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ARTICLE

Effects of hormonal contraceptives on dry eye disease: a population-based study

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Abstract

Background Hormonal contraceptives (HCs) are a known risk factor for dry eye disease (DED), yet the relationship between HCs use and DED in women of child-bearing age remains debatable. The aim of this study was to determine the association between HCs and DED in females of reproductive age.

Methods This was a retrospective cohort study using data from IQVIA's electronic medical record (IQVIA, USA). 4,871,504 women (age 15–45) between 2008 and 2018 were followed to the first diagnosis of DED as defined by an ICD-9/10 code. DED cases also required at least two prescriptions of cyclosporine or lifitegrast topical drops within 60 days of the first code. The date of the first code was designated as the index date. Regular HCs users needed to have at least two prescriptions in both the first year and second year prior to the index date. For each case, five controls were selected and matched to cases by age and follow-up time. A conditional logistic regression model was used to adjust for confounders of DED and to calculate odds ratios (ORs).

Results HCs users were at a higher risk for DED than non-users. Regular users of HCs were more likely to develop DED (ORs = 2.73, 95% CI [2.21–3.73]) than irregular users. Those who used a greater number of HCs were at a higher risk for DED.

Conclusions This study indicates an increased risk of DED with HCs use in women of child-bearing age.

Introduction

Dry eye disease (DED) is a chronic, multifactorial ocular surface disease characterised by symptoms of eye discomfort, ocular dryness, irritation, and fluctuating vision [1]. Women are disproportionally affected by DED, with a global prevalence rate of ~20%, and are diagnosed at an earlier age compared to men [2, 3]. In addition, women report greater intensity, frequency and duration of symptoms compared to their male counterparts [3]. DED is a serious public health concern, with studies demonstrating corneal complications leading to visual compromise [4], psychological distress [5], and economic burden [6] in women with untreated DED. Annually, DED is estimated to cost the healthcare system over 3.8 million dollars [7].

One of the risk factors for DED is the use of hormonal contraceptives (HCs) [8], and worldwide, an estimated 800 million women of reproductive age use some form of HCs [9]. A study by Schaumberg et al. looked at women who were either never (never used HCs) or ever (used HC at some point from baseline to 3 years of study follow-up) users of HCs and found the risk for developing DED to be significantly higher for each 3-year increase in duration of HCs use [10]. However, the authors were not able to address whether the number of different HCs used influences the risk of DED nor control for confounders such as other medical conditions and medications that are known to be associated with dry eye syndrome [11–14]. The aim of this study was to investigate associations between DED and HCs utilisation in a large cohort of women of child-bearing age.

Materials and methods

This was a retrospective cohort study with a case-control analysis (nested case-control study) as this methodology is most practical for pharmacoepidemiologic studies that

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examine the effect of a time-dependent exposure (HCs use) over time [15]. Data were obtained from the IQIVA Ambulatory EMR database (IQVIA, USA), which contains medical records of over 74 million patients from the United States of America. These records, which include information on patient age, sex, race, geographical location and medical diagnosis (ICD-9/10 codes), were acquired from more than 100,000 physicians and from all 50 states. The database also contained relevant prescription drug information such as drug name and strength, the number of refills, and the start and stop dates.

Our study cohort comprised of 4,871,504 women (age 15–45) between 2008 and 2018 who were followed to diagnosis of DED or latest available time in the database. DED cases were defined as those with a first ICD-9 (375.15) or ICD-10 (H04.121, H04.122, H04.123, H04.129, H16.221 H16.222 H16.223) code for *unspecified tear film insufficiency, dry eye syndrome of unspecified lacrimal gland, dry eye syndrome of right lacrimal gland, dry eye syndrome of left lacrimal gland, dry eye syndrome of bilateral lacrimal glands*, *keratoconjunctivitis sicca of right eye, keratoconjunctivitis sicca of left eye and keratoconjunctivitis sicca bilateral*. DED cases also had to have at least two prescriptions of cyclosporine or lifitegrast topical drops within 60 days of the first code to capture symptomatic patients where artificial tears would not have been sufficient. The date of the first code was designated as the index date or date of diagnosis. For each case, five controls from the database who did not use any HCs and had no diagnosis of DED were selected using density-based sampling and matched to the cases by age and follow-up time.

Those who received at least two prescriptions in both the first year and second year prior to the index date were classified as regular contraceptive users, and anyone who did not meet the criteria for regular use were classified as irregular contraceptive users. Regular users were further subclassified to recent users (those who received at least one prescription in days 0–90) and past users (those who had received at least one prescription in days 91–365 prior to the index date). The HCs included were combined oral contraceptives, medroxyprogesterone injection, etonogestrel vaginal ring and intrauterine levonorgestrel. Given that intrauterine levonorgestrel prescriptions can last for several years, in our study, they were assumed to have last for at least 1 year and therefore were not included in the classification for regular nor irregular use. Confounding variables of DED were selected for if they satisfied the criteria of a true confounder (i.e. they were causes of both the exposure (hormonal contraceptive use) and the outcome (DED)) [16] and these included thyroid disease, autoimmune disorders, and use of tricyclic antidepressants, isotretinoin, and beta blockers. Smoking was not adjusted for as only 5% of the subjects were smokers. A conditional logistic regression model was used to adjust for DED confounders and to calculate odds ratios (ORs). All ORs were compared to subjects with no HCs use. All analyses were done using SAS version 9.4. Approval for the study was obtained by the University of British Columbia's Clinical Research Ethics Board.

Table 1 Characteristics of cases and controls.

	Cases	Controls
Number	1799	7196
Age (mean ± s.d.)	35.0 ± 5.7	35.0 ± 5.7
Body Mass Index	26.8 ± 5.7	28.0 ± 5.8
Follow-up	2.2 ± 2.2	2.2 ± 2.2
Conditions (N (%)):		
Hypothyroidism	163 (9.1)	426 (9.6)
Hyperthyroidism	8 (0.4)	28 (0.4)
Rheumatoid arthritis	52 (2.9)	52 (0.7)
Sjogren's	58 (3.2)	16 (0.2)
Lupus	35 (2.0)	39 (0.5)
Drugs (N (%)):		
Tricyclic antidepressants	106 (5.9)	177 (2.5)
Isotretinoin	10 (0.6)	7 (0.1)
Beta blocker	115 (6.4)	262 (3.6)

Results

There were 1,799 DED cases and 7196 controls (Table 1). Both cohorts had similar covariate distributions and a mean age of 35.0 ± 5.7. There was an increased risk of DED with regular HCs use (ORs = 2.73, 95% CI [2.21–3.73]) compared to irregular use (ORs = 1.80, 95% CI [1.58–2.04]) (Table 2). Among regular users of HCs, recent users who had at least one prescription in days 0–90 prior to the index date were at a higher risk for DED (ORs = 2.79, 95% CI [2.05–3.74]) compared to regular users who used at least one prescription in days 91–365 prior to the index date (ORs = 2.70, 95% CI [2.06–3.54]). The risk for DED also increased with the number of different types of HCs used, with a ORs of 1.66 (95% CI [1.42–1.94]) among women who used 1–2 HCs, and a ORs of 2.16 (95% CI [1.74–2.69]) for those who used 3–4 HCs. Women who used more than four different types of HCs were at greatest risk, with a ORs of 2.35 (95% CI [1.98–2.79]).

Discussion

This is the first population-based study to investigate the association of DED with the duration and quantity of HCs use. There was an increased risk of DED in all HCs users,

Table 2 Adjusted[a] Odds Ratios (ORs) of cases of dry eye disease with respect to regular exposure of contraceptives 1 year prior to index.

	Cases	Controls	Odds ratios	95% CI
Number of subjects	1,799	7,196		
No use of HC (%)	60.42	74.47	1.00	Reference
[b]Regular use of HC (%)	10.01	4.70	2.73	2.21–3.73
Recent use (0–90 days)	4.45	2.00	2.79	2.05–3.74
Past use 91days+	5.56	2.70	2.70	2.06–3.54
[c]Irregular use of HC (%)	29.57	20.83	1.80	1.58–2.04
Risk with number of prescriptions				
1–2 HC	16.84	12.73	1.66	1.42–1.94
3–4 HC	7.84	4.75	2.16	1.74–2.69
>4 HC	14.90	8.05	2.35	1.98–2.79

[a]Adjusted for variables in Table 1.

[b]Regular use of HCs was defined as at least 2 HCs prescriptions in first year prior to index, and at least 2 HCs prescriptions in the second year prior to index date. All HCs except for intrauterine levonorgestrel were included.

[c]Irregular use included anyone who were not classified as regular users of HC. All HCs except for intrauterine levonorgestrel were included.

and regular users had a higher risk for DED than irregular users. Among women who used HCs regularly, recent use was associated with a higher risk for DED than past use. In addition, women who took a greater number of different types of HCs were at a higher risk for DED than women who took fewer prescriptions.

While previous studies in the literature have reported on the relationship between dry eye syndrome and hormone replacement therapy, results have been conflicting. Chen et al. conducted a study on tear osmolality and dry eye symptoms in women using oral contraception and contact lenses, and concluded that neither oral contraceptive pills use nor oestrogen dose of the pills had any significant effect on tear osmolality and dry eye symptoms [17]. In this study however, tear osmolarity, an objective DED marker, was measured only once, even though the literature recommends at least three consecutive measurements for greater reliability [18]. Similarly, other studies have found no difference in Schirmer I or tear breakup time between women using OCP and controls [19, 20]. At the same time however, some authors have reported increased risk of DED with HCs use [21–23] while others have noted the opposite [24, 25]. Nevertheless, none of these studies have specifically evaluated the time-dependency or quantitative effects of HCs and DED.

The tear film on the ocular surface is composed of three layers, with the outer lipid layer produced by meibomian glands, the middle aqueous layer secreted by lacrimal glands and the inner mucin layer supplied by conjunctival goblet cells. Dry eye syndrome occurs when there is decreased aqueous tear production or excessive tear evaporation [26]. While the exact pathophysiologic mechanism underlying HCs use and DED remains unclear, sex steroids hormones, including oestrogens, androgens, and progestins, are thought to be implicated in DED pathophysiology [27]. Specifically, oestrogen receptors are known to be found on meibomian glands [28], and oestrogen administration may promote suppression of meibomian gland function [29]. Furthermore, oestrogen have been reported to decrease the activity, lipid production and size of sebaceous glands, possibly by promoting the release of lysosomal enzymes within sebocytes that lead to premature cellular destruction and attenuated sebum elaboration [30]. Similarly, progesterone in mice studies has been observed to be a key player in altering gene expression and molecular processes of lacrimal and meibomian glands [29, 31].

Androgen deficiency, as seen in menopause, aging and Sjogren's syndrome, is associated with meibomian gland dysfunction, including acinar cell atrophy and ductal epithelium hyperkeratinisation [32]. This leads to significant alterations to the chemical composition and lipid profiles of the glandular secretions [33], resulting in decreased tear film stability and evaporative dry eye [30]. In fact, patients who take anti-androgen therapy are more likely to have a greater frequency of tear film debris, an abnormal tear meniscus, and reduced tear film breakup time compared to age-matched controls [34, 35]. Androgens are also partially responsible for the function and structure of the lacrimal gland via the regulation of gene transcription [36], and reduced serum androgen levels were associated with inflammatory changes of the lacrimal gland, leading to aqueous-deficient dry eye [36, 37]. Interestingly, the secretory function of lacrimal glands does not seem to be influenced by androgen level nor lacrimal gland size as an increase in tear volume has been reported in castrated male rats [38] while no changes in lacrimal secretion were noted in ovariectomized female rabbits despite lacrimal tissue regression [39]. Finally, a significant reduction in the numbers of conjunctival goblet cells have been observed following castration of male rabbits, suggesting a potential role for androgen in the production of the mucin layer [40]. Evidently, more research is needed to clarify the relationships of these hormones and DED and what influence do the hormones have on tear film production and quality.

In summary, we found that longer duration and higher quantities of HCs use are significantly associated with greater likelihood of developing DED. The strengths of our study include the large sample size and the control of potential confounders variables. We were also able to quantify the risk of DED and also confirm with a dose response analysis that greater number of HCs increase the risk of DED. Limitations of this study include the lack of

power for different dosages and content formulation of HCs, as well as uncontrollable confounders such as contact lens wear and refractive surgeries. As well, this study did not examine mild cases of dry eye for which topical lubrication alone was sufficient. Further studies are needed to confirm the associations observed and elucidate whether different dosages or formulations of HCs impart a greater risk for DED.

Summary

What was known before

- Hormonal contraceptives (HCs) are a known risk factor for DED.
- The relationship between HCs use and DED in women of child-bearing age remains debatable.

What this study adds

- There is an increased risk of DED with HCs use in women of child-bearing age.
- Longer duration and higher quantities of HCs used increases the risk of DED.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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References

1. Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, et al. TFOS DEWS II Epidemiology Report. Ocul Surf. 2017;15:334–65.
2. Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. Am J Ophthalmol. 2003;136:318–26.
3. Schaumberg DA, Uchino M, Christen WG, Semba RD, Buring JE, Li JZ. Patient reported differences in dry eye disease between men and women: impact, management, and patient satisfaction. PLoS ONE. 2013;8:e76121.
4. Pflugfelder SC, de Paiva CS. The Pathophysiology of Dry Eye Disease: what We Know and Future Directions for Research. Ophthalmology. 2017;124:S4–S13.
5. Wan KH, Chen LJ, Young AL. Depression and anxiety in dry eye disease: a systematic review and meta-analysis. Eye. 2016;30:1558–67.
6. McDonald M, Patel DA, Keith MS, Snedecor SJ. Economic and Humanistic Burden of Dry Eye Disease in Europe, North America, and Asia: a Systematic Literature Review. Ocul Surf. 2016;14:144–67.
7. Yu J, Asche CV, Fairchild CJ. The economic burden of dry eye disease in the United States: a decision tree analysis. Cornea. 2011;30:379–87.
8. Schaumberg DA, Buring JE, Sullivan DA, Dana MR. Hormone Replacement Therapy and Dry Eye Syndrome. JAMA. 2001;286:2114–9.
9. United Nations Department of Economic and Social Affairs, Population Division. Contraceptive Use by Method 2019: Data Booklet. United Nations. 2019;435.
10. Schaumberg DA, Buring JE, Sullivan DA, Dana MR. Hormone Replacement Therapy and Dry Eye Syndrome. JAMA. 2001;286:2114–9.
11. Fraunfelder FT, Sciubba JJ, Mathers WD. The role of medications in causing dry eye. J Ophthalmol. 2012;2012:285851.
12. Neudorfer M, Goldshtein I, Shamai-Lubovitz O, Chodick G, Dadon Y, Shalev V. Ocular Adverse Effects of Systemic Treatment With Isotretinoin. Arch Dermatol. 2012;148:803–8.
13. Kassan SS, Moutsopoulos HM. Clinical Manifestations and Early Diagnosis of Sjögren Syndrome. Arch Intern Med. 2004;164:1275–84.
14. Alanazi SA, Alomran AA, Abusharha A, Fagehi R, Al-Johani N, El-Hiti G, et al. An assessment of the ocular tear film in patients with thyroid disorders. Clin Ophthalmol (Auckl, N. Z). 2019;13:1019–26.
15. Suissa S. The Quasi-cohort approach in pharmacoepidemiology: upgrading the nested case-control. Epidemiology. 2015;26:242–6.
16. Hernán MA, Robins JM. Causal Inference: What If. Boca Raton: Chapman & Hall/CRC; 2020.
17. Chen SP, Massaro-Giordano G, Pistilli M, Schreiber CA, Bunya VY. Tear osmolarity and dry eye symptoms in women using oral contraception and contact lenses. Cornea. 2013;32:423–8.
18. Khanal S, Millar TJ. Barriers to clinical uptake of tear osmolarity measurements. Br J Ophthalmol. 2012;96:341–4.
19. Frankel SH, Ellis PP. Effect of oral contraceptives on tear production. Ann Ophthalmol. 1978;10:1585–8.
20. Tomlinson A, Pearce EI, Simmons PA, Blades K. Effect of oral contraceptives on tear physiology. Ophthalmic Physiol Opt. 2001;21:9–16.
21. Sharma A, Porwal S, Tyagi M. Effect of oral contraceptives on tear film in reproductive age group women. Int J Reprod, Contracept, Obstet Gynecol. 2018;7:861.
22. Uncu G, Avci R, Uncu Y, Kaymaz C, Develioğlu O. The effects of different hormone replacement therapy regimens on tear function, intraocular pressure and lens opacity. Gynecol Endocrinol. 2006;22:501–5.
23. Saif MYS, Sayed MA, Saif ATS. Effect of hormonal contraception on lacrimal gland function. Guoji Yanke Zazhi (Int Eye Sci). 2016;16:1207–11.
24. Feng Y, Feng G, Peng S, Li H. The effects of hormone replacement therapy on dry eye syndromes evaluated by Schirmer test depend on patient age. Contact Lens and Anterior. Eye. 2016;39:124–7.

25. Feng Y, Feng G, Peng S, Li H. The Effect of Hormone Replacement Therapy on Dry Eye Syndrome Evaluated with Schirmer Test and Break-Up Time. J Ophthalmol. 2015;2015:420302.
26. Clayton JA. Dry Eye. N Engl J Med. 2018;378:2212–23.
27. Truong S, Cole N, Stapleton F, Golebiowski B. Sex hormones and the dry eye. Clin Exp Optom. 2014;97:324–36.
28. Esmaeli B, Harvey JT, Hewlett B. Immunohistochemical evidence for estrogen receptors in meibomian glands. Ophthalmology. 2000;107:180–4.
29. Suzuki T, Schirra F, Richards SM, Jensen RV, Sullivan DA. Estrogen and Progesterone Control of Gene Expression in the Mouse Meibomian Gland. Investig Ophthalmol Vis Sci. 2008;49:1797–808.
30. Sullivan DA, Yamagami H, Liu M, Steagall RJ, Schirra F, Suzuki T, et al. Sex Steroids, the Meibomian Gland and Evaporative Dry Eye. In: Sullivan DA, Stern ME, Tsubota K, Dartt DA, Sullivan RM, Bromberg BB, editors. Lacrimal Gland, Tear Film, and Dry Eye Syndromes 3: Basic Science and Clinical Relevance Part A and B. Boston, MA: Springer US; 2002. p. 389–99.
31. Suzuki T, Schirra F, Richards SM, Treister NS, Lombardi MJ, Rowley P, et al. Estrogen's and Progesterone's Impact on Gene Expression in the Mouse Lacrimal Gland. Investig Ophthalmol Vis Sci. 2006;47:158–68.
32. Sun M, Moreno IY, Dang M, Coulson-Thomas V. Meibomian Gland Dysfunction: what Have Animal Models Taught Us? Int J Mol Sci. 2020;21:8822.
33. Driver PJ, Lemp MA. Meibomian gland dysfunction. Surv Ophthalmol. 1996;40:343–67.
34. Sullivan BD, Evans JE, Dana MR, Sullivan DA. Impact of androgen deficiency on the lipid profiles in human meibomian gland secretions. Adv Exp Med Biol. 2002;506:449–58.
35. Sullivan BD, Evans JE, Krenzer KL, Reza Dana M, Sullivan DA. Impact of Antiandrogen Treatment on the Fatty Acid Profile of Neutral Lipids in Human Meibomian Gland Secretions1. J Clin Endocrinol Metab. 2000;85:4866–73.
36. Richards SM, Liu M, Jensen RV, Schirra F, Yamagami H, Lombardi MJ, et al. Androgen regulation of gene expression in the mouse lacrimal gland. J Steroid Biochem Mol Biol. 2005;96:401–13.
37. Sullivan DA, Bélanger A, Cermak JM, Bérubé R, Papas AS, Sullivan RM, et al. Are women with Sjögren's syndrome androgen-deficient? J Rheumatol. 2003;30:2413–9.
38. Sullivan DA, Allansmith MR. Hormonal modulation of tear volume in the rat. Exp Eye Res. 1986;42:131–9.
39. Azzarolo AM, Wood RL, Mircheff AK, Richters A, Olsen E, Berkowitz M, et al. Androgen influence on lacrimal gland apoptosis, necrosis, and lymphocytic infiltration. Investig Ophthalmol Vis Sci. 1999;40:592–602.
40. Luo F, Zhang H, Sun X. The change of tear secretion and tear film stability in castrated male rabbits. Zhonghua Yan Ke Za Zhi. 2001;37:458–61.