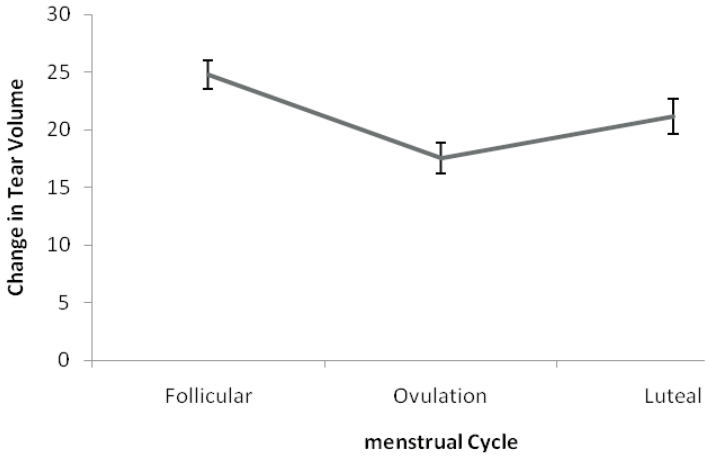


**Figure 1: Changes in Tear Volume during the Menstrual Cycle**

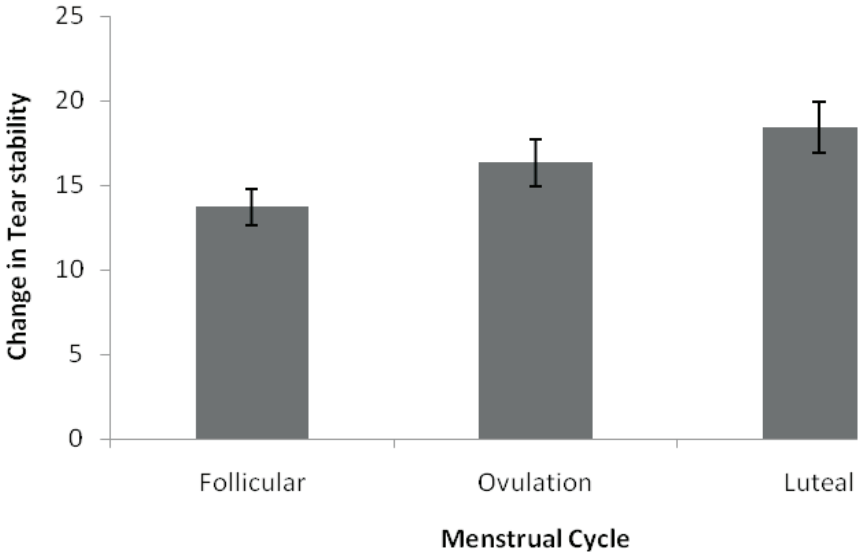


**Figure 2: Changes in Tear Stability during the Menstrual Cycle**

## DISCUSSION

The cyclical variation in ovarian hormonal levels during the menstrual cycle is associated with transient ocular changes. In this study, it was observed that there was increase in tear stability across the three phases of the menstrual cycle, with the highest occurring during the luteal phase. The difference in tear stability between the follicular and ovulatory phases was significant, while that between the ovulatory and the luteal phase was not statistically significant. This study agrees in part with the Nigerian study by Iwaugwu[6], which reported a significant increase in tear stability in the follicular and ovulatory phases, but no significant difference between the ovulatory and luteal phases. This result is also consistent with studies in developed countries [14, 15] that reported tear stability to be significantly higher in ovulatory and luteal phases. Similarly, our findings agree with the results of the work by Nancy[11] which reported an increase in tear stability in the follicular stage and concluded that there was no significant difference in stability during the ovulatory and luteal phases. The findings are also consistent with that of Patel et al[15], who concluded that tear production and stability are related to hormonal fluctuations in menstrual cycle. However, the results obtained from this study do not agree with the findings of Tomlinson et al[18] who reported no effect on tear stability induced by either use of oral contraception or by normal cyclic hormonal variations. While the methodologies in this study and that by Tomlinson et al[18] are similar, Tomlinson et al[18] recruited only 18 cases and controls. It is, therefore, likely that the differences in sample size, sampling techniques and racial constitution of the two studies explain the differences in findings.

A major reason for changes in tear stability during the menstrual cycle has been reported to be the effects of estrogen on the meibomian gland. The meibomian gland secrets the tear film's lipid layer and is very important in preventing the evaporation of the tear film and maintaining its stability, thus it is likely that an increased hormonal influence on the functions of the meibomian gland would cause an improvement in tear stability and a decreased hormonal influence on the meibomian gland will cause a decline or deterioration in tear stability[15,16].

A marked reduction in tear volume was recorded at ovulation. This increased significantly during the luteal phase. There was significant difference in mean tear volume between ovulatory and luteal phase. Estrogen and progesterone are the hormones secreted at these phases and are suspected to be the cause of increase in tear volume.Studies[17,18] have suggested that progesterone may help protect against dry eye condition. Tear stability was significantly high in the luteal phase meaning a less likelihood of dry eye condition. Previous studies[14-16] have suggested that estrogen has an effect on the lacrimal glands, meibomian glands, eyelids, palpebral and bulbar conjunctiva and the cornea, this indicates that changes in tear stability may result from a complex hormonal influence. There is the probability that estrogen could be acting directly on the meibomian gland and influencing its secretions. The estrogen peak which occurs during the follicular phase is associated with impairment of tear production[20].

Observations in patients taking anti androgen therapy are consistent with the hypothesis that androgen deficiency is a

critical etiological factor in the pathogenesis of meibomian gland dysfunction and evaporative dry eye[19,20]. In further support of this hypothesis are the findings that reduced serum levels of testosterone are more prevalent in women with dry eye and correlate with the subjective severity of ocular symptoms, serum levels of total androgens decline during menopause and aging in both sexes and these time periods coincide with an increased appearance of meibomian gland dysfunction and dry eye[13-15].

As an additional consideration, this apparent inter relationship between androgen deficiency, meibomian gland dysfunction, and dry eye might help to explain why systemic androgen administration has been reported to alleviate the signs and symptoms of dry eye. Given these results, it is possible that efforts directed at alleviating this endocrine imbalance like topical application of androgens may prove beneficial as a treatment for meibomian gland dysfunction and the associated evaporative dry eye, in androgen-deficient individuals[22,24].

**Limitations of the study**

The limitations of this study include the fact that the authors did not find any prevalence studies on dry eye syndrome in Nigerian women hence the calculation of sample size was done using prevalence rates reported in Caucasian women. The implication is that there is a possibility that if prevalence rates in Nigerian women are different and possibly higher, the sample size utilized in this study may have been inadequate to give power to the study. In addition, the study assumed that the women ovulated between the 13-15$^{th}$ days of their cycle. There is a possibility that some ovulated earlier or later. While the authors recognized that it would have been more appropriate to confirm ovulation using hormonal assays, this requires collection of blood samples which may not have been acceptable to many of the women presenting for outpatient consultations making participant recruitment difficult. In addition, the results of the assays are not usually immediately availability and this would have increased both the cost and duration of the project. It is hoped that our findings will stimulate further studies including those in which ovulation is definitively confirmed.

## CONCLUSION

The findings of this study suggest that hormonal variation that occur during the different phases of the menstrual cycle influence tear volume and tear stability in healthy young women of reproductive age. These changes may be clinically significant particularly in contact lens wearers where fluctuations in ocular parameter may alter the contact lens fit, leading to a possible change in comfort and reduced visual acuity. ▬

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