Original Article

The Effect of Combined Oral Contraceptive on the Parotid Salivary Gland of Female Albino Rats (Light and Transmission electron microscopic study)

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ABSTRACT

Introduction: Combined oral contraceptives (COCs) are nowadays from the most commonly used medications in developed countries. The combination birth control pill of drospirenone with ethinyl estradiol (Yasmin®) is considered an effective contraceptive that is used by many women worldwide.

Aim of the Study: To investigate the possible effects of Yasmin administration on the parotid gland of female Albino rats.

Materials and Methods: Fourteen adult female Albino rats weighing between 200-220 gm were divided randomly into two equal groups, seven rats each. The control group: where rats received distilled water by gastric gavage daily. The Oral contraceptive group (COC): where rats have received Yasmin® tablets dissolved in distilled water and was then given daily (0.6 mg/kg body weight) by gastric gavage as 5-day cycles (4-day treatment with 1-day break) for 8 oestrous cycles (32 days). Parotid glands were prepared for both light and transmission electron microscopic examination.

Results: Light and transmission electron microscopic examination of the oral contraceptive group showed that the serous acini appeared with cytoplasmic vacuoles, nuclear pleomorphism, dilated rough endoplasmic reticulum cisternae and swollen mitochondria with damaged cristae. Duct system has also shown various degenerative changes. Striated duct cells showed apparent loss of cell height, shrunken nuclei and swollen mitochondria while, excretory ducts appeared with loss of pseudo-stratification. Statistical analysis of acinar diameter has shown a high significant increase in the oral contraceptive group than the control group.

Conclusions: From this study, we concluded that when combined oral contraceptive pills were administrated to female Albino rats, it revealed degenerative changes in acinar and ductal cells of parotid gland.

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Key Words: Combined oral contraceptives; parotid; transmission electron microscope.

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INTRODUCTION

Oral contraceptive pills (OCs) are widely consumed by many females among the world. So, information regarding their benefits and risks is very important. Several evidences have proved that OCs induce oxidative stress and deplete serum antioxidants[1].

The OCs are either of two types; Estrogen and progestins that have been used by women as effective combined oral contraceptives (COCs), or only progestin, both offer effective, safe as well as reversible fertility regulation[2].

Estrogen/progestin combination is the most efficient type of OCs formulations, as they tend to prevent ovulation primarily by interfering with the release of gonadotropin-releasing hormone from the hypothalamus and also inhibiting pituitary gland gonadotropin producing cells[3].

The COC is composed of an estrogen component (oestradiol, ethinyloestradiol, mestranol, or its prodrug oestradiolvalerate) and a progestogen (drospirenone, norethisterone, levonorgestrel, desogestrel, gestodene, nomegestrol, cyproterone or dienogest). Yasmin is a COC tablet that contain synthetic progestogen, drospirenone and synthetic estrogen, ethinyloestradiol[4,5].

Histological changes associated with using OCs have been described in many body tissues, the endometrium, cervix, myometrium, breast, ovaries, liver and blood vessels. Many types of lesions and degenerative changes have been found to occur frequently with administration of these hormonal contraceptives[6]. So, the aim of this study was to investigate the possible effects of COCs on the parotid gland (PG) of female Albino rats histologically and ultrastructurally.

MATERIALS AND METHODS

Animals

Fourteen adult female Albino rats (age between 8 to 10 weeks) weighting between 200-220 gm were used in this study. The rats were housed in the animal house of the medical research center, Ain Shams University. They were kept under good ventilation and adequate stable diet ad libitium. This was reviewed and accepted by the research ethics committee of the faculty of Dentistry, Ain Shams University, Cairo, Egypt (final approval number is (FDASU-Rec R102107).

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Experimental groups

After one week of accommodation, rats were randomly divided into two equal groups, seven rats each.

1. Control group: where rats received distilled water by gastric gavage daily.
2. Oral contraceptive group: where rats received Yasmin® tablets which is a brand of COCs containing (0.03 mg ethinyl estradiol and 3 mg drospirenone) manufactured by Bayer Weimar GmbH & Co. KG, Germany. The drug was dissolved in of distilled water and was given daily (0.6 mg/kg body weight) by gastric gavage as 5-day cycles (4 day treatment with 1-day break) for 8 oestrous cycles (32 days)[1,7].

Tissue preparation for light microscopic examination

At the end of the experiment, rats were sacrificed separately by overdose of anesthesia. PGs were dissected and half of the specimens were fixed in 10 % formalin solution, then washed under running water to remove all fixative residues. Then specimens were dehydrated and embedded in paraffin blocks to be cut by microtome to four to five microns thickness. Slides were stained by Hematoxylin and Eosin (H & E) stains for routine histological examination[8].

Tissue preparation for transmission electron microscopic (TEM) examination

For the TEM study of the glands, fixation of the other half of the specimens were done using in glutaraldehyde and osmium tetroxide. The tissues were then dehydrated and embedded in Epon resin and semithin sections (1 µm thick) were cut and stained with 1% toluidine blue, then examined by a light microscope to select the proper areas. Ultra-thin sections (80-90 nm) were cut using a diamond knife and stained by Uranyl acetate and lead citrate[9]. The electron microscopic study was done using a JEOL 1010 TEM (Japan) at 80 Kv at the Regional Center for Mycology and Biotechnology (RCMB), Al-Azhar University, Egypt.

Histomorphometric analysis

Examination of H & E stained sections was done using a light microscope (Model BX40F, 7E12569) Olympus Optical Co., LTD. Japan. Photographing was done using a mounted camera (Olympus soft imaging solutions, Munster, Germany, Model LC20,59001227). This was done at Oral Biology Department, Faculty of Dentistry, Ain Shams University, Cairo, Egypt.

Sections (400X) were randomly selected, and diameters of acini were measured from five fields from each sample as thirty-five acini in each group. Computerized calculation was done using Image j software.

Statistical analysis

Analysis of the recorded data was done using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA) and data was expressed as mean± standard deviation (SD). Independent Sample t-test was also used to compare between both groups.

RESULTS

Light and TEM results

The Control group

Light microscopic examination of PG Showed normal histological architecture (Figure 1). Acini appeared spherical with pyramidal cells and basally situated nuclei. The intercalated ducts linings were cuboidal cells with central large rounded nuclei. The striated ducts lining was tall columnar cells with central rounded nuclei and deep eosinophilic cytoplasm and basal striations (Figure 1A). The excretory ducts showed pseudostratified columnar epithelium and were surrounded by fibrous connective tissue (Figure 1B).

Electron microscopic examination of the PG of the control group showed normal architecture of acini and ducts (Figure 2). Acinar cells appeared as pyramidal cells with basal, spherical nuclei with apical zymogen granules of varying electron densities and mitochondria with normal cristae scattered throughout the cell (Figure 2A). Intercalated ducts were lined by cuboidal cells with round, central nucleus and normal microvilli bordering the lumen (Figure 2B). Myoepithelial cells appeared normal (Figure 2E). Striated duct lining exhibited tall columnar cells with vesicular, rounded nucleus and numerous, normal, mitochondria (Figure 2C). Excretory duct appeared with pseudostratified cell arrangement (Figure 2D)

Oral contraceptive (OC) group

Examination of the H&E stained sections of this group under light microscope showed serous acini with ill-defined outline. Nuclei of the acinar cells appeared hyperchromatic, pleomorphic and many were pyknotic. Many acini had cytoplasmic vacuoles of varying sizes and acini were widely separated (Figures 3 A,B). Intercalated duct (ICD) appeared with apparent normal architecture, but some showed fewer nuclei (Figure 3A). Striated ducts showed apparent decrease in cell height. Striated duct cells showed flattened nuclei and apparent loss of basal striations (Figure 3 B). Presence of congested blood vessels was also detected (fig 3B). Some excretory ducts appeared to be flattened with loss of pseudo-stratification in some areas of its lining. (Figure 3 C).

Electron microscopic examination of the PG of this group showed apparently larger acinar and ductal cells. Acinar cells presented nuclei with variation in size, shape (pleomorphism) and site while others have shown pyknotic nuclei, irregular nuclear membrane and some were fragmented (Figures 4 A,B,C,D,E). Dilated RER cisternae were found throughout the cytoplasm of some acinar cells and swollen mitochondria, which had ill-defined outline and damaged cristae (Figures 4 A,B,D). Interstitial tissue

between serous acini was infiltrated with inflammatory cells (Figure 5E). Intercalated ducts showed slight dilatation in their lumens. ICD cells appeared almost with normal cell architecture, but exhibited enlarged nuclei with pleomorphism, mitochondria with damaged cristae as well as damaged microvilli, other showed apparent thickening of the plasma membrane (Figures 5 A,B). Striated duct cells showed apparent loss of cell height, shrunken nuclei, swollen mitochondria with damaged cristae as well as apparent thickening of the plasma membrane (Figure 5C). Excretory ducts showed loss of pseudo-stratification, damaged microvilli, also showed apparent thickening of the plasma membrane (Figure 5D). Myoepithelial cells appeared almost normal (Figure 5 F).

Statistical results

The diameter of acini in control group ranged from 31.89–37.22 with (mean 34.79±1.99), compared to OC group ranged from 56.14–63.97 with (mean 60.30±2.79), there was highly statistically significant higher mean in OC group compared to control group with *p-value* ($p<0.001$ highly significant) (Table 1, Figure 6).

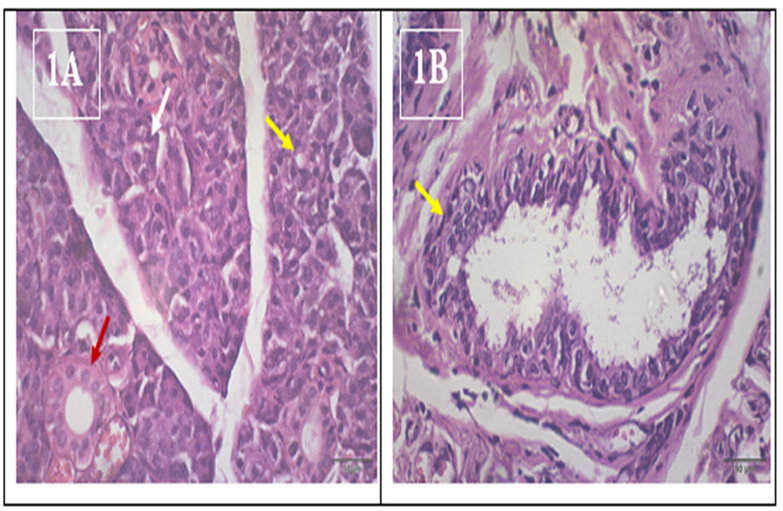

Fig. 1: A, B photomicrographs of the PG control group showing: 1A: Serous acinar cells lined by pyramidal cells with basophilic cytoplasm and basal rounded nuclei (white arrow). ICD lined by cuboidal cells and centrally placed nuclei (yellow arrow). Striated duct lined by columnar cells with central nuclei, having esinophilic cytoplasm and basal striations (red arrow). 1B: Excretory duct lined by pseudostratified columnar epithelium (yellow arrow), surrounded by fibrous connective tissue. (H&E x400)

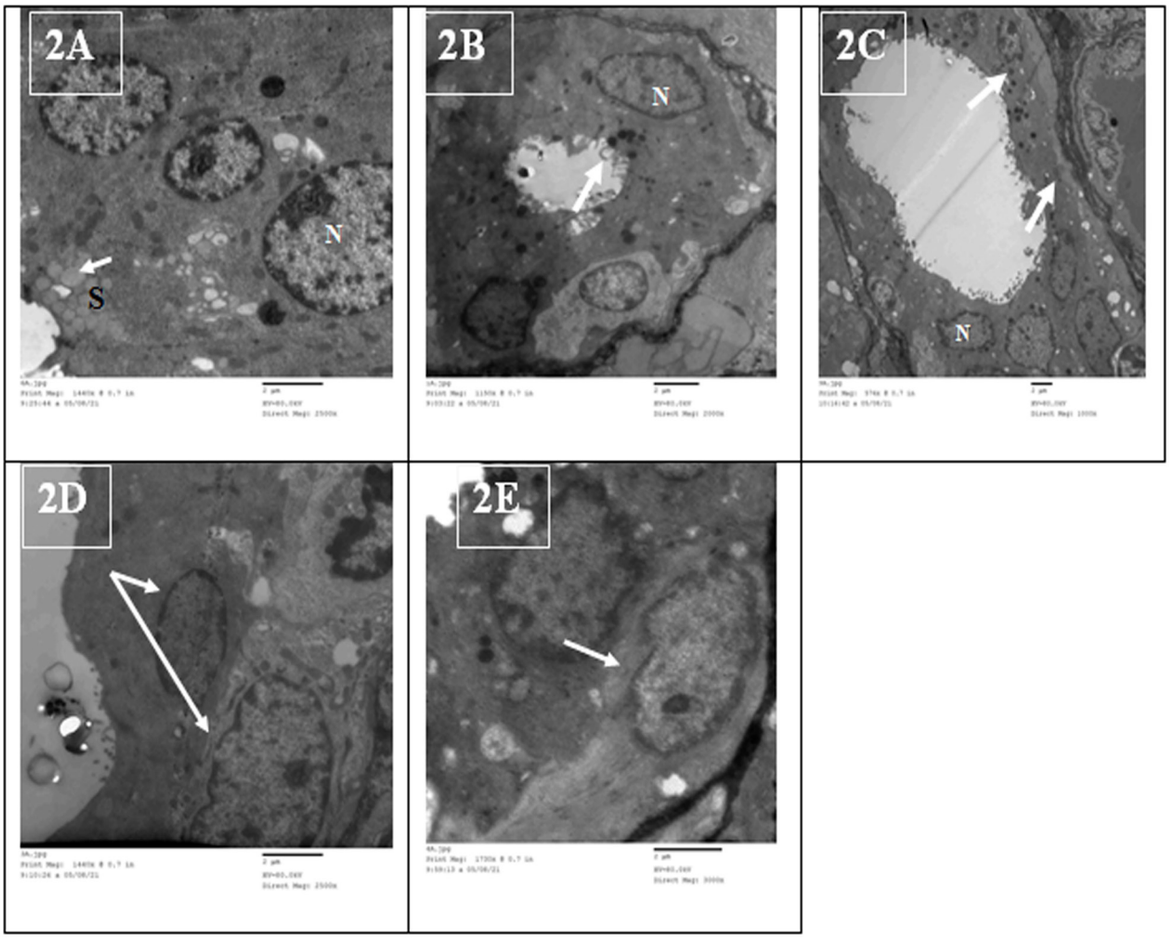

Fig. 2: A,B,C, D & E electron micrographs of PG from control group showing: 2A: serous acinus with basal nucleus (N) and secretory granules (S) of varying electron densities located apically (arrow) (x2500). 2B: ICD lined by cuboidal cells with round nucleus (N) and normal microvilli (arrow) (x2000). 2C: Striated duct with central rounded nucleus (N) and normal mitochondria (white arrows) (x1000).2D: excretory duct with pseudostratified cell arrangement (arrows) (x2500).2E: Myoepithelial cell (arrows) (x3000).

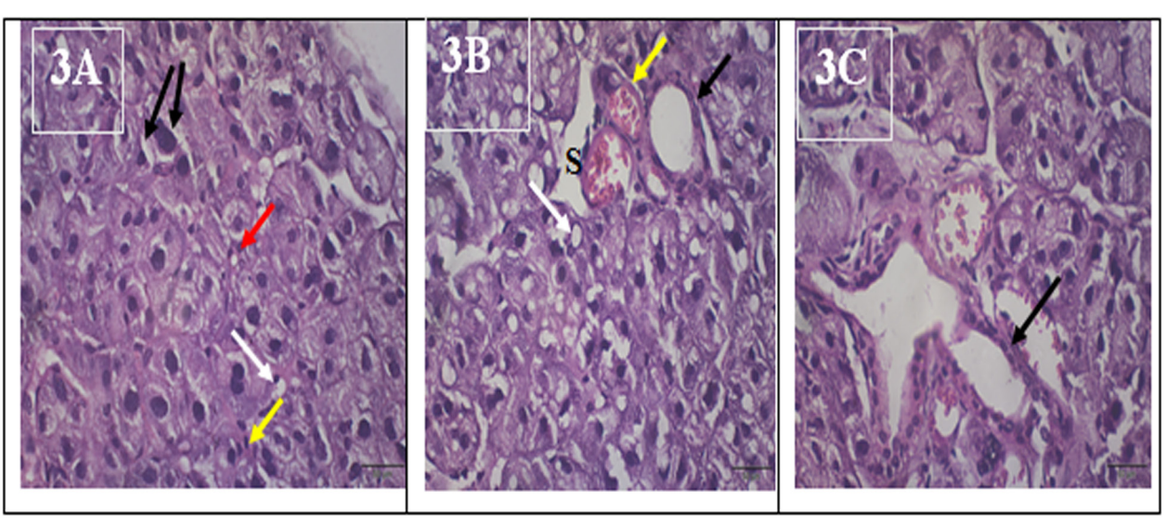

Fig. 3: A, B & C photomicrographs of the OC group showing: 3A: Serous acini showing pleomorphism of its nuclei (black arrows), darkly stained pyknotic nuclei (yellow arrow), cytoplasmic vacuolations (white arrow) and ICD with fewer nuclei (red arrow). 3B: Widely separated serous acini (S), vacuolations (white arrow), striated duct with apparent loss of cell height, flattened nuclei and loss of basal striations (black arrow) and congested blood vessel (yellow arrow).3C: Excretory duct with loss of pseudo-stratification (arrow). (H&E x400)

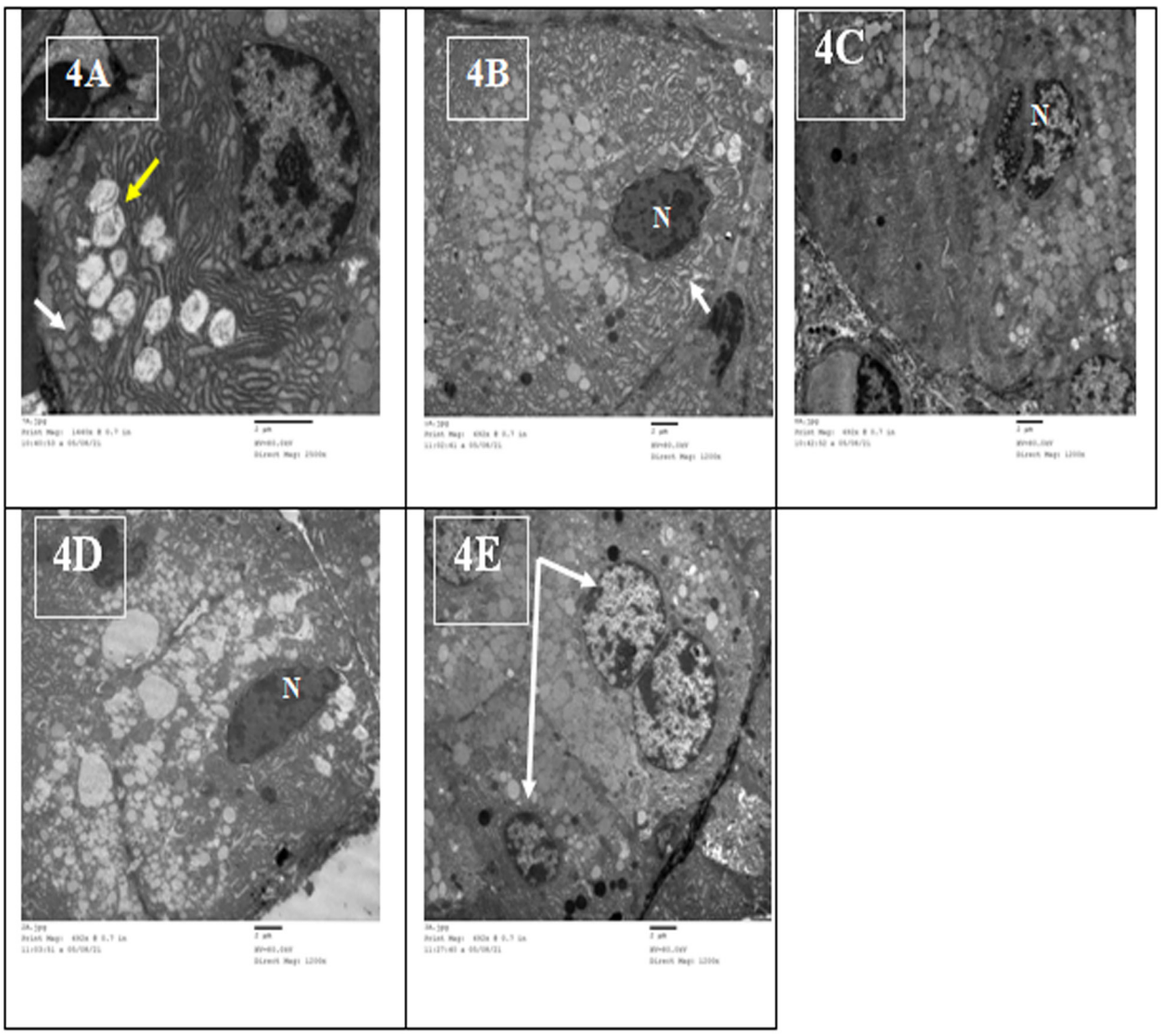

Fig. 4:A, B, C, D & E electron micrographs of PG from the OC group showing: 4A: serous cell showing dilated cisternae of RER (white arrow), swollen mitochondria (yellow arrow) with ill-defined outline and damaged cristae (x2500). 4B: serous cell showing nuclei with irregular nuclear membrane (N) and dilated cisternae of RER (arrow), (x1200). 4C: Acini cells with fragmented nucleus (N) (x1200). 4D: serous acinar cells showing pyknotic shrunken nucleus (N) (x1200). 4E: acinar cells with nuclear pleomorphism (arrows) (x1200).

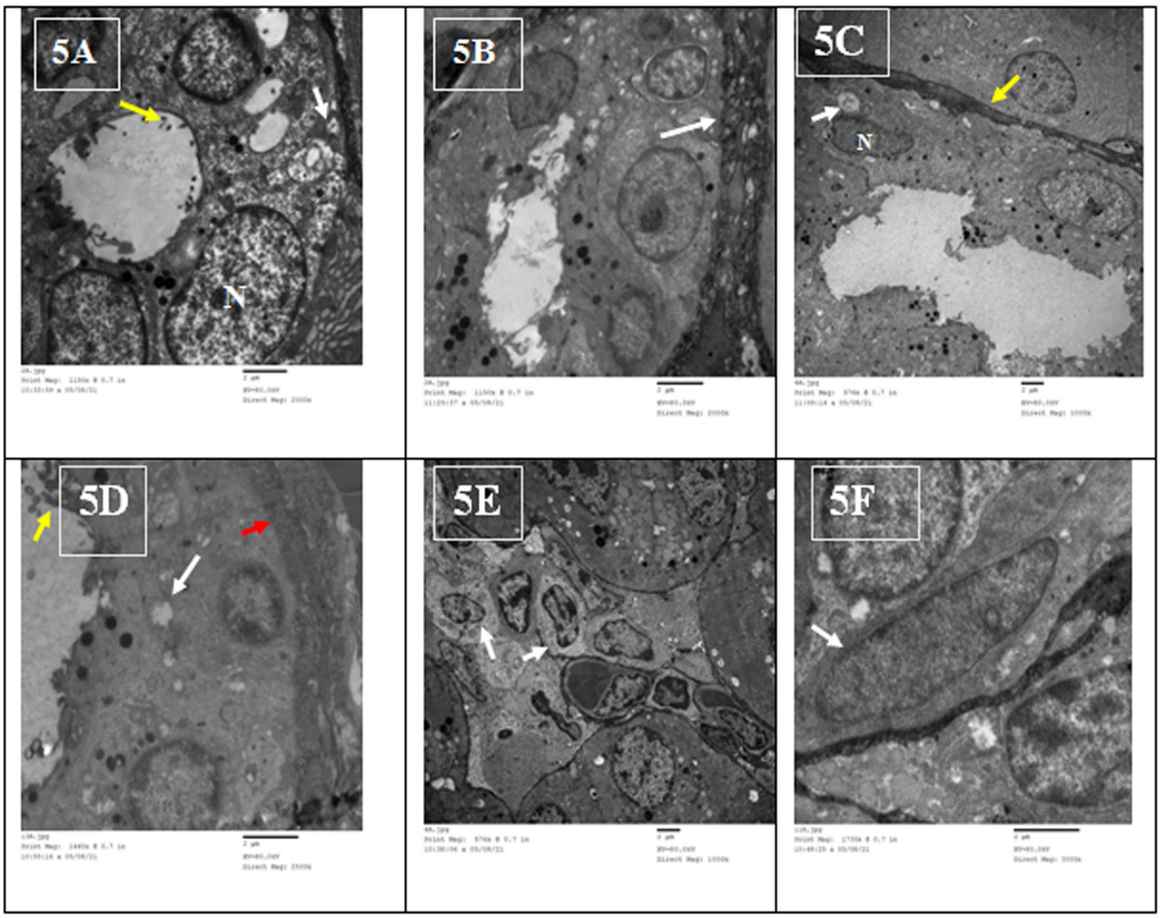

Fig. 5: A, B, C, D, E & F electron micrographs of PG from the OC group showing: 5A: ICD cells with enlarged nuclei (N), mitochondria with damaged cristae (white arrow), as well as damaged microvilli (yellow arrow) (x2000). 5B: ICD showing apparent thickening of the plasma membrane (arrow) (x1200). 5C: striated duct cells with pyknotic nuclei (N), swollen mitochondria with damaged cristae (white arrow), apparent thickening of plasma membrane (yellow arrow) (x1000). 5D: Excretory duct with loss of pseudo-stratification, mitochondria with damaged cristae (white arrow), damaged microvilli (yellow arrow) and apparent thickening of the plasma membrane (red arrow) (x2500). 5E: Inflammatory cell infiltration between acini (arrows) (x1000). 5F: Myoepithelial cell (arrow) (x3000).

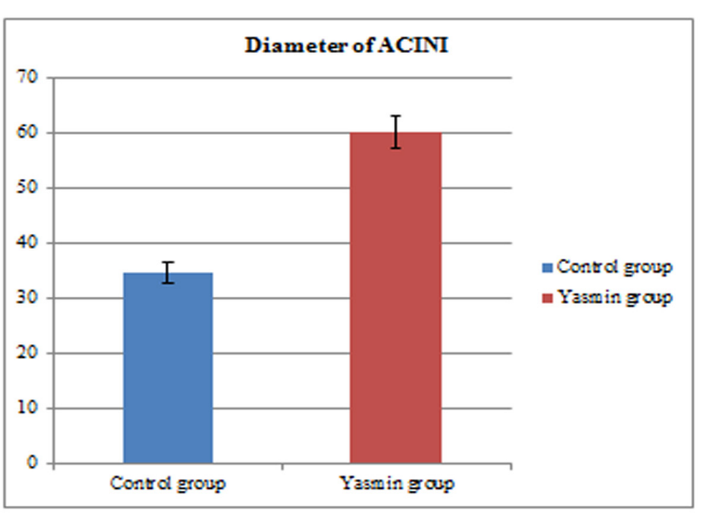

Fig. 6: Bar chart for comparison between control group and Yasmin group according to diameter of acini.

Table 1: Comparison between control group and OC group according to diameter of acini

Diameter of acini	Control group (n=7)	OC group (n=7)	Test value	*p-value*
Mean±SD	34.79±1.99	60.30±2.79	19.704	<0.001**
Range	31.89–37.22	56.14–63.97		

Using: Independent Sample t-test; ***p-value* <0.001 HS

DISCUSSION

There are several choices when considering oral contraceptive therapy, therefore, it is very crucial to investigate possible effects of different types of OCs on oral tissues[10]. They contain mainly two active components: the estrogen and the progestin that have proven to generate oxidative stresses on various body tissues[11,12]. This is either by direct action of estrogenic and pregestational compounds on the target tissues or due to their indirect actions[6].

Sex steroid hormones in OCs have been proven to affect the physiology of the human oral cavity. Several studies suggested that the changes in female sex steroid-blood levels affects oral soft tissues significantly[13]. The researchers stated the presence of tissue-specific estrogen receptors subtype distribution in oral tissues. These are the estrogen receptors-β, which have been expressed in both the oral epithelium and the salivary glands. Estrogen receptors identification within these tissues suggested the direct regulation of estrogen to the physiology of oral tissues.

In Another study by[14], the researchers also supported the presence of estrogen receptor-β in acinar and ductal cells in the human parotid, submandibular as well as minor salivary glands, in both men and women. As for progesterone receptors,[15,16] reported their high presence within intercalated, striated, and excretory ducts. Immunohistochemical investigation reported occasional detection of progesterone receptors on acinar cells.

Estrogen generally has antioxidant potentials that can reduce oxidative stress and lipid peroxidation[17]. However, it has been reported that when both estrogen and progesterone are co-administered, these useful effects of estrogen were found to be mitigated[18,19,20,21] noted an increase in the oxidative stress after COCs administration in both women and rats, which supports our results.

The current study revealed several degenerative changes in both acinar and ductal cells, histologically and ultra-structurally upon administration of Yasmin,[1] explained this. The researchers reported the association of the COC pills with the generation of free radicals and disruption of the oxidative status, which in turn resulted in degenerative changes within the tissues. Several studies were also conducted to investigate the effects of OCs on oxidative stress and reported a significant increase in lipid peroxides in women using OC pills[22,23,24,25].

In the current study, COC administration showed many ultrastructural degenerative changes in the PG in the form of nuclear pleomorphism and pyknosis, dilated RER cisternae as well as swollen mitochondria with ill-defined outline and damaged cristae in both acinar and ductal cells which was explained by[26] to be as a consequence of high levels of release of free radicals or reactive oxygen species (ROS) that has been known to be directly responsible for lipid damage. The main sources of endogenous ROS are the mitochondria, plasma membrane, endoplasmic reticulum, and peroxisomes.

In the present study, the pyknosis that occurred in the acini and ducts of the OC group histologically and ultra-structurally has been explained by[27] that its occurrence indicates the loss of functional efficiency of the cells.

Moreover, OC administration resulted in an apparent increase in the size of acini and ducts of the current study which was explained by[28] to be as a result of generation of free radicals through production of O2 and O2-free radicals. This in turn leads to an increase in lipid peroxidation and acts as an important messenger for many pathological conditions through increasing cytosolic-free calcium and membrane permeability as well as swelling of cells which supports our results.

Furthermore, this increase in the acinar cell size following OC administration in the current study showed high statistically significant difference when compared to the control group. This was found in agreement with[29], who have found that there was an increase in the cell number, cell size as well as tissue water retention in renal tissues with the use of contraceptives.

In the present study, the lumen of the ICDs of the OC group have shown a slight dilatation with an apparent decrease in the number of microvilli ultra-structurally and was supported by[30] in their study on the effects of OCs on liver cells. The researchers have found sinusoidal dilatation, microvilli diminished in number as well as inflammatory cell infiltration which supports our results.

Apparent thickening of the plasma membrane was revealed ultra-structurally in the acini and ducts of the OC group of the current study which was consistent with[31] who discussed the effects of estrogen on rat kidneys and reported that there was a noticeable increase in the thickness of the tubular and glomerular basement membrane when compared to the control group.

The existing study also revealed that treatment with Yasmin resulted in inflammatory cell infiltration and congested blood vessels which were explained by[32] as the researchers stated that progesterone resulted in increasing vascular permeability, proliferation as well as inflammatory cell infiltration.[33] also proved that OCs increased the frequency of gingivitis and reported that prolonged usage of hormonal contraceptives led to attachment loss which was significantly higher in females taking OCs compared with controls. Therefore, variations in the level of sex

steroid hormones can also have an impact on inflammatory response of oral tissues[34].

In another agreement with the present study,[35] have found that OCs caused several histological and ultrastructural changes in adult female Albino rats in renal tissues, in the form of renal tubular degeneration, renal blood vessels congestion and inflammatory leukocytes infiltration.

Recognizing the adverse oral side effects of oral contraceptives is very important for comprehensive care and will allow treatment plans to meet each patient's individual needs. Since one of the important responsibilities in clinical practice is patient's education, dental professionals should inform patients about any possible signs and symptoms to pursue when taking any medication[10].

CONCLUSIONS

From this study, we concluded that when COC pills were administrated to female Albino rats, it revealed degenerative changes within acini and ductal cells of PG. Thus, we recommend further studies on different oral tissues.

ABBREVIATIONS

COCs: Combined oral contraceptives; **OCs:** Oral contraceptive pills; **H & E:** Hematoxylin and Eosin; **TEM:** transmission electron microscopic; **PG:** parotid gland; **ICD:** intercalated duct; **RER:** rough endoplasmic reticulum; **ROS:** reactive oxygen species.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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الملخص العربى

تأثير موانع الحمل الفموية المركبة على الغدة اللعابية النكفية لإناث الجرذان المهق (دراسة بالميكروسكوب الضوئي والإلكتروني النافذ)

هند المسيري وصفاء اسماعيل حسين

قسم بيولوجيا الفم- كلية طب الاسنان - جامعة عين شمس

نبذة مختصرة: إن وسائل منع الحمل الفموية المركبة إحدى أكثر الأدوية المسنخدمة هذه الأيام في الدول المتقدمة. يعتبر مزيج حبوب منع الحمل المكون من الدروسبيرينون و الايثينيل استراديول (ياسمين) وسيلة حمل فعالة تستخدمها الكثير من النساء حول العالم.

هدف الدراسة: هو فحص التأثير المحتمل لاعطاء الياسمين على الغدة النكفية في الجرذان البيضاء.

طرق ومواد البحث: قسمت أربعة عشر جرذا أبيض من الاناث إلى مجموعتين متساويتين. المجموعة الضابطة: حيث أعطيت الجرذان الماء المقطر عن طريق أنبوب المعدة يوميا. مجموعة منع الحمل: حيث أعطيت الجرذان أقراص الياسمين مذابة في الماء المقطر عن طريق أنبوب المعدة يوميا (٠,٦ مجم / كجم من وزن الجسم) و ذلك بمعدل دورة الخمسة أيام (أربعة أيام دواء و يوم راحة) لمدة ثمانية دورات للشبق (إثنان و ثلاثين يوما). تم تحضير الغدد النكفية للفحص بالميكروسكوب الضوئي و الإلكتروني النافذ.

النتائج: أظهر الفحص بالميكروسكوب الضوئي و الإلكتروني النافذ لمجموعة دواء منع الحمل العنيبات المصلية ذات فراغات سيتوبلازمية ، تعدد الاشكال النووية ، إتساع في الشبكة السيتوبلازمية الداخلية الخشنة و إنتفاخ في الميتوكوندريا. كما أظهرت القنوات تغيرات إنتكاسية. أظهر التحليل الإحصائي لقطر العنيبات زيادة بارزة في مجموعة منع الحمل بالمقارنة مع المجموعة الضابطة.

الاستنتاجات: أظهرت هذه الدراسة عند إعطاء حبوب منع الحمل المركبة لإناث الجرذان البيضاء تغيرات إنتكاسية في خلايا العنيبات والقنوات للغدة النكفية.