Ferning Test Evaluation on Combined Oral Contraseptive User as a Predictor Factor for Dry Eye Syndrome

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Abstract. *Purpose:* To evaluate ferning test on the combined oral contraceptive user (COCs) as a predictor factor for Dry Eye Syndrome (DES)

Method: This was an observational analytic design with a cross sectional approach. The assessed of this study were ferning test examination using electron microscope. Statistical analysis used was chi square test and Mann Whitney test.

Result: Most subjects were aged 36-50 years old, the average use of COCs was 11,52 years, the shortest use was 1 years and the longest use was 30 years. From the chi square test, there was a significant difference between those who used COCs and who did not use COCs on the ferning test (p<0,001) prevalence ratio value of 9 times (95% Cl 4,182-19.360) and TBUT (p<0,001) prevalence ratio value of 17 times (95 % Cl 5.603-51,579), sensitivity and specificity value of ferning test were 92,6% and 85,7%.

Conclusion: This study showed that COCs had prediction factor of 9 times greater in suffering DES compared to those who did not use combined oral contraceptive. Ferning test could be used as an indicator in the DES examination.

Keywords: Ferning Test, Dry Eye Diseases, Dry Eye Syndrome, Combined Oral Contraceptives

Introduction

Dry Eye Syndrome (DES) based on Tear Film Ocular Surface Dry Eye Workshop II (TFOS DEWS II) in 2017 is a multifactorial disease on the surface of the eyeball that represents homeostasis of tear layer dissatisfaction, and symptoms of tear stability and hyperosmolarity, breakdown to the eye surface, and abnormality neurosensory (Craig et al., 2017).

A multifactorial disease of the tear film and ocular surface that causes impaired ocular function and quality of life. The prevalence DES in Indonesia is estimated to be around 27.5% of the total population in Indonesia and increasing related to age. The most prevalent in women, the incidence rate at 30-60 years of age is around 10% and 15% at older ages (65 years) (Lemp & Foulks, 2007; Galor et al., 2011; Gayton, 2009; Badan Kependudukan dan Keluarga Berencana Nasional, 2014).

In several studies conducted on women of reproductive age regarding the effect of oral contraceptives on dry eyes, oral contraceptives are an important cause of androgen deficiency which can reduce mucin production and sensation of objects so that the risk of dry eyes in women using contraceptive pills is increased (Cantor et al., 2020; Sharma et al., 2018; Moschos & Nitoda, 2017; Lemp, 2013; Masmali et al., 2014; Schaumberg et al., 2003; Rolando et al., 2001; Schaumberg, Sullivan, & Dana, 2002; Sing, Nagpal, & Tyagi, 2018; Chen et al., 2013; Skalicky, 2016). According to Schaumberg et al. (2003), sex hormones play a role in the functional structure of the ocular tissue which is the cause of the pathogenesis of DES. Likewise with Sullivan et al. (2017), oral contraceptives can cause changes in the quality of tears, namely reduced mucin production, causing a foreign body sensation in the eye. Tomlinson et al. (2001)

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found no significant differences in symptoms, changes in the structure of the tear film, evaporation, volume, and tear protein levels in women who took and did not take contraceptive pills. This is in line with Chen et al. (2013) which in their study also did not find a significant difference in tear osmolarity and no dry eye symptoms were found between women who took contraceptive pills and those who did not take contraceptive pills.

Knowledge of biochemical analysis and components of the tear film is important to diagnosis and implementation of DES. TBUT is an examination to assess the instability of tear film, another less well-known test for assessing the composition and quality of the tear film is ferning test. It is an inexpensive diagnostic test that can be carried out in handling suspicion in DES and can be done in a clinical environment to assess the tear film, especially the mucin layer. The sample of the tear fluid on a clean slide that will produce a crystallization pattern that is typical with evaluation under an electron microscope (Chen et al., 2013; Skalicky, 2016; Tsubota et al., 2017; Norn, 1994; Riordan-Eva & Whitcher, 2007). Sing, Nagpal, and Tyagi (2018) in their research concluded that the ferning test is an inexpensive and simple test that can assess the stability of the tear film, especially the mucin layer. This is comparable to the research of Masmali et al. (2014), which states that the ferning test can assess the eye dry, the results of which correlate with clinical symptoms, and have good potential for biochemical mechanisms affecting DES.

Based on the background above, the researcher was interested in conducting the research on evaluating the ferning test as a predictor factor for the occurrence of DES in COCs.

Materials and Methods

This cross-sectional and observational analytic study was approved by Health Research Ethical Committee of Medical Faculty, University of Sumatera Utara (Registration number: 698/ KEP/USU/2020). This study was conducted at the External Disease and Cornea Division of Opthalmology Department - University of Sumatera Utara General Hospital and satellite hospital from September-December 2020. The study population was women who used COCs and did not use the COCs. All participants fill out informed consent, and all methods comply with the Helsinki Declaration. Inclusion criteria was women aged ≥ 18 years - 50 years who take COCs. Exclusion criteria were patients with infectious diseases of the ocular surface and eyelids, glaucoma patients who have received medical therapy and surgery, cataract patients who have undergone cataract extraction surgery, patients wearing contact lenses, use of systemic drugs that cause dry eyes, have a habit of smoking and drinking alcohol, patients with diabetes, hepatitis, thyrotoxicosis, and HIV. Control criteria were women aged ≥ 18 years – 50 years who did not consume COCs or other hormonal contraceptive and were not excluded.

Participants who fulfilled the criteria were examined for TBUT by applying fluorescence to the lower eyelid observing with a cobalt blue filter using a biomicroscope @Appasamy (normal :10-30 seconds, DES < 10 seconds), then the ferning test was done using an electron microscope @olympus, namely by drying the tears filmon the glass object taken using a micropipatte and observing the fern pattern formed under an electron microscope with magnification of 10 X- 40 X (normal: type 1 and type 2, DES type 3 and 4)

Statistical analysis in this study used was chi square. Bivariate analysis was used to evaluate the description of each variable by displaying the amount and percentage. Bivariate analysis was used to determine the relationship between COCs and occurrence of DES by using chi-square test at the 95% confidence level.

Result

Table 1 presents the data on the characteristics of the two groups conducted on 62 participants. The largest subjects age group in the two groups was 36-50 years old, while in the group using birth control pills there were 24 people (77.4%) and 25 people (80.6%) in the group

who did not use birth control pills. The average user of birth control pills was 11.52 years with the shortest use for 1 year and the longest for 30 years**.**

Table 1. Research subject category

Category	Birth control pills		P
	Yes (n=31)	No (n=31)	
Age			
18-36 years old	7 (22,6)	6 (19,4)	0,755[a]
36-50 years old	24 (77,4)	25 (80,6)	
Duration of use birth control pills, years			
Average	11,52		
Median	11		
Standard deviation	7,11		
Min-mak	1 – 30		

Note: [a]*Chi Square*

Table 2 shows the relationship between age and dry eye syndrome based on the diagnosis of TBUT. Of all subjects using and not using birth control pills, it appears that there was no significant relationship between age and dry eye syndrome (p = 0.910). Of the 26 eyes of subjects aged 18-35 years, only 8 eyes (30.8%) had dry eye syndrome. And from 98 eyes of subjects aged 36-50 years, 46 eyes (46.9%) had dry eye syndrome.

Table 2. Relationship between age and dry eye syndrome

Age	Eye Syndrome Dry (TBUT)		P	RP
	Yes	No		95% IK
Entirely				
18-35 years old	8 (30,8)	18 (69,2)	0,910[a]	1,526
36-50 years old	46(46,9)	52 (74,3)		(0,826-2,818)

Note: [a]*Chi Square*

Table 3 shows that there was a significant relationship between COCs on the occurrence of dry eye syndrome based on the Ferning test (p <0.001) with a Prevalence Ratio value of 9 (95% CI 4.182-19.360), which means that COCs tend to be at risk of developing dry eye syndrome. Dry eye syndrome based on the ferning test was 9 times greater when compared to subjects who did not COCs.

Table 3. The Relationship of combination birth control pills with dry eye syndrome (ferning test results)

	Ferning Test		P	RP
	Abnormal	Normal		95% IK
Using birth control pills, n (%)				
Yes	54 (87,1)	8 (12,9)	<0,001[a]	9
No	6 (9,7)	56 (90,3)		(4,182-19,369)

Note: [a]*Chi Square*

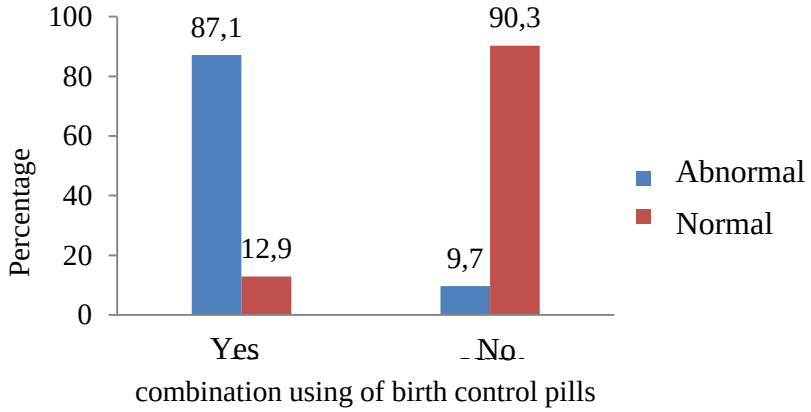

Figure 1. Bar graph of the difference in the proportion of dry eye syndrome based on the ferning test on the user and non-user groups of birth control pills

In Table 4, of the 62 eyes of the subjects COCs, 51 eyes (82,3%) experienced dry eye syndrome from the results of the TBUT examination. Meanwhile, only 3 eyes (4,8%) experienced dry eye syndrome in the subject group who did not use birth control pills. The results of the analysis using the Chi Square test show that there is a significant relationship between the use of birth control pills against dry eye syndrome based on TBUT examination ($p<0.001$) with a Prevalence Ratio value of 17 (95% CI 5.603-51.579) which means COCs tends to have a risk of experiencing dry eye syndrome based on TBUT examination by 17 times greater when compared to subjects who did not COCs.

Table 4. The relationship of combination birth control pills against dry eye syndrome (TBUT results)

	Result TBUT		P	RP
	Abnormal	Normal		95% IK
Using birth control pills				
Yes	51 (82,3)	11 (17,7)	<0,001[a]	17
No	3 (4,8)	59 (95,2)		(5,603-51,579)

Note: [a]*Chi Square*

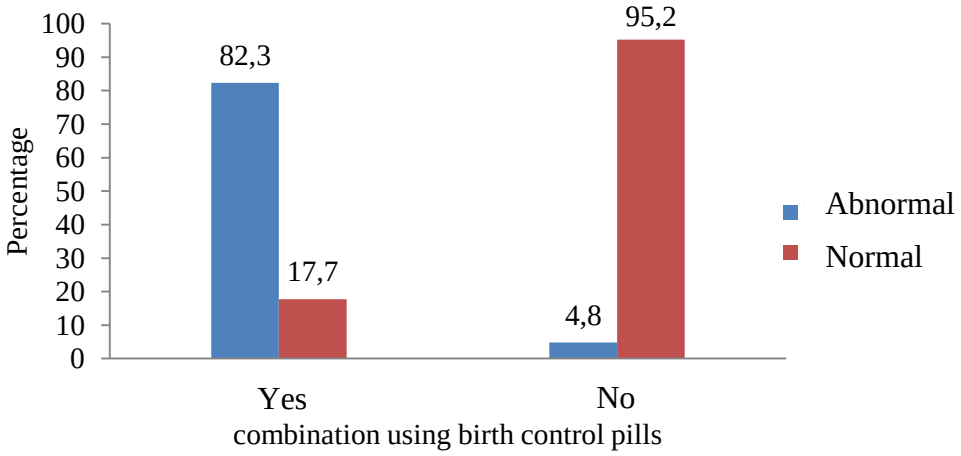

Figure 2. Bar graph of the difference in proportion of dry eye syndrome based on TBUT examination in the user and non-user groups of birth control

Based on Table 5, it can be seen that of the 54 eyes of the subjects who were considered abnormal (dry eye syndrome) based on the TBUT assessment, there were 51 eyes that were considered abnormal by the Ferning test, so it can be concluded that the sensitivity value of the Ferning test was 92,6%. Meanwhile, of the 70 eyes that were considered normal with the TBUT examination, there were 60 eyes that were also considered normal by the Ferning test, so it was concluded that the Ferning test specificity value was 85,7%.The level of accuracy of the ferning test for dry eye syndrome examination based on TBUT examination.

Table 5. Ferning test sensitivity and specificity value for assessing dry eye syndrome

	TBUT		Sensitivity	Specificity	NPP	NPN
Ferning test	**Abnormal**	**Normal**				
Abnormal	50	10	92,6	85,7	83,3	93,8
Normal	4	60				

Discussion

Table 1 presents the data on the characteristics of the two groups conducted on 62 participants. The largest subjects age group in the two groups was 36-50 years old, where in the group COCs there were 24 people (77.4%) and 25 people (80.6%) in the group who did not use COCs (control group). The average user of birth control pills was 11.52 years with the shortest use for 1 year and the longest use for 30 years. Saif et al. conducted a study on women aged 18-50 years with a mean age of 33.20 ± 7.43 in the combination contraceptive pill group and in the control group with a mean of 35.3 ± 3.16. The study of Sharma et al. (2018) involved women of childbearing age between 18-40 years.

In Table 2, the study presents the relationship between age and dry eye syndrome based on the diagnosis of TBUT. From all of the subjects who use and did not use COCs, it appears that there was no significant relationship between age and dry eye syndrome (p = 0.910). From the 98 eyes of subjects aged >35 years, 46 eyes (46.9%) had dry eye syndrome. And from 26 eyes of subjects aged ≤ 35 years, only 8 eyes (30.8%) had dry eye syndrome. This is comparable to the research of Saif et al. (2016) where the research subjects were women aged 18-50 years and the results did not find a significant difference between the age of the research subjects and the incidence of dry eye syndrome (Sing, Nagpal, & Tyagi, 2018).

Table 3 is the relationship between the COCs to dry eye syndrome, where from the 62 eyes that used the combination pill there are 54 eyes (87.1%) that have dry eye syndrome from the results of the ferning test, while only 6 eyes (9.7%) in the group of subjects who did not use COCs. The results of the analysis using the chi square test showed that there was a significant relationship between the use of COCs to the occurrence of dry eye syndrome based on the ferning test (p <0.001) with a Prevalence Ratio value of 9 (95% CI 4.182-19.360), which means that birth COCs tend to increase the risk of experiencing dry eye syndrome based on the ferning test which was 9 times greater when compared to subjects who did not take combined oral contraceptive. This is comparable to the research of Sharma et al. (2018) that of women who use combination birth control pills suffers more from dry eyes than those who did not use birth control pills. Combination research by Masmali et al. (2014) that the ferning test is reliable and has the sensitivity to differentiate between groups of dry eyes and not dry eyes (Sharma et al., 2018; Masmali et al., 2014; Tsubota et al., 2017; Riordan-Eva & Whitcher, 2007; Tomlinson et al., 2001; Kogbe et al., 1991).

In Table 4 of the 62 eyes of the subjects using the birth control pill, 51 eyes (82,3%) experienced dry eye syndrome from the results of the TBUT examination. Meanwhile, only 3 eyes (4,8%) experienced dry eye syndrome in the subject group who did not use birth control pills. The results of the analysis using the Chi Square test show that there is a significant relationship between the use of birth control pills against dry eye syndrome based on TBUT

examination (p <0.001) with a Prevalence Ratio value of 17 (95% CI 5.603-51.579) which means pill users tends to have a risk of experiencing dry eye syndrome based on TBUT examination by 17 times greater when compared to subjects who do not use birth control pills (Tomlinson et al., 2001; Kogbe et al., 1991; Versura, Giannaccare, & Campos, 2015; Cavdar et al., 2014). This is comparable to the study of Sharma et al. (2018) that in women who use COCs there were reduction in TBUT results than women who did not use COCs.

In Table 5, there were 54 eyes of the subjects who were considered abnormal (dry eye syndrome) based on the TBUT assessment, and there were 50 eyes that were considered abnormal by the Ferning test, so it can be concluded that the sensitivity value of the Ferning test was 92.6%. Meanwhile, of the 70 eyes that were considered normal with the TBUT examination, there were 60 eyes that were also considered normal by the Ferning test, so it was concluded that the Ferning test specificity value was 85.7%. Based on Norm M study that compared the Ferning test in DES with normal eyes, the sensitivity was 94% and the specificity was 92%, while the Rolando study on the ferning test got a sensitivity of 92% and specificity of 83%, the negative value (NPP) of the Ferning test was 83,3%, the negative predictive value (NPN) was 93,8% and accuracy rate was 88,71%

Conclusion

From the ferning test result was found that COCs had prediction factor of 9 times greater in suffering DES compared to those who did not use combined oral contraceptive. Ferning test could be used as an indicator in the DES examination.

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