Cairo University

KASR ALAINY
CAIRO UNIVERSITY - FACULTY OF MEDICINE

Faculty of Medicine, Cairo University Postgraduate Research Protocol Template

(Please read carefully provided guidance documents for a comprehensive understanding and proper formulation of your thesis protocol and required forms)

1. Study

a- Proposed Study Title: *The effect of polycystic ovarian syndrome treatment on ocular surface.*

b- Degree : MD.

c- Date of Registration of MSc or MD: March 2021.

2. Candidate

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4. Scientific committee approval

(Was it scientifically approved by the department?) Yes.
Date of approval: 1-11-2022

5. Background and Rationale: (Describe the research question and justification for undertaking the study explaining the aspects of novelty in the study)

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies, affecting approximately 9% to 18% of women in reproductive age.(1) Although the exact pathogenesis of PCOS remains unclear, the characteristic symptoms include oligoanovulation, polycystic ovarian morphology could be explained by hyperandrogenism and hyperestrogenemic not balanced by progesterone.(2) The endocrine, inflammatory, and metabolic changes associated with PCOS have consequences for vision, including neurovascular, metabolic changes in the retina, macular and optic nerve thickness changes.(3)

In recent years it has been discovered that female sex steroids have both systemic and ocular effects, Estrogen, progesterone and androgen receptors have been found in the cornea, lens, iris, ciliary body, retina, lacrimal glands, meibomian glands and conjunctiva,(4) The influence of hormone replacement therapy in menopausal women remains unclear, as some authors support the idea that it improves the quality and the volume of the tear film, whereas others have shown that it increases the risk of dry eye, It's possible that HRT may alleviate postmenopausal dry-eye symptoms by increasing goblet cell density.(5) However, other studies suggest that HRT worsens dry-eye symptoms in some cases, and estrogen-only HRT seems to be worse than a combined estrogen and progesterone therapy.(6)

Reports are stressing on the effect of PCOS on tear film stability rather than amount of the tears denoting the possible effect on meibomian glands (MGs) functions, Loss and morphological deterioration of the MGs are observed in PCOS patients(7),Yonca Asfuroglu et al. reported that Dry eye was well established in patients with PCOS. They proposed that hyperandrogenism, insulin resistance and subclinical inflammation may be possible contributing factors to the Dry eye spectrum in these patients, They correlated the severity of the Dry eye with the level of inflammation and hyperandrogenism.(8)

For Treatment of Non-fertility outcomes, combined oral contraceptive pills (COCPs), metformin and anti-androgen drugs are used. COCPs are recommended as first-line medical treatment for the management of hyperandrogenism and regulation of menstrual cycles,(9) A study by Chen et al. reported that COCPs have no direct

impact on Dry eye, They found no significant differences in Dry eye, as measured by tear osmolarity and ocular surface disease index (OSDI) or Symptom Assessment in Dry Eye (SANDE) questionnaires, between patients taking OCPs and those not taking OCPs. However, results were not conclusive.[10]

Because of the metabolic features of PCOS such as insulin resistance and hyperinsulinemia; insulin-sensitizing agents, especially metformin, have been used as a treatment option for PCOS with OCPS as the second line of treatment. [11] Metformin has a protective effect in diabetic retinopathy, glaucoma, and age related macular degenerations,[12] It can also improves objective measures of Dry Eyes and focus score in Sjögren′s Disease.[13]

The role of antiandrogens in the treatment of hirsutism in PCOS is controversial; however, there is some weak evidence that flutamide and spironolactone reduce hirsutism.[14] Ilaria Macche et al. found that ocular surface findings are improved by systemic anti-androgen treatment in PCOS and correlate with the severity of the androgen excess-related skin signs.[15]

For Treatment of Fertility Indications, Pharmacological options include ovulation induction with clomiphene citrate (CC), letrozole (aromatase inhibitor), metformin, and gonadotrophins[16]; The effect of clomiphene citrate (ovarian stimulant) on vision is minimal; reduction in foveal flicker sensitivity was the only observed visual disturbance.[17]

Although visual disturbance is a possible side effect of aromatase inhibitors use, its incidence is quite variable.[18] Studies found increased tear osmolarity and meibomian gland drop out in women on letrazole with symptomatic dry eye.[19]

6. Objectives: (describe specific objectives or hypotheses behind the study)

The purpose of this study is to prospectively evaluate the ocular surface effects of polycystic ovarian syndrome and different drugs used in its management.

7. Study Design: (Please fill in the appropriate study design, see attached PDF guide)

- Descriptive: - Survey (cross sectional) ☐
  - Qualitative ☐

- Analytic: - Observational: - Case-control study ☐
  - Cross sectional analytic study ☐
  - Cohort (Longitudinal) study ■

- Experimental: - Randomized Clinical Trial Phase: ☐
  - Non-randomized clinical trial ☐
  - Animal study ☐
  - Cellular study ☐

- Others: Please describe:

8. Study Methods

- **Population of study:** (Please provide all details regarding participants including gender, age range and disease conditions. Also indicate if this protocol involves children, prisoners, pregnant women or cognitively impaired or mentally disabled subjects)

Two groups with confirmed laboratory and ultrasonography diagnosis of PCOS , First group will include 30 eyes of 30 females in childbearing period (18-40 years old) scheduled for treatment for non- fertility indications with oral contraceptive pills (as a first line of treatment), and the second group will include 30 eyes of 30 females in childbearing period (18-40 years old) scheduled for treatment with Clomiphene citrate (as a first line of treatment), for fertility indications.

- **Study location:** (Please provide where the study will be conducted and from where study participants will be recruited)

Patients will be recruited from gynecology and dermatology Kasr Al-Ainy clinics and will undergo their ophthalmic examination and investigations at the department of ophthalmology, Kasr Al-Ainy school of medicine.

- **Inclusion criteria:**
  1. Females at child bearing period (18-40 years old).
  2. Patients recently diagnosed with polycystic ovarian syndrome.

- **Exclusion criteria:**
- 1.Patients who were diagnosed with Dry eye disease.
  2.Patients who were treated with hormonal replacement therapy, Metformin, Aromatase inhibitors, clomiphene citrate or androgen antagonists.
  3. Patients who underwent ocular surgeries.
  4. patients with history of diabetes mellitus or hypertension.

- **Methodology in details:**

Two groups with confirmed laboratory and ultrasonography diagnosis of PCOS, First group will include 30 eyes of 30 females in childbearing period (18-40 years old) scheduled for treatment for non- fertility indications with Estradiol valerate / Norgestre tablets for six months, The second group will include 30 eyes of 30 females in childbearing period (18-40 years old) scheduled for treatment with Clomiphene citrate for fertility indications for 6 months.

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- Follicle stimulating hormone (FSH), luteinizing hormone (LH) , androgen, estrogen, progesterone , fasting insulin and neutrophil to lymphocyte ratio (NLR) will be obtained.
-The two groups will undergo complete ophthalmic examination including :

*Full history.
*Standard Patient Evaluation of Eye Dryness Questionnaire (SPEED) in order to quickly track the progression of dry eye symptoms over time.
*Manifest refraction.
* Corrected distance visual acuity.
* Anterior segment examination using slit lamp, Schirmer's test and tear film breakup time test.
* Fundus examination.
* Measuring central corneal thickness (CCT) using Corneal pachymetry.
•Beside Schirmer's test, tear film breakup time test and fluorescein break-up patterns, Dry eye assessment will be performed using Dry Eye Diagnostic System device (D130, Medi-Works Precision Instruments; Shanghai, China). Device to have a Dry eye diagnosis brings out an automatic result of non-invasive break up test (NIBUT) and tear meniscus height after taking one video. It is a fully automatic analysis system to provide efficient quantified evaluation for the overall stability of the tear film. Also it uses identification system that depicts the tear meniscus area and measures the tear height automatically.
The device also automatically analyses the meibomian glands, lipid layer thickness, and eyelid margin. The built-in infrared lighting system helps to obtain the enormous image scope of the meibomian glands. Finally the device identifies and calculates percentages of

conjunctival congestion and ciliary congestion, Thus evaluating the severity of eye congestion. If the degree of severity of eye congestion is more than two, it is abnormal.
*Examination and laboratory tests will be done before, 3 months after starting treatment and after finishing the treatment course.

- **Intervention:**

■ Diagnostic intervention (please describe):

Imaging ocular surface using dry eye diagnostic system.

☐ Therapeutic intervention (please describe):

☐ No intervention

- **Does the research involve?**

■ Human participants

☐ Biological samples/Tissues

☐ Identifiable private data/Information

- **Type of consent of study participants:**

■ Written consent

☐ Oral consent

☐ No consent needed (Please justify)

- **Potential risks:**
(Please mention all risks involved even mild ones as pain, discomfort, chance of infection or psychological effects)

1- No possible risks

- **Confidentiality of data:** (Please explain how privacy and confidentiality of data and records will be maintained)
- Names and private data of patients will not be published, only the results of the study will be analyzed and published.

9- Study outcomes:

- **Primary outcomes** (Most important measurable outcomes)

  1- Measuring changes in meibomian glands function, break up time, tear meniscus height, and lipid layer thickness in polycystic ovarian syndrome and with different drugs used in managing it.

- **Secondary outcome parameters** (other outcomes to be assessed)

  1- Measuring eye lid margin, conjunctival hyperemia, and ocular surface staining in polycystic ovarian syndrome and with different drugs used in managing it.

  2- Measuring the central corneal thickness (CCT) changes in polycystic ovarian syndrome and with different drugs used in managing it.

10- Sample size (number of study subjects included and justification including the clinical and statistical assumptions supporting sample size calculation)

$$\left(\frac{Z_{a/2} + Z_B}{P_1 - P_2}\right)^2 (p_1q_1 + p_2q_2)$$

(Takazawa & Morita, 2020)

n = sample size

Z a/2 (The critical value that divides the central 95% of the Z distribution)

ZB (The critical value that divides the central 20% of the Z distribution)

p1 = prevalence in case group

p2 = prevalence in control group.

q = 1-p

Epi Info STATCALC was used to calculate the sample size by considering the following assumptions:- 95% two-sided confidence level, with a power of 80%. & α error of 10% [20]. The final maximum sample size taken from the Epi- Info output was 26. Thus, the sample size was increased to 30 subjects with total 30 eyes in each group to assume any drop out cases during follow up.

11- Statistical analysis (Please describe your data analysis plan)

Data management and analysis will performed using Statistical Package for Social Sciences (SPSS). Median and range for non-parametric measures and ordinal (scores) data. Numerical data will be presented as means ± standard deviations (SD). Categorical data will be presented as number and percentages %. Pairwise comparisons between the two groups for normally distributed variables will be done using the Student's t-test; the Mann–Whitney test, a nonparametric test equivalent to the t-test, will be used in non-normally distributed variables. The Repeated measures ANOVA test will be used to compare the effect change within and between the study groups at different visits. The chi-square test or the Fisher's exact test will be used to compare between the groups with respect to categorical data. All p-values will be two-sided. P-values < 0.05 will be considered significant

12- Source of funding: (Please include source of funding even if self funding)

- Faculty of Medicine, Cairo University ☐
- Other sources: ■

  Please specify: Self-funding

13- Time plan:

- When to start? Immediately after acceptance.

- When expected to finish? After 18 months

- When to publish? After 18 months

14- References:

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