WHY ARE ETHYLOESTRADIOL AND D-NORGESTREL CAPABLE OF EMERGENCY CONTRACEPTION?

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Abstract

The author investigated the effects of 0.05mg ethyloestradiol and 0.25mg d-norgestrel on endrometrium. He established that this combination is capable of emergency contraception, because it prevents the implantation of the fertilized ovum.

Key words: emergency contraception, contraception for young people, endometrium.

Introduction

With optimal administration of d-norgestrel no cells of chorial origin were detectable in the pre-menstruation histological samples. Moreover, no sign of secretion or predecidual reaction was seen (FARKAS et al., 1982).

Serum progesteron levels measured on the 21. day of the cycle proved that in most cases the drug can have an ovulation-inhibitory effect even at optimal administration, therefore, the prevention of nidation was not possible (FARKAS et al., 1982).

The drug can be taken as effective for post-coital contraception even at low dosage and in the case of multiplied intercourses (FARKAS and SAS, 1984).

A sperm needs 90 seconds to get to the cervix, while the inhibition of the penetration of sperms develops after 3 hours of administration of the drug (KESERŰ and PARRADA, 1975).

Frequent occurrance of extrauterine pregnancy indicated the tubamobility-decreasing effect of the drug (FARKAS, 1994).

In order to reduce the side effects, we proposed to bring out a contraceptive drug with low estrogen content (FARKAS et al., 1981, FARKAS and SAS, 1984, FARKAS, 1978).

In the course of contraception with Ovidon (0.05 mg ethyloestradiol and 0.25 mg d-norgestrel) we observed a shortening of the proliferation period without presecretion period to occur (OUTLOOK..., 1966).

Prolonged administration of Ovidon pills frequently led to functional infertility (GOLDZICHERT et al., 1964).

The clinico-pharmacological studies carried out so far indicate that the active compounds of Ovidon can be used, in addition to the inhibition of ovulation, for the inhibition of nidation, as well (FARKAS, 1979, FARKAS et al., 1976).

Yuzpe (FARKAS and KAJTÁR, 1996) reported about the success of com-bined administration of de-norgestrel and ethyloestradiol.

Material and methods

Changes in the endometrium were analysed following administration of Ovidon pills (0.05 mg ethyloestradiol and 0.25 mg sd-norgestrel). Therefore, 15 patients underwent a stripe-curettage between the 16th and 25th day of the cycle.

The small pieces of corpus mucosa obtained from the curettage were transferred immediately into 10% (v/v) neutral formaline. Duration of the fixation was usually 20 to 24 hours. The fixed and cleaned samples were then embedded in paraffin and series of slices were produced from them.

The series of slices are useful to detect changes in any histological sample, even if they are best visible at another cutting plane.

After deparaffinization and dehydration, the samples were investigated by light microscopy after haematoxylin-eosin staining following a routine histological operation. The histological samples were compared with those obtained in the physiological and secretion period, as well as with histological alterations on the effects of high-dose drugs from our own earlier samples and from literature observations.

Results

In those cases where the cycle was built up by Ovidon administration (a relatively short duration of drug treatment) significant alterations were detected in the endometrium, as compared with that of normal cycle.

Several glands were found to exhibit atrophy of differing extent. Some of them became narrow, others became large, sometimes they became microcystic and their lumen became empty. These are usually lined by a single layer of cuboidal epithelial cells.

These glands which are lined by different types of epithelia can be found next to each other quite often. In some glands even flattened, endothel-like epithelial lining can also be observed.

In several cases small vacuoles are seen near the nuclei which contain glycogen by PAS staining. These vacuoles are very variable in location, they do not show the regularity which is detectable in the corresponding period of the normal cycle and only in several glands or gland epithelium.

The presence of glycogen is anticipated mainly in those cases where the progesteron derivative is in excess. In no cases was glygogen detected in the lumen. In the second part of the cycle, no mitosis can be seen in the cells of gland epithelium.

The focal oedema of the stroma is well detectable. The oedematous, loose areas in the neighbourhood of densely packed regions are especially well visible (Fig. 4/a).

It is well seen that the ratio of glands to stroma is shifted in favour of the stroma. No expressed predecidual transformation of the stroma cells was observed, indicating that the progestogene component of the drug was not dominant.

Differentiation of stroma cells was not detectable following administration with Ovidon in these short administration periods. Predecidual transformation took place only in small areas, although these areas contain relatively large number of

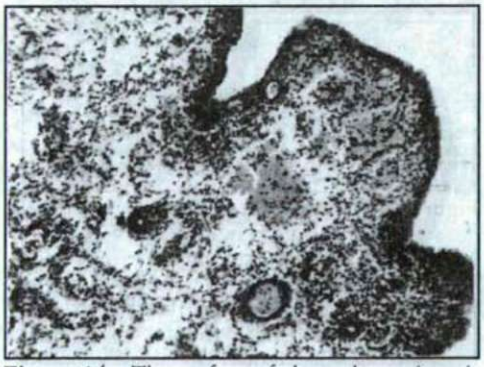

Figure 1/a. The surface of the endometrium is uneven. The stroma contains signs of focal oedemas and bleedings. The glands are tight, their epithelia are not secernating.

Age: 24 years. Last normal menstruation: 15 June. Duration of drug admi-nistration: 2 years. Date of biopsy: 9 July (24th day)

Quantity of drug administered during the cycle: 4.25 mg d-norgestrel and 0.085 mg ethyloestradiol. Obstetrical events: obstesy: 1, abortion: 0. Last obstetrical event: obstesy on 15 May, 1981.

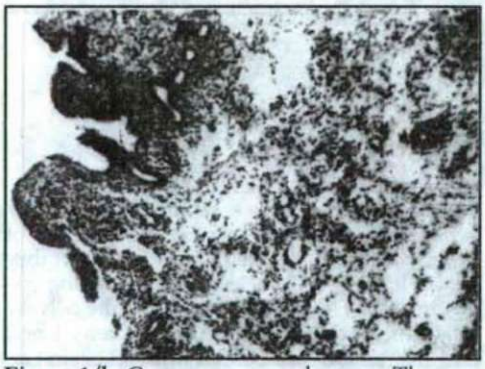

Figure 1/b. Corpus mucosa polyposus. The stroma is loosened, narrow inactive glands are visible in it, their number is reduced. Stroma cells are slightly swollen.

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Quantity of drug administered during the cycle: 4.25 mg d-norgestrel and 0.085 mg ethyloestradiol. Obstetrical events: obstesy: 1, abortion: 0. Last obstetrical event: obstesy on 15 May 1981.

endometrial granulocytes. In the other areas of the stroma, however, no sign of cellular differentiation can be seen.

The reticulum fibre network of the stroma is variable. It is well developed in the densely packed areas, whereas it is underdeveloped in the loose regions.

The spiral arteries are usually underdeveloped: only small, linear capillaries can be seen, with dilatated thin-walled arteries in other areas (Figs. 4/b and 4/c).

Long-term treatment (up to several years) resulted in a surprising histological pattern. Abortive secretion was seen only occasionally in the glandular epithelium (Figs. 1/a and 1/b).

The number of glands is decreased from cycle to cycle, finally they disappear or only their residues can be seen. These residues are glands with endothel-like epithelium lining which can be easily mistaken for the capillaries (Figs. 2/a, 2/b, 2/c and 2/d).

The stroma does not exhibit atrophy in all cases. Decrease in the number of stroma cells and their replacement by collagen was detectable only focally (Figs. 3/a and 3/b).

Figure 2/a. The surface of the mucous membrane segment is uneven, the number of glands is reduced, their lumen is narrow, they are lined by one-nucleus non-secernating epithelium. The stroma is in excess, the cells are slightly swollen, its structure is loose. 1 or 2 thick arteries can be seen instead of spiral arteries.

Age: 33 years. Last normal menstruation: 16 June. Duration of drug administration: 2 years. Date of biopsy: 12 July (25th day).

Quantity of drug administered during the cycle: 4.5 mg d-norgestrel and 0.090 mg ethyloestradiol. Obstetrical events: obstesy: 3, abortion: 1. Last obstetrical event: obstesy on 30 November 1981.

Figure 2/b. Only tight inactive glands cen be seen. The stroma is in excess.

Age: 33 years. Last normal menstruation: 16 June. Duration of drug administration: 2 years. Date of biopsy: 12 July (25th day).

Quantity of drug administered during the cycle: 4.5 mg d-norgestrel and 0.090 mg ethyloestradiol. Obstetrical events: obstesy: 3, abortion: 1. Last obstetrical event: obstesy on 30 November, 1981.

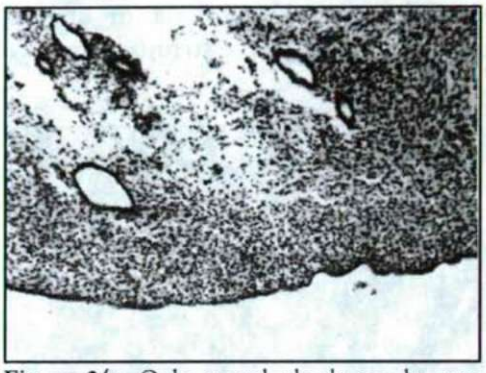

Figure 2/c. Only several glands can be seen which are not secernating and are lined by iinactive epithelium. The stroma cells are slightly swollen, with several thin-walled capillaries between them. No spirtal arteries are developed.

Age: 33 years. Last normal menstruation: 16 June. Duration of drug administration: 2 years. Date of biopsy: 12 July (25th day).

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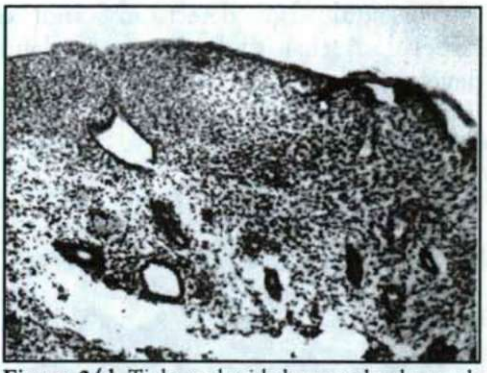

Figure 2/d. Tight and wide-lumen glands are also detectable. The epithelium is not secernating. The stroma is made up of moderately swollen cells. The number of endometrial granulocytes is small. Spiral arteries are not developed.

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Quantity of drug administered during the cycle: 4.5 mg d-norgestrel and 0.090 mg ethyloestradiol. Obstetrical events: obstesy: 3, abortion: 1. Last obstetrical event: obstesy on 30 November, 1981.

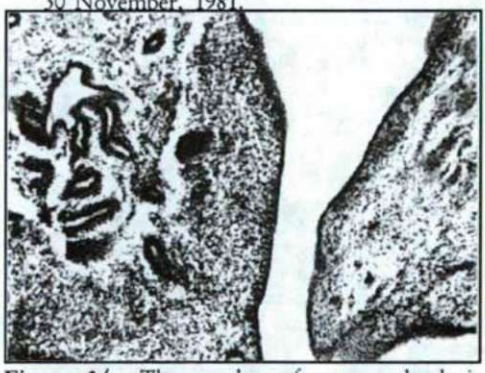

Figure 3/a. The number of corpus glands is small, or they can be observed focally in smaller or bigger groups. The glandular epithelium is inactiove. The stroma predominates. The cells are slightly swollen, or the structure is loosened.

Age: 33 years. Last normal menstruation: 15 June. Duration of drug administration: 7 years. Date of biopsy: 6 July (22th day).

Quantity of drug administered during the cycle: 3.75 mg d-norgestrel and 0.085 mg ethyloestradiol. Obstetrical events: obstesy: 2, abortion: 2. Last obstetrical event: obstesy on 8 December, 1977.

Figure 3/b. In the predominating stroma only very few glands can be seen which are lined by low cylindrical or cubic epithelium. The epithelium is inactive. Several wide-lumen arteries can be seen.

Age: 33 years. Last normal menstruation: 15 June. Duration of drug administration: 7 years. Date of biopsy: 6 July (22th day).

Quantity of drug administered during the cycle: 3.75 mg d-norgestrel and 0.085 mg ethyloestradiol. Obstetrical events: obstesy: 2, abortion: 2. Last obstetrical event: obstesy on 8 December, 1977.

We could not detect any sign of glandularcystic hyperplasia or stroma hyperplasia, that is why no atypic glandular epithelium or atypic stroma cells were developed.

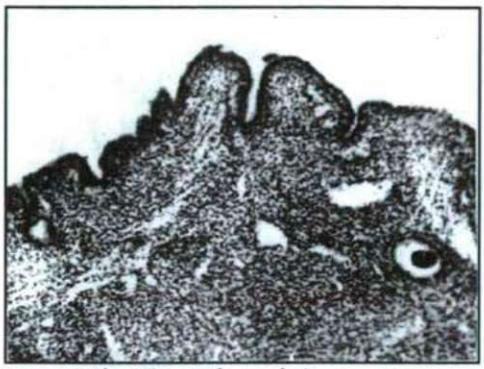

Figure 4/a. The surface of the mucous membrane is slightly uneven. The number of glands is reduced, in some parts secretion of variable extent, mainly abortive, can be seen. In other areas the glandular epithelium is not secernating.

Age: 28 years. Last normal menstruation: 24 June. Duration of drug administration: 1 year. Date of biopsy: 10 July (16th day).

Quantity of drug administered during the cycle: 2.25 mg d-norgestrel and 0.35 mg ethyloestradiol. Obstetrical events: obstesy: 2, abortion: 1. Last obstetrical event: obstesy on 16 June, 1980.

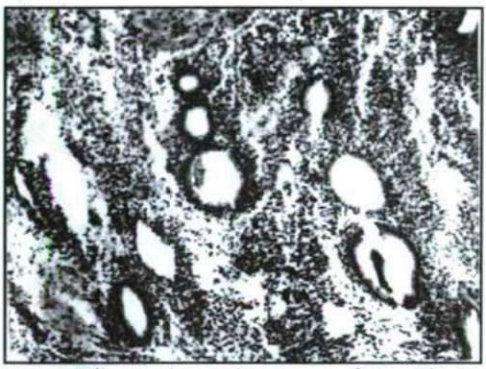

Figure 4/b. Similar to the picture of Fig. 4/B. In the stroma signs signs of focal bleedings and oedema can be seen. The loosening of the stroma is more expressed.

Age: 28 years. Last normal menstruation: 24 June. Duration of drug administration: 1 year. Date of biopsy: 10 July (16th day).

Quantity of drug administered during the cycle: 2.25 mg d-norgestrel and 0.35 mg ethyloestradiol. Obstetrical events: obstesy: 2, abortion: 0. Last obstetrical event: obstesy on 16 June, 1980.

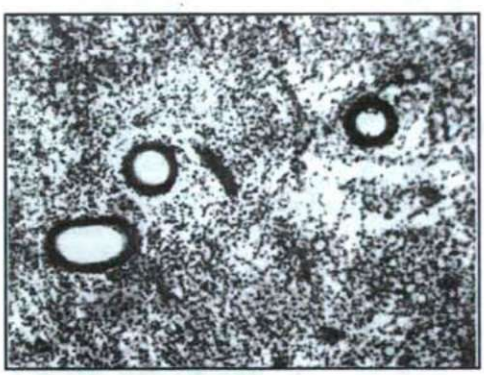

Figure 4/c. The structure of the stroma is loose, in it reduced number of inactive corpus-glands and thin-walled wide arteries can be occasionally seen. No sign of any secretion.

Age: 28 years. Last normal menstruation: 24 June. Duration of drug administration: 1 year. Date of biopsy: 10 July (16th day).

Quantity of drug administered during the cycle: 2.25 mg d-norgestrel and 0.35 mg ethyloestradiol. Obstetrical events: obstesy: 2, abortion: 1. Last obstetrical event: obstesy on 16 June, 1980.

Discussion

After the treatment we observed a gestagene-induced suppression phenomenon, characterized by the shortening of the proliferation period and by a premature reduced secretion activity (FARKAS, 1979, FARKAS et al., 1976, OUTLOOK..., 1966).

The glycogen present in the glandular epithelium was abundant in those cases where the gestagene component was dominant in the applied drug (SIEDEL and HEINEN, 1965).

The majority of the glands became dormant after the 15th day of treatmen. We could not detect any unequivocal sign of predecidual or decidual stroma cell transformation, indicating the harmonized gestagenous action of the drug (OUTLOOK..., 1966).

Dominant gestagenous effect results in predecidual or decidual transformation in an early stage ascompared with the normal cycle, usually between the 15th and 20th days of the created cycle (RYAN et al., 1964, STARUP, 1967, TAYLOR, 1961).

The spiral arteries of the stroma did not develop at all, or if they did, they became small, linear capillaries, sometimes dilatated thin-walled arteries (OBER et al., 1964, OBER, 1966).

Long-term administration resulted in a reduction of the number of glands.

Abortive secretion was detectable only occasionally, it was not present in many cases (KESERŰ and PARRADA, 1975, RYAN et al., 1964).

Such a histological pattern is difficult to distinguish from physiological atrophy, the atrophy present in the endometrium of castrated women (CHARLES, 1964, SHEFFIELD et al., 19691).

During the 9 days until the 16th day of the cycle, altogether 2.25 mg d-norgestrel and 0.35 mg ethyloestradiol were taken up by the patients, which prevented the advantegous physiological changes necessary for the implantation of the morula.

In the early 1980s more than 200 under-18 curettage were performed at the Department of Gynaecology. In 5 month, 11 out of 49 under-18 curettages were necessary because the women had been taking Postinor as a contraceptive drug; 30 out of them employed interrupted intercourse, while 8 had not used any means of contraception.

The 11 curettages mentioned above were carried out on under-16 patients. It can be concluded that administration of Postinor requires rigorous attention as unattentive administration leads to unwanted pregnancy.

Hungarian bibliographical data vary considerably in terms of reliability of the drug, too. The value of the PEARL-index changes between 0 and 12.8 with similar number of patients and cycles. This high variability is not seen in the international literature (variability is between 0 and 5.8), although the active content of the drug is lower there than that of Postinor.

The total dose recommended by YUZPE (YUZPE and LANCEE, 1977) was 200 ng ethyloestradiol and 2 mg dl-norgestrel. 70.4% of the women were treated within 24 hours of the intercourse, 22.7% of them between 24 and 48 hours, and 6% of them were treated between 48 and 72 hours after the intercourse. Of the 464 women having normal cycle the sexual intercourse was in the middle of the cycle. Only 1 pregnancy happened, caused by a mistake of the method, as compared with the minimally expectable 12–30 pregnancies. According to the cumulative rate, 48% of the patients had menstrual bleeding within the first 6 days of the treatment, 71% of them within the first 9 days, 95% of them within the first 15 days and the rest of them within the first 25 days.

In the combined treatment (50 mg ethyloestradiol and 0.25 mg levonorgestrel, also called as Yuzpe-method) the women take 2 pills within the first 72 hours after the intercourse, followed by 2 more pills during the next 12 hours.

The efficiency of the method is highlighted by the fact that following 1 contraception-devoid intercourse only 2% of the women following combined treatment got pregnant, as compared with the 8% of pregnancy of women without using urgency contraceptive pills (OUTLOOK, 1966). This means that the combined treatment reduces the chance of pregnancy by 75%.

During 3 days of administration with Fertilin, altogether 1 mg d-norgestrel and 0.20 mg ethyloestradiol were taken up by the patients. Supposedly the active content in this short period can prevent the physiological changes that are necessary to take place in the stromal and glandular region of the mucous membrane necessary for the implantation of the fertilized ovum. The drug-induced peripheral change taking place during 72 hours does not provide an optimal milieu for the nourishment of the morula, which then dies in a short time. The drug, therefore, can prevent pregnancy by inhibiting implantation.

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