Effects of a Combined Oral Contraceptive on the Endocrine Organs: Histopathological Effects on the Adrenal Glands

KOMBİNE BİR ORAL KONTRASEPTİF'İN ENDOKRİN ORGANLAR ÜZERİNE ETKİLERİ: ADRENAL BEZLER ÜZERİNE HİSTOPATOLOJİK ETKİLER *

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Summary

In this study, adrenal glands of female mice which were administered a combined oral contraceptive (COC) including ethinyl estradiol+ethynadiol diacetate for one year were examined light microscopically. Total dimensions and thickness of cortex and its zones and thickness of medulla in adrenal glands were evaluated according to morphometric data with micrometric ocular in the treatment and the control groups.

Nodular construction in zona reticularis (21.3%), excessive lipid vacuolization (12.3%) and leucocytic infiltration (0.62%) in cortex and slight changes in dimensions of the adrenal glands were observed in COC administered mice. It was concluded that, low doses of COC cause no significant morphometric changes, but it provokes some histopathologic changes in the adrenal glands.

Key Words: Ethinyl estradiol, Ethynadiol diacetate, Adrenal glands

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Özet

Bu çalışmada, bir yıl süreyle ethinyl estradiol (EE) + ethynadiol diacetate içeren kombine bir oral kontraseptif (COC) verilen dişi farelerin adrenal bezleri ışık mikroskobik olarak incelendi. Kontrol ve deney gruplarında adrenal bezlerin, kortex ve zonları ile medulla kalınlıkları ve total boyutları mikrometrik oküler yardımıyla morfometrik verilere göre değerlendirildi. COC verilen farelerin adrenal bezlerinde zona reticularisde nodularite (%21.3), kortekste aşırı lipid vakuolizasyonu (%12.3) ve lökositik infiltrasyon (%0.62) ve bez boyutlarında hafif bir değişim bulundu. Düşük dozlu kombine bir OC'in adrenal bez boyutlarında istatistiki olarak anlamlı bir değişiklik oluşturmadığı, fakat bazı histopatolojik değişimlere yol açabileceği sonucuna varıldı.

Anahtar Kelimeler: Etinil östradiol, Etinadiol diasetat, Adrenal bezler

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It is known that long-term use of oral contraceptives (OCs) may cause various side effects on endocrine functions in the recipients (1, 2). It has been reported that administration of OC leads to metabolic change. (3-5). It has been shown that adrenal glands increased in weight in ewes grazing oestrogenic subterranean clover (6). Plasma 11-OHCS (hydroxycorticosteroids) levels were measured in order to investigate effects of different OCs on adrenocortical function (7). Significant impairment of adrenocortical function and alteration of adrenocortical morphology occured in groups treated with megesterol acetate (8). In another study it has been suggested that there were no changes in metabolic and endocrine functions in women taking OC (Norinyl 1/50) with a medium-dose for 6-12 months (9). The number of histological studies regarding effects of OCs on adrenal glands is limited. In some medical and veterinary studies it has been suggested that OCs cause an increase in adrenal weight (10-14), involution of adrenal glands (15), hypoadrenalism (16); an increase in epineph-

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rine levels of adrenal gland (17); a decrease in epinephrin content of adrenal gland (18), an increase in corticosteroid-binding globulin and total plasma Cortisol levels (19-21), induction of aldosteron secretion (20, 21), atrophia in zona fasciculata and zona reticularis in cortex (22). In this study, we planned to evaluate adrenal glands of female mice histopathologically which were administered COC for one year.

Material and Method

Thirty adult albino female mice (25-30 g) were employed for this investigation. Mice (control group involving 10 and treatment group 20) were kept in small groups in the laboratory with standard diet and water ad libitum. A COC containing EE + ethynadiol diacetate was dissolved in tap water. Low-dose COC (0.001 mg/mouse/day EE + 0.02 mg/mouse/day ethynadioldiacetate) were administered orally to the treatment group for one year (23). All the mice were killed by decapitation and adrenal glands were quickly dissected out, fixed in 10% buffered formaldehyde solution and processed for histological study and 5 mm thick paraffin sections were stained with Haematoxylin & Eosin (H& E) and Masson's trichrome techniques (24). The difference of histopathological findings between the control and the treatment groups were evaluated by "Fischer's X^2 Test". Thicknesses of cortex, cortical zones, medulla and total dimensions of adrenal glands were measured with micrometric ocular with regard to direct optical measurements as a classical method for small particles (25). According to these measurements, differences between control and treatment groups were evaluated by "Mann-Whitney U-Wilcoxon sum W Test" (26).

Findings

a) Macroscopic findings: Macroscopically there were no differences between the adrenal glands of the treatment group and the control group. They were located on the upper poles of the kidneys at their normal position.

b) Microscopic findings

Control group. The mouse adrenal gland were bound externally by a thin fibrous capsule containing adipose tissue. Collagenous fibres and vessels were entered to inside of adrenal gland from the capsule. The adrenal cortex was comprised about 90% of the gland and surrounds the centrally located medulla. Three cortical zones were observed. The zona glomerulosa was about 15% of the cortex under the capsule and contained foci of cells. Cells of zona fasciculata, about 65% of the cortex, appeared to be vacuolated or clear on stained sections because of their high cholesterol content. The ill-defined zona reticularis, about 7% of the cortex contained more compact cells with less lipid. In the control group, zona reticularis cells were arranged in a spongelike meshwork of gently buckled anastomosing one-cell wide rows of cells that were separated by dilated capillaries. The well-outlined cells were smaller than those of the zona fasciculata and these cells had cytoplasm that is granular, acidophilic, and relatively lipid sparse (Figure 1-2).

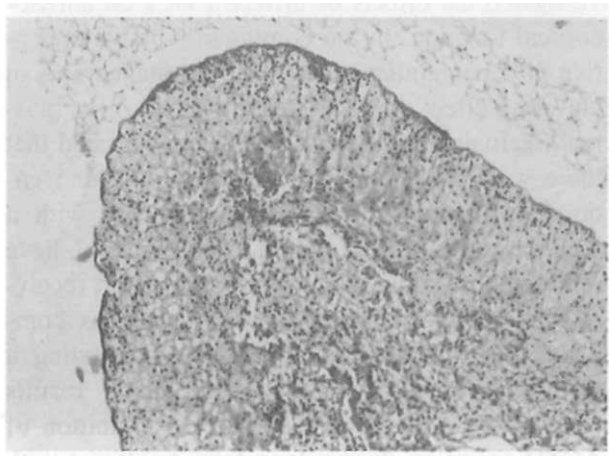

Figure 1. Adrenal gland showing cortex and medulla in normal control mouse. H & E . X 100.

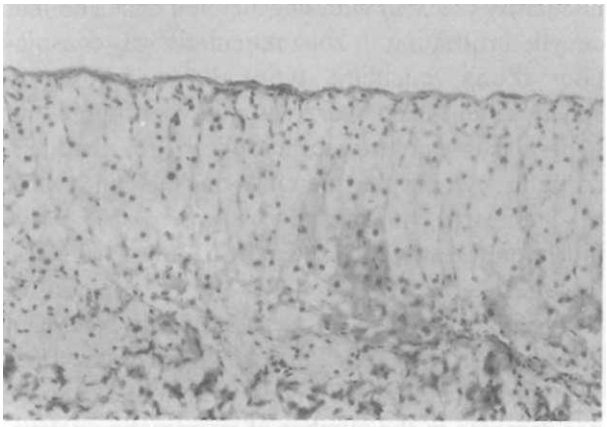

Figure 2. Adrenal gland showing cortex and medulla in normal control mouse. H & E . X 200.

Table 1. The means of total dimensions, thickness of cortex, zona glomerulosa, zona fasciculata, zona reticularis and medulla in the adrenal glands and their standard deviations and U and P values in the control and the treatment groups

Dimensions of adrenal glands	Variables (micrometric oculer units) (10 X)			
	The control group (n=10)	The treatment group (n=20)	U Values	P Values
Means ± Standard deviations	X±SD	X±SD		
Total dimensions	86.67 ± 5.77	87.00 ± 22.92	20.0	0.55 *
Thickness of cortex	26.67 ± 7.64	27.06 ± 6.01	22.5	0.74 *
Thickness of medulla	43.33 ± 5.77	43.38 ± 15.76	22.5	0.74 *
Thickness of z.glomerulosa	4.00 ± 1.00	4.23 ± 19.18	19.0	0.41 *
Thickness of z.fasciculata	15.67 ±4.04	14.56 ± 3.33	22.0	0.68 *
Thickness of z.reticularis	5.00 ± 0.00	5.82 ± 1.89	24.0	0.86 *
Ratio of z.reticularis/cortex	0.20 ± 0.05	0.22 ± 0.06	20.0	0.52 *

** The differences were not statistically significant (P> 0.05).*

Treatment group. There was a slight increase at the means of total dimensions and thickness of cortex and its zones (exception zona fasciculata) in the treatment group. Furthermore ratio of zona reticularis/cortex of adrenal glands in treatment groups increased when it was compared with the control group. However there were no statistically significant difference (P>0.05) according to the means of total dimensions and thickness of cortex and its zones and ratio of zona reticularis/cortex in the adrenal glands between the treatment and the control groups (Table 1).

Some histological changes in the treatment group was noticed. It was determined that excessive lipid vacuolization (12.5%) in cortex and nodularity (21.3%) with degenerated cells and leucocytic infiltration in zona reticularis was conspicuous. Zona reticularis type-cells were roughly spherical, uncapsulated areas of hypertrophic and hyperplastic were present and these areas had acidophilic cytoplasm, picnotic nucleus and most of them had no nucleus (Figure 3-5). Polymorphonuclear leucocytic infiltration (0.62%) in cortex and cortico-medullar junction and an increase of connective tissue around this areas and nodularity in zona reticularis were seen in the treatment group (Figure 3-5). Neither noticible increase nor decrease in the number of eucromatic nucleus, cytoplasmic material and basophilia stained H & E sections in chromaffin cells of medulla in the treatment groups were observed compared to the control groups. In terms of statistical values no significant differences were found as to histopathological findings in the treatment group.

Discussion

Most of the studies on the adrenal gland is associated with physiological activity (1-10, 16-20, 27-29). It is known that long-term use of OCs could cause various side effects on endocrin functions in the recipients (1,2). It has been reported that administration of OC leads to metabolic change. It has been noted that the changes were mainly due to estrogen component (3-5). Kauppila et al. have investigated the effects of different OCs on adrenocortical function. In the combined type contraceptive pills containing estrogen and gestagen had an elevating effect on the 11-OHCS level of the plasma (7). In another study it has been suggested that there were no changes in the metabolic and endocrine functions in women taking OC with a medium-dose for 6-12 month (9). Leiba et al. have reported a considerable number of women receiving antiovulatory compounds or estrogens complain of weakness and fatigability, suggesting a state of clinical hypoadrenalism. Their results showed that there was a significant inhibition of ACTH secretion during long-term treatment with antiovulatory compounds or estrogens, and in half of the cases there was a delay in normalization of

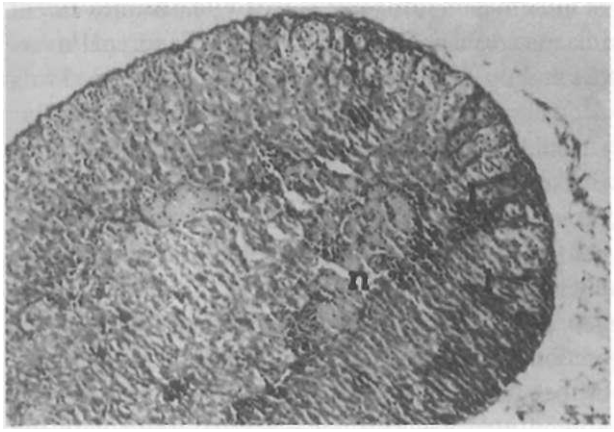

Figure 3. Adrenal gland showing cortex and medulla in the treatment group. Note nodularity (n) of zona recicularis with degenerative cells and leucocytic infiltration (l) in cortex. H&E. X 100.

the pituitary-adrenal axis following interruption of the drug, supporting a state of transitory hypoadrenalism (16). Ruokonen et al. have reported effects of OC combinations of 0.125 mg desogestrel + 0.050 mg EE, and of 0.125 mg levonorgestrel + 0.050 mg EE on serum Cortisol and the urinary excretion of 17-oxogenic steroids and free Cortisol in healthy female volunteers. Both OCs have increased (PO.001) serum Cortisol concentrations. It was suggested that the abnormalities seen were due to an increased serum binding capacity of Cortisol induced by EE and not a sign of pathologic changes in adrenal function (19). For many years used estroprogestative drugs (EPD) have multiple secondary effects concerning mainly the glucidic and lipidie metabolisms have been reported by Lemay et al. They have determined some clinical features occurring with administration of EPD: diminution of hirsutism and/or acne, augmentation of body weight, appearance of hypertension (20). Meulenberg and Hofman (1990) have studied the effects of OCs on the daily rhythm of Cortisol and,

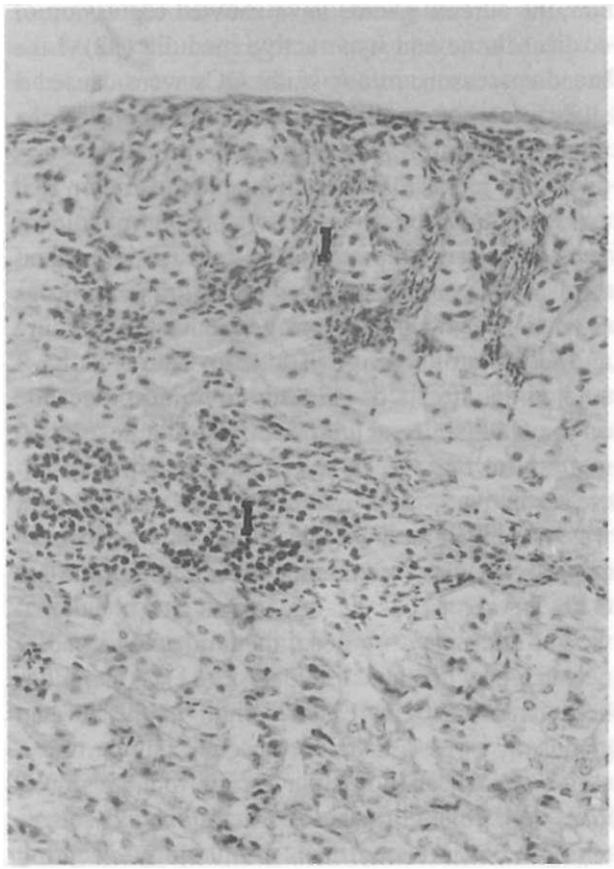

Figure 4. Adrenal gland showing cortex and medulla in the treatment group. Note leucocytic infiltration (l) in cortex and cortico-medullar junction. H & E. X 200.

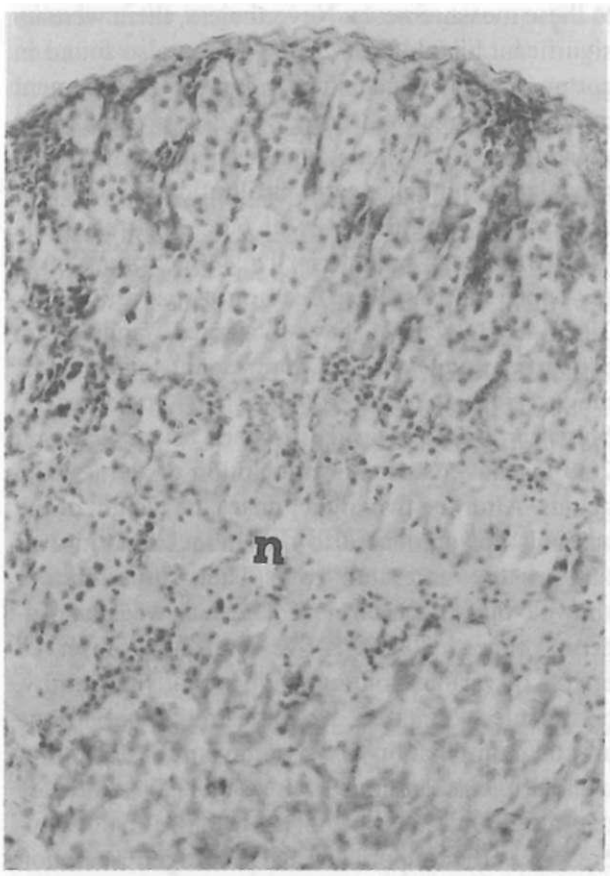

Figure 5. Adrenal gland showing cortex and medulla in the treatment group. Note thickness and nodularity (n) of zona recicularis (about 40% of the cortex) in cortex. H & E. X 200.

its metabolite cortisone in plasma and saliva in the OC users being intermediate dose (27). Afolabi et al. have examined the role of the adrenal cortex in the pathogenesis of hypertriglyceridaemia associated with the intake of OCs containing oestrogen in rats. It has determined that in animals with intact adrenals the administration of oestradiol: (a) raised plasma triglyceride levels, and increased the adrenal cortex/body weight ratio. The results have suggested a regulatory role for the adrenal cortex in the homeostasis of plasma triglyceride concentration and that the hypertriglyceridaemia induced by the oestrogen containing preparations might be secondary to alterations in adrenocortical function (10). In our histological study there was a slightly increase at the means of total dimensions, thickness of cortex, thickness of cortical zones (exception zona fasciculata) and zona reticularis / cortex of adrenal glands in treatment groups when it was compared with the control group. However there were no statistically significant difference (P>0.05) according to these measurements. Nevertheless, there were no significant histological changes were also found in cortex in terms of statistical values in the treatment group. We have observed excessive lipid vacuolization (12.5%) in zona fasciculata and zona reticularis and leucocytic infiltration (0.62%) in cortex and nodularity with degenerated cells (21.3%) in zona reticularis. This effect of OC may be upon suppressive effect on zona reticularis. Tisell and Salander have observed "androgenic properties and adrenal depressant activity of megesterol acetate in castrated male rats". Megesterol acetate in daily doses of 0.2, 2.0 and 20.0 mg have caused an involution of the adrenal glands. After the two higher doses the weight of the adrenals has amounted to only about one third of that of the untreated rats. Their investigation showed that megesterol acetate has weak androgenic properties (15). Klove et al. have observed effects of various contraceptive steroids in healthy, nonhirsute women. Levonorgestrel (1-Ng) alone and the combination of 1 -Ng have not affect adrenal androgen secretion. Their results have indicated that norethindrone, but not 1-Ng has a major suppressive effect upon adrenal androgen secretion (27). Lemay et al. have showed that the triphasic OC has significantly improved acne in postpubertal women for whom acne was the main manifestation of mild hyperandrogenic activity. The improvement in acne corresponded to a decrease in adrenal/ovarian androgens and free testosterone, which led to a decreased metabolism to 3-a-androstenediol glucuronide, presumably by the sebaceous glands (30). Burkman has suggested that the potential mechanism of action by which OCs correct excess'androgen states include gonadotrophin suppression, reduction of circulating androgens, increased androgen binding, suppression of adrenal androgen secretion and inhibition of 5 alpha reductase, and androgen receptor binding. In normal women, there is a good evidence that these actions occur with the use of OCs (31). Ramachandran and Patel have studied "seasonal histomorphological alterations of adrenals in domestic pigeons ". In their study, histologically, during the breeding season adrenals showed an active condition with active adrenocortical cell columns. It has thought that increased cortical/medullary ratio could be easily discerned in the adrenal sections. During the non-breeding season, the adrenal glands have showed regression of cortical tissue and hyperactive medulla (32). Like breeding season, in our study OCs were caused a slightly active condition of adrenal glands in the treatment group. Although zona reticularis was thickened it was also degenerated. It is known that estrogens and progestogens have antiandrogenic effects. EE, medroxyprogesteron acetate and megesterol acetate can be used as antiandrogenic drugs (33). It is known that estrogens change structure and function of adrenal gland (34). Zaki et al. have studied the effects of EE and norethindron acetate on the adrenal cortex in the rat. EE in a dose of 10 mg/day for two weeks has caused a significant increase in the weight of adrenal. When treatment was prolonged to six weeks no effect was seen on adrenal weight. Treatment with norethindrone acetate for six weeks has caused a rise in adrenal weight with the 7 mg dose, then a decline in adrenal weight with the 21 mg dose (11). Adams has been determined increased weight in the adrenal glands of ewes grazing oestrogenic subterranean clover (6). Chastain et al have been found a significant impairment of adrenocortical function and alteration of adrenocortical morphology occurred with treated megesterol acetate groups (8). However it is known that information on truly normal adrenal weight is difficult to obtain because the

organ (specifically the cortex) respond rapidly to stress by an increase in mass. For accuracy the thickness should be determined microscopically with an ocular micrometer, it is impractical to detect small alterations in the thickness using metric scale (35). Scardein has stated that for two years at dosage levels (0.006-0.008 and 0.06-0.08 mg/kg EE) in a combination OC treated females had adrenal enlargement. In their other study, albino rats were fed norethisterone acetate in the diet for two years at dosage levels of 0.3-0.4 mg/kg in a combination with estrogen-progestogen. OC treated females had increased adrenal gland weights (12-13). Letherland and Renfree have considered that after the corpus luteum (CL) removed, estrogen injections given in adult tammar wallabies (Macropus eugeni) adrenal weight, adrenal somatic index, adrenal cortex, thickness of zona fasciculata and zona reticularis were greater than the control group (14). Yardimoglu and Misirhoglu have observed histopathological effects of EE + Desogestrel containing COC on the rat adrenal gland in different doses and times. Hyperemia and vascular dilatations and even cystic dilatations in cortex and medulla and lipid vacuoles in the zona reticularis cells was seen in the high dose treatment groups. They couldn't find a significant difference in thickness of cortex and medulla with micrometric ocular between the control and the treatment groups. It has concluded that adrenal glands were affected from OC in the high dose treatment, but not affected in the low dose treatment (36). In the present study, we have also determined similar findings but, we couldn't find hyperemia and cystic dilatations in cortex in the treatment group. We observed nodularity in cortex and excessive lipid vacuolization in zona fasciculata and zona reticularis and leucocytic infiltration in cortex of adrenal glands in mice which were administered a COC containing EE + ethynadioldiacetate with low dose and for one year. Although the histopathological findings had no significance, even long-term COC with low-dose effects may have pathologic results. In the treatment group, there were no significant changes in cortex and medulla dimensions according to the control group. Gupta et al. have studied " role of catecholamines in the central and peripheral actions of steroidal contraceptives". The steroidal contraceptive pills (Lyndiol and Ovulen) were found to decrease the adrenaline content of adrenal glands significantly without affecting the catecholamine content of heart and uterus (18). Maiti (1982) has studied effect of prolonged treatment of norethisterone (a progestogen-only contraceptive) on adrenomedullary activity in albino rats. Administration of this synthetic steroidal contraceptive in a dose of 0.5 mg/rat/day, consecutively for 75 days, has raised the epinephrine level of the adrenal gland. No other perceptible change has marked in the medullary histology, mitotic incidence or in the norepinephrine level of the adrenal gland after the treatment. It was concluded that prolonged treatment with an even progestogen-only contraceptive, like norethisterone, causes untoward effect at least on adrenomedullary hormonal activity in the albino rat (17). In present study, we have determined neither a noticible increase nor a decrease in the number of eucromatic nucleus, cytoplasmic material and basophilia in chromaffin cells of the medulla in the adrenal glands of the treatment groups when compared to the control groups.

In conclusion, our findings showed some histopathological changes on adrenal glands of female mice which were administered a COC for one year. In the treatment group, nodular construction in zona reticularis (21.3%), excessive lipid vacuolization (12.3%) and leucocytic infiltration (0.62%) in cortex were observed and there was slight changes in dimensions of the adrenal glands. It has been considered that low dose of COC didn't cause a significant morphometric change, but it provoked some histopathologic changes in the adrenal glands.

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