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English Translated

Ovulation Preventives: The Significance of the Estrogen Dose

[Abstract]

The large prospective studies on adverse effects of oral contraceptives have unanimously revealed an increased risk of thromboembolic diseases, which seem to be associated with the dose of ethinylestradiol (EE). According to the recommendations of several medical committees, the dose of EE has, therefore, been more and more reduced; in some countries there are now ovulation inhibitors containing 20 µg EE. Since serious reactions, which have a relatively low incidence, are highly underreported (less than 10%), it is difficult to prove dose-dependent differences in the rates of cardiovascular diseases. There is, however, virtually no doubt that not only the incidence of thromboembolic diseases and stroke, but also that of benign liver tumours and gall bladder diseases is increased in relation to the EE dose.

A series of metabolic serum parameters, e.g. serum binding proteins, coagulation and fibrinolysis factors, angiotensinogen, is changed by EE in a dose-dependent manner which is, however, limited when the effects are receptor-mediated. Higher doses of EE have been shown to facilitate fibrin deposits on vascular subendothelium. The pharmacological effects of EE are to a large extent dependent on the dose, e.g. the irreversible reactions of EE and other ethinylated steroids with hepatic enzymes which are involved in the metabolism of steroids, drugs and toxic compounds. After long-term treatment with combinations containing 50 µg EE, in half of the women, abnormal liver function tests with pathological morphological alterations have been found.

As combinations with low EE doses and a sufficiently effective progestogen component do not differ from higher dosed oral contraceptives in their contraceptive safety and cycle control, there are no indications for pills containing 50 µg EE, except the normophasic sequential preparations for women with sustained irregular bleedings when taking low dose combinations.

Introduction

Oral contraceptives contain highly effective synthetic sex steroids, the purpose of which is to reliably prevent ovulation and pregnancy and maintain a regular menstrual cycle. At the same time, however, they also cause some significant changes in metabolism, especially in liver metabolism, and affect the

circulatory system, with the estrogen component playing a decisive role. These changes are dose-dependent in a certain range and can lead to serious complications if there is a corresponding individual predisposition or if other risk factors are present.

The recommendations of many medical committees were to primarily prescribe preparations with the lowest possible EE dose in order to keep the health risk as low as possible. This recommendation can only be applied to the progestin to the extent that each progestin should be dosed as low as possible. However, since the progestins differ significantly in terms of their potency and serum concentrations, the progestin dose per se is not a criterion. In contrast to Great Britain, where the proportion of ovulation inhibitors with 30 or 35 µg EE has now reached 95%, in Germany a considerable percentage of combination preparations with 50 µg EE are still prescribed. There is no doubt that there is no difference between the monophasic preparations of 30 µg or 50 µg in terms of contraceptive reliability (1). There are also no differences with regard to cycle control if the progestin component is sufficiently effective.

The progestin component is primarily responsible for the contraceptive effect. The dose is determined empirically, usually using twice to three times the ovulation-inhibiting amount. This means that the "pill" is overdosed for most women. The main task of the estrogen component is to ensure a stable cycle. However, lower doses of the EE than is generally assumed are sufficient – provided the type and dose of the progestogen that are selected are appropriate.

The requirement to primarily prescribe low-dose ovulation inhibitors

In principle, the guiding principle of any therapeutic use of medication "as much as necessary, as little as possible" should be enough to demand a reduction in the dose of EE, which is responsible for most serious complications, to the necessary minimum, provided that the important criteria are reliable contraception and good cycle control. However, the requirement to only prescribe low-dose ovulation inhibitors can only be upheld if it can be demonstrated that

1. The metabolic changes are smaller with a decrease in the EE dose,
2. The extent and frequency of clinical side effects and complications decrease and
3. There are no justified reasons for the use of higher-dose preparations.

The problems of clinical and epidemiological investigations

With the determination of relevant clinico-chemical parameters, the extent of changes in various metabolic functions can be recognized, so that a possible individual or statistical risk for the manifestation of diseases can be estimated on the basis of medical knowledge. Such metabolic investigations enable clinical data to be compiled relatively quickly. Unfortunately, one has to state again and again that different investigators come to different results when using the same preparation; on the other hand, in a direct comparison of two different ovulation inhibitors, no significant difference is often found. Here the question of the justification of a new preparation should actually arise. In comparative studies, it can be difficult to demonstrate statistically significant differences when the difference in the doses used to treat the comparator populations is not large, when the methodology has flaws, the subjects are not carefully managed, and when the dependence of the changes on the duration of use is not taken into account. However, the occurrence of a null hypothesis (a statistical technique very popular today) in such studies does not mean that there is actually no difference; it simply means that no difference was found under the given experimental conditions and methods (2). The causes are manifold. Within a group, the physiological spread is usually very large. The serum concentrations of EE and progestins measured after

ingestion of a specific dose show differences that can exceed an order of magnitude. Both the intra- and the inter-individual coefficients of variation average 40 to 60% and amount to 90% in individual cases (3). This can lead to a strong overlap between the serum concentrations of the contraceptive steroids and the measured clinical-chemical serum parameters in groups with different composition. Strong intra-individual fluctuations can be compensated for by examining each subject several times. Large inter-individual variations require crossover studies. In this way it can even be shown significant differences in the effects of 5, 10 and 20 µg EE on CBG, TBG, SHBG and angiotensinogen (4). In these studies, however, it also becomes clear that with higher dosages the differences in the effect become smaller and smaller, since the maximum effect is approached. In the case of receptor-dependent processes, this phenomenon can be explained by the fact that when the receptors, which are limited in number, are completely occupied, the maximum effect is reached and cannot be increased any further, even with higher doses or higher concentrations. On the other hand, receptor-independent effects such as interactions with enzymes, changes in membrane structures, reactions with proteins, etc. continue to increase even at higher doses or concentrations. Among the most important effects of this type is the irreversible blockage of cytochrome P-450-dependent oxygenases in the liver and elsewhere by EE and other ethynylated steroids (5, 6). When comparing different ovulation inhibitors, it is often overlooked that these preparations are combinations of different steroids, the effects of which are usually opposed to one another. For example, a comparison between a preparation containing 30 µg EE + 150 µg levonorgestrel and one containing 50 µg EE + 250 µg levonorgestrel revealed that the effects on cholesterol, α- and β-lipoprotein, triglycerides, antithrombin III, ceruloplasmin and ascorbic acid were identical (7). From this it can by no means be deduced that the risk potential of the two ovulation inhibitors is the same.

In order to assess the health risk, one is dependent on epidemiological data on the incidence of certain side effects after prolonged use of the preparations. However, the validity of such studies depends on the quality of the study, and it is almost impossible to exclude all sources of error. The decisive factors are the composition of the comparison group, which should ideally be identical, a long treatment period, large comparison collectives and the largest possible number of cases. The latter is usually not the case, especially in the case of serious complications, so that significant differences can hardly be detected and the results are burdened with a considerable uncertainty factor. In addition, in most countries today, mainly low-dose preparations are prescribed, so that a current comparison with higher-dose ones is practically no longer possible. In addition, it is becoming increasingly difficult to put together suitable control groups, since most young women use hormonal preparations. Thanks to better information, women with risk factors are less likely to be in the treatment group, but are more likely to appear in the comparison group (selection error). The same also applies to the phase III and IV studies, in which, according to the previous screening and the exclusion criteria, a test group is examined that has little in common with reality. If, due to the imponderables mentioned, it is not possible to demonstrate significant differences in relatively rarely occurring or reported diseases, this does not mean that the relative risk is the same for preparations with 50 µg, 30 µg or 20 µg EE. Due to recent events, it must also be pointed out that the number of unreported cases of diseases associated with the use of oral contraceptives is over 90% – also in Great Britain (8); even in the case of deaths from thromboembolic diseases in which the responsible physicians were aware that they were taking oral contraceptives, the reporting frequency was only 15% (8).

Medical board recommendations

In 1970, the British Committee on Safety of Drugs (9) recommended prescribing 50 µg EE instead of 100 µg, because the frequency of pulmonary embolism, deep vein thrombosis, cerebral and coronary thrombosis occurring during the use of ovulation inhibitors in the UK, Sweden and Denmark correlated

with the dose of estrogen. The Royal College of General Practitioners, one of the most important institutions in this field, followed this recommendation with the following statement (10): “preparations that contain no more than 50 µg of EE or mestranol prevent pregnancy just as reliably as higher doses, they should be preferred". In 1970, the American Food and Drug Administration also recommended prescribing oral contraceptives with low estrogen content, without referring. The final sentence read: "The mark of good medical practice is the use of the lowest effective dose of estrogen that is acceptable" (11).

In 1977, the Family Planning Association (12) recommended prescribing preference for preparations containing 30 µg EE because there was a reasonable assumption that such preparations are safer, even in the absence of epidemiological evidence to support this. There is now a general consensus that the preparation with the least health risks is one that minimizes the dose of estrogen and the proportion of progestogen (13). Since the Federal Republic of Germany had lagged behind in this development, the Zurich discussion group recommended in 1988 that only preparations with 35 µg EE or less should be prescribed, since these have less of an effect on the metabolism than high-dose ones and, among other things, the thromboembolic risk is reduced (14). At its 5th meeting in 1990, the Zurich discussion group recommended giving preference to preparations with a low estrogen content, with 30 µg EE evidently not yet having reached the lower limit. Suitable higher-dose preparations (2-phase preparations) are only justifiable in the case of additional indications, for example poor cycle control. The proportion of progestogen should be selected so that the effects on metabolism are as small as possible (15).

Epidemiological results

In 1970, Inman et al. (8) reported that there was a correlation between the estrogen dose in oral contraceptives and the risk of pulmonary embolism, deep vein thrombosis, and cerebral and coronary thrombosis. The study was based on 1,305 spontaneous reports received by the British Committee on Safety of Drugs between January 1, 1965 and June 30, 1969. Data from Sweden and Denmark were also analyzed in the same study. In all three countries, reducing the EE dose from 100 to 50 µg reduced the risk of thromboembolic diseases by about half. The authors expressly point out that, despite the great public interest in this subject at the time, only 15% of deaths and even less than 10% of cases were reported. In their detailed discussion of the possible sources of error ("bias"), the authors nevertheless come to the conclusion that their findings are conclusive, correct and consistent with the experiences of other investigators.

Boettiger et al. (16) compared the incidence of thromboembolic diseases in Sweden in the period between 1966 and 1970, when ovulation inhibitors with more than 50 µg EE were predominantly used, with the period between 1973 and 1977, when preparations with 30 to 50 µg EE were predominantly used. While the authors found no difference in mortality, the incidence of thromboembolic disease was significantly reduced, from 25.9 per 100,000 women to 7.2 per 100,000 women. From their results, Böttiger et al. concluded that there was a real relationship between the EE dose and the occurrence of venous thrombosis.

In the major report published in 1974 by the Royal College of General Practitioners (17) on the side effects of oral contraceptives, it was found after 5 years of observation of 46,000 women that the risk of thrombosis under treatment with 100 µg EE was 25% higher than with 50 µg EE.

The results of the Oxford Family Planning Association Study (18), in which 17,000 women have been followed continuously since inclusion in the study between 1968 and 1974 to date, show that reducing the EE dose reduced the number of strokes has fallen sharply. While there were 13 cases in 39,400

woman-years of treatment with preparations containing 50 µg EE and more, not a single case was reported in 9,100 woman-years with preparations containing less than 50 µg EE. In a review of the association between oral contraceptive use and stroke, Longstreth & Swanson 1984 (19) came to the conclusion that despite the problems with the relatively small numbers, both the various case-control studies and the large cohort studies indicated an increased risk of the higher-dosed preparations, especially for women over 35 and smokers. The calculated relative risk ranges from 2 to 26 for thrombotic stroke, while it is less increased for subarachnoid hemorrhage. Another 1986 report by the Oxford Family Planning Association (20) found that the relative risk of venous thromboembolism was 0.62 for those taking preparations containing 50 µg EE or more and only 0.39 per person for preparations containing less than 50 µg EE per 1,000 woman-years. This applies above all to deep vein thrombosis and pulmonary embolism, with the risk only increasing during administration but not after discontinuation: this is a clear indication that the reversible influence of the estrogen component on the coagulation system plays a causal role.

In a 1988 review, Meade, using the results of the three major British studies, concluded that the risk of thromboembolic disease increases with increasing estrogen dose. The most recent report of the Oxford Family Planning Association (22) states that the mortality from ischemic heart disease increases four-fold and that from subarachnoid hemorrhage seven-fold under treatment with oral contraceptives. Although the influence of the estrogen dose could not be analyzed because of the small numbers, only one death was reported during the intake of low-dose preparations. The authors see this as a clear indication of a lower risk when using ovulation inhibitors with a reduced EE dose.

Undoubtedly, the EE plays the decisive role in the development of cardiovascular diseases. However, there are also clear indications of a dose-dependent involvement of the progestin component, at least in arterial diseases. An interim analysis of the prospective study by the Royal College of General Practitioners found a significant association between the incidence of hypertension (23) and total arterial disease (24) and the dose of norethisterone or levonorgestrel. With combinations of 50 µg EE with 1 mg norethisterone, the incidence of cerebrovascular diseases was 0.38 per 1000 woman-years and increased to 1.25 per 1000 woman-years with a norethisterone dose of 4 mg (24). The mechanism is still unknown. It is unclear to what extent the drop in HDL cholesterol, which correlates with the dose of norethisterone or levonorgestrel (24), plays a role. Despite the unfavorable changes in the lipoprotein pattern during treatment with ovulation inhibitors with a relatively strong androgenic partial effect, the risk of atherosclerosis does not appear to be increased (25). The cause may be a stimulation of the apolipoprotein E receptors in the liver originating from EE, which leads to increased elimination of atherogenic IDL and remnants. Nevertheless, there is no reason to classify a decrease in HDL serum concentrations as meaningless; because the role of HDL is not limited to the return transport of excess cholesterol from the periphery or the vessel walls to the liver. Namely, HDL also stimulates prostacyclin synthesis in the endothelium, inhibits smooth muscle cell proliferation, and promotes fibrinolysis, endothelial repair, and the catabolism of triglyceride-rich lipoproteins (26).

Although benign liver tumors are very rare complications, they have a high mortality rate due to the risk of rupture with life-threatening massive intraperitoneal bleeding. A 1979 study (27) showed that the incidence increases from 1 case per million woman-years to 3.4 per 100,000 woman-years when anti-ovulation drugs are used. The duration of intake and the dose of the EE play a decisive role. A certain connection with the family history points to genetic influences. In a retrospective cohort study, in which 139,000 women who had taken ovulation inhibitors were compared with 341,000 women in a control group, a significantly increased risk of gallbladder disease depending on the estrogen dose was demonstrated, but this was only pronounced in younger women and in older women declined (28). This

also points to the influence of a predisposition, which becomes noticeable during the first years of treatment; according to this, oral contraceptives are contraindicated for the affected women.

As mentioned at the beginning, it is almost impossible to carry out error-free epidemiological studies. There has also been no lack of attempts to portray the available epidemiological studies on the side effects of the pill as meaningless because of their sometimes serious deficiencies (29). The undoubtedly well-founded suspicion that oral contraceptives are involved in the development of serious complications and our knowledge of the diverse in-vitro and in-vivo effects of synthetic sex steroids make such nihilism appear unsuitable for a further development of hormonal contraception in the contribution to minimizing the health risk. As long as there are no epidemiological studies that – applying the same strict criteria – prove without any doubt that the pill does not increase the risk of cardiovascular diseases and liver damage, the existing epidemiological results will remain the valid standard.

Dose-dependent effects of EE on metabolic parameters

Many serious side effects and complications during treatment with oral contraceptives are related to changes in liver function, primarily caused by EE. The primary liver passage of the steroids after ingestion or after absorption in the intestinal tract is of particular importance, since during this phase there are very high concentrations in the liver sinusoids, which are four to five times higher than peripherally. Compared to natural estrogens such as estradiol, EE exerts a disproportionately strong effect on liver metabolism (30), so that it is recommended in all cases in which natural estrogens can be used – for example in the treatment of menopausal symptoms – not to use EE. In the case of oral contraception, however, one is (still) dependent on EE. However, the influence of EE on the liver metabolism and the cardiovascular system should be kept as low as possible, i.e. the dose of EE should be reduced as much as possible.

The extent of the changes in various relevant parameters of liver function during the intake of preparations containing EE is – at least in the dose range up to 50 µg – largely dose-dependent. For example, in postmenopausal women, the serum concentration of SHBG increases by about 100% with 10 µg EE and by 300% with 50 µg, that of CBG by 50% or 100%, that of TBG by 50% or 100%, and that of angiotensinogen by 130% and 300% respectively (4, 31–34). SHBG influences the effect of sex steroids, TBG that of thyroid hormones, CBG that of adrenal steroids, and angiotensinogen is important for blood pressure regulation. Taking an ovulation inhibitor with 50 µg EE leads to a 40% increase in cortisol levels and a 50% decrease in 17-ketosteroid excretion; on the other hand, taking an ovulation inhibitor with 20 µg EE has no effect on either parameter (35). Normally, the strong increase in angiotensinogen is well compensated by endogenous regulatory mechanisms, so that there is only a slight increase in blood pressure. Occasionally, however, treatment with preparations containing EE leads to the development of hypertension in predisposed women (36). This risk is lower when taking low-dose preparations than when taking ovulation inhibitors with 50 µg EE (37). Interesting in this context is the finding that women who developed hypertension while taking ovulation inhibitors had particularly high concentrations of EE (38, 39). Since their caffeine levels were also elevated, it can be assumed that the oral contraceptives inhibited hepatic enzymes that are responsible for the breakdown of EE and caffeine (39). EE has a strong, dose-dependent effect on lipid metabolism and increases the synthesis of various apolipoproteins and triglycerides and inhibits hepatic lipoprotein lipase (40). It is not known whether the latter is based on a similar mechanism as in the inhibition of cytochrome P-450-dependent oxygenases in the liver. Glucose tolerance is practically unaffected by low-dose EE, while ingestion of 50 µg EE results in a slight deterioration and increase in insulin (41–43). The progestin component is primarily responsible for the impairment of carbohydrate metabolism, with EE increasing this effect in higher doses (43, 44).

Effects on hemostasis

EE increases the production of various coagulation factors in a dose- and time-dependent manner; among other things, the plasma concentrations of factors VII, VIII, IX and X increase, with the maximum changes being reached after 2 to 3 months and the changes often regressing thereafter (45–48). A clear dose relationship was found between the EE contained in the ovulation inhibitors and the increase in factor VII, which increased by 16% with 30 µg and by 46% with 50 µg (47). Sabra & Bonnar also found a significantly greater change in haemostasis in oral contraceptives with an estrogen content of 50 µg than with 30 µg (49).

The determination of fibrinopeptide A (FPA) is a good indicator of the extent of the coagulation processes. The plasma level of FPA increased by 239% under treatment with a combination of 30 µg EE + 75 µg gestodene, by 94% with 30 µg EE + 150 µg desogestrel, and with 20 µg EE + 150 µg desogestrel only by 30% (50). A comparison of two three-stage preparations with the same EE dose (30 µg/40 µg/30 µg) but different progestin components (levonorgestrel or gestodene) showed that the preparation containing gestodene produced a much greater increase in fibrinogen (+50% versus +12%), factor VII (+43% versus +26%), and factor X (+27% versus +4%) than the levonorgestrel-containing one, while the increase in factor XII (+28%) and the decrease in antithrombin III (–20%) were similar (51). These results demonstrate the influence of the progestin component on coagulation.

Ovulation inhibitors with 30 µg EE reduce the production of prostacyclin in the vessel walls far less than those with 50 µg EE (52); prostacyclin inhibits platelet aggregation and widens the vessels, thus counteracting the development of thrombosis. EE increases the hematocrit and blood viscosity and reduces the elasticity of the erythrocytes, which can lead to blockages in the capillary vessels, which can cause sudden hearing loss or visual disturbances (53).

A certain amount of compensation for the unfavorable effects of oral contraceptives on coagulation comes about because various fibrinolytic factors and fibrinolytic activity also increase under the effect of EE (46, 54). However, the level of the EE dose and the progestogen component decide whether the higher level of equilibrium is sufficient to prevent thrombosis when the coagulation cascade is activated due to vascular damage. Experiments with vascular subendothelium from rabbit aorta exposed to the flowing blood of the test subjects involved showed that the observed fibrin deposits were doubled under the influence of a preparation containing 50 µg EE, while a preparation containing 20 µg EE produced no significant effect (54). Although the available epidemiological data demonstrate the dependency of the increased incidence of thromboembolism and other vascular diseases on the EE dose and the progestogen component, some links in the chain of evidence are missing with regard to the mechanism. Possibly the key lies in the influence of the contraceptive steroids on antithrombin III activity. Although ovulation inhibitors cause an average decrease in the antithrombin III concentration of 10 to 20%, this alone is not sufficient to explain an increased risk of thrombosis. Inhibition of the thrombin-neutralizing effect of antithrombin III through direct binding of EE and progestins, as demonstrated in vitro by Nagasawa et al. (55) could provide the missing explanation. When measuring the activity of antithrombin III, however, there are not only major differences in the reproducibility of the results depending on the method used (56); if one wants to record direct interactions of the contraceptive steroids with antithrombin III, it may be decisive that the physiological conditions be changed as little as possible during the determination (57). Since most AT determination methods use highly diluted citrated plasma, possible steroid-antithrombin III interactions cannot be detected. This could also explain why most studies find no effect of oral substitution therapy with estradiol on antithrombin III, while Conard et al. found a decrease in antithrombin activity of about 30% while taking 2 mg estradiol or estradiol valerate (58), using the method

of Kaullas (57). In addition to the serum concentration of EE, that of the progestogen component should then also be of importance, especially if it has a high binding affinity.

Pharmacological effects on the liver

It has long been known that steroids with an ethynyl group have toxic effects on the liver, which depend on the one hand on the structure and on the other hand on the dose of the hormone. When performing liver function tests, abnormal values are usually found in only about 1% of women. Under treatment with ovulation inhibitors containing 50 µg EE or more, this rate increases to over 10%, while significantly fewer abnormal values are found with preparations containing only 35 µg EE (59). During long-term treatment with preparations containing 50 µg EE, half of the women experience pathological changes in partial liver functions (^{15}N-ammonium test), which also manifest themselves morphologically (focal ectasia of the sinusoids, perisinusoidal fibrosis, hypertrophy of the mitochondria, hypertrophy and hyperplasia of the endoplasmic reticulum, fatty liver) (60, 61). Alanine aminotransferase (ALAT) is increased by 50%, hematocrit by 19%, and leukocytes by 50%, while gamma-glutamyl transferase (γ-GT) is decreased by 30%; however, the values remain in the normal range (60). Oral contraceptives are responsible for 84% of all drug-related and histologically verified liver damage. Of the cases that occurred during treatment with an ovulation inhibitor containing 50 µg EE, 80% were noncholestatic and 20% were cholestatic hepatoses (62).

These pathological changes in the liver are most likely not hormonal effects, but the result of pharmacological interactions. In addition to the receptor-dependent effects of EE and progestins, there are also interactions in which saturation is only likely to occur in higher concentrations. A number of studies have shown that EE and other synthetic steroids are irreversibly bound to microsomal proteins in vitro and in vivo (63–65). In the case of EE, it is necessary to convert it into its most important metabolite, 2-hydroxy-EE, from which a further oxidation step produces an extraordinarily reactive intermediate product – presumably a semiquinone – which reacts chemically with proteins (66). The first step in this chain of reactions, the formation of 2-hydroxy-EE, occurs by cytochrome P-450 dependent enzymes (67). Because such a reactive intermediary has a short lifespan, it mostly attacks nearby protein structures. These include the enzymes that metabolize EE. The result is irreversible destruction of these enzymes and a temporary decrease in metabolic capacity.

Another important interaction mechanism is via the ethynyl group. The same cytochrome P-450-dependent monooxygenases convert the triple bond oxidatively into an extremely reactive group, which attacks the catalytic center of the enzyme, the heme group, at the moment of its formation. The reaction produces alkylated porphyrins that are excreted in the bile and urine (5, 68, 69). This type of reaction is called "mechanism-based inactivation" or "suicide inhibition" because the enzyme destroys itself by activating the substrate. In addition to EE, other ethynylated steroids (e.g., norethisterone, levonorgestrel, 3-keto-desogestrel, gestodene, danazol) can also react with cytochrome P-450. Although the affected enzymes are newly synthesized or they replace the destroyed heme from the heme pool (5), there is a temporary reduction in the metabolic capacity of the enzyme systems. Such cytochrome P-450 dependent enzymes play an important role not only in hepatic inactivation of endogenous and synthetic steroids, many drugs, toxic substances and carcinogens, but also in adrenal and ovarian steroid synthesis, in activation of vitamin D, synthesis of the prostaglandins (e.g. prostacyclin and thromboxane) and are an essential component of the aromatase system in the placenta and in the entire organism. Similar suicide inhibitors, which are 1,000 times more potent than aminoglutethimide, are currently being clinically tested as aromatase inhibitors in the treatment of breast cancer.

The importance of the inhibition of cytochrome P-450-dependent enzymes in the liver by EE and certain progestins is reflected in an increase in the serum levels of contraceptive steroids and – when certain drugs are used at the same time – in an increase in the half-life and decrease in the clearance of these substances. Although the liver has a large metabolic capacity, there are strong inter-individual differences and presumably also strong intra-individual fluctuations. During the primary passage through the liver (after oral administration), the EE and progestin concentrations in the liver sinusoids reach local values that are several times higher than the peripheral serum levels. Accordingly, in this phase the high substrate supply in the hepatocytes can noticeably influence the metabolic capacity of the liver.

In contrast to estradiol or nortestosterone-type progestogens, EE is not bound by SHBG but exclusively by albumin, the serum concentration of which is not altered by the oral contraceptives. Despite this, there is a rapid increase in EE levels between days 1 and 10 while taking the pill, which is thought to be due to inhibition of metabolism (70, 71). With multiple ingestion of EE alone, steady-state EE levels are reached after 7 to 8 days with a daily dose of 50 µg, while it takes longer with a dose of 30 µg (72). With the appropriate progestin component, this equilibrium is reached earlier. The importance of the EE dose is also reflected in the fact that the EE levels achieved after 21 days of treatment with a combination of 20 µg EE + 150 µg desogestrel are only half those with 30 µg EE + 150 µg desogestrel (own results), although the ratio of the EE doses is 2:3. The explanation can be found in the fact that with the 20 µg dose of EE, the steady state has not yet been reached after 21 days. The serum concentrations of the gestagen component are also influenced by the inhibition of hepatic degradation. The EE-induced increase in SHBG during treatment with estrogen-dominant ovulation inhibitors plays an important role in the increase in progestin levels between days 1 and 21. However, the strong increase in the levonorgestrel level during treatment with a combination of 30 µg EE + 150 µg levonorgestrel cannot be explained by increased binding to SHBG and the resulting reduced clearance of the progestin, since SHBG is not changed due to the strong androgenic partial effect of levonorgestrel (73).

The reactivity of the oxidatively activated ethynyl group is manifested in metabolites that can be isolated from urine. The chemical reaction of the high-energy intermediary expands the 5-ring of the EE or the progestins to a 6-ring and the so-called D-homo-metabolites are formed in the liver.

The effects of inhibition of hepatic cytochrome p-450 enzymes on the clearance of various drugs have received little attention so far. During treatment with the pill, the metabolism of, for example, prednisolone, antipyrine, aminopyrine, theophylline, caffeine, imipramine, chlordiazepoxide or diazepam is slowed down (74). There is an increase, among other things, in the caffeine level (39, 75) and a parallel increase in the serum concentrations of EE and theophylline (76) in the course of an intake cycle.

The described pharmacological effects of EE, which are probably not limited to the cytochrome P450-dependent enzymes of the liver, make it appear imperative to minimize such interactions by reducing the EE dose as much as possible. This also reduces the risk potential that could be associated with possible reactions with other physiologically important enzymes and proteins in the liver, other organs and vessels. The same applies to the progestins, of course, although it is not primarily the dose that matters, but rather the serum concentrations and the structure-dependent interactions.

Do combination preparations with a higher EE dose offer advantages?

The use of combination preparations with 50 µg EE or more is often justified by the fact that they inhibit ovulation more reliably and have better cycle control than the low-dose ones, and that they reduce the occurrence of ovarian cysts and concomitant treatment with drugs – those by induction metabolizing

enzymes can compromise efficacy – would offer benefits. In particular, their use would be indicated in women with high metabolic capacity, in whom serum concentrations of steroids are very low, causing intermenstrual bleeding.

Pearl-Index

All clinical studies that have been carried out since the introduction of low-dose ovulation inhibitors have shown that monophasic combination preparations with 30 µg EE are just as reliable in their contraceptive effect as higher-dose ones. There are no differences in the Pearl Index (1.77). The explanation can be found in the fact that EE is of no importance for the inhibition of ovulation in combination preparations, since the progestin component is primarily responsible for this. In a comparative study with the combinations 20 µg EE + 1 mg norethisterone acetate (NETA), 30 µg EE + 0.6 mg NETA and 30 µg EE + 1.5 mg NETA, identical Pearl indices between 0.13 and 0.15 were found found (78). Another study with the combinations 20 µg EE + 1 mg NETA, 30 µg EE + 1.5 mg NETA and 40 µg EE + 2 mg NETA also showed that all preparations reliably inhibited ovulation (79). Although EE synergistically enhances the effect of the progestin component on gonadotropin secretion, this is superfluous in combination preparations in which the progestin is present in a two- to three-fold ovulation-inhibiting dose. In addition, there is the additional contraceptive effect of the gestagen component on cervical mucus, endometrium and ovarian steroid synthesis.

Bleeding between periods

Intermenstrual bleeding is the most common reason for stopping oral contraceptives. They appear mainly in the first intake cycle and then decrease. Even if these side effects are basically without clinical relevance, for most women they are of far greater practical importance than the theoretical possibility of thromboembolic disease (80). For this reason, good cycle control is essential for the acceptance of a preparation.

The etiology of spotting and breakthrough bleeding during oral contraceptive use is largely unknown. Morphological investigations show a premature but incomplete transformation (rigid secretion) under the early onset of the dominant progestin effect of the combination preparations, with large individual differences occurring (81, 82). A sufficiently strong progestin effect is important, which ensures a stable, glycogen-rich stroma and an intact endothelium of the endometrial vessels. A comparison of the morphological changes in the endometrium between the first and, for example, the 60th intake cycle is quite revealing in view of the frequent bleeding between periods at the beginning of treatment with the pill. The progressive changes from early secretory to irregular secretory to suppressed endometrium is delayed in the first administration cycle, while after 5 years of treatment a suppressed or inactive endometrium is already found between the 7th and 10th day of the cycle in 72% of women (81). Since a combination with a very strong progestin component was used in this study, one might assume that intermenstrual bleeding occurs when the progestin effect is too weak.

The idea that the highest possible EE dose in the combination preparations is necessary for good cycle control has neither a physiological nor a molecular-biological basis. In a normal cycle (in the absence of a progestin), the maximum mitotic rate of the endometrium is already reached in the early follicular phase at estradiol levels of about 50 pg/ml (83). Since the concentration of EE in the endometrium – with the same serum concentrations – is higher than that of estradiol because of the lower local inactivation in the cells (84), EE levels of 50 pg/ml or even less should also be sufficient to achieve a maximum effect of the to induce EE on the endometrium. Even with a daily dose of 20 µg EE, average EE levels of 60 pg/ml are

achieved about 1 to 2 hours after ingestion (own results). In addition, it is known that the proliferating effect of EE decreases at higher doses. With 50 or 100 µg EE daily, the mitotic index is only 14 to 15, while in the early and middle follicular phase of a normal cycle it is more than twice as high at 32 (85). Since the number of estrogen receptors in the endometrium tends to be lower during treatment with combination preparations under the influence of a strong progestin component (78), even low doses of EE should be sufficient for the complete occupation of the estrogen receptors in the endometrium. It is also known from studies with postmenopausal women that the maximum clinical and metabolic effect of EE is already reached with an average daily dose of 15 µg and that increasing the dose does not improve the effect (4, 87, 88).

It has been assumed that intermenstrual bleeding occurs in women who have particularly low levels of EE or progestin, or in whom the ratio between EE and progestin levels is unfavorable. Our own results from pharmacokinetic studies with the combination preparations 35 µg EE + 2 mg cyproterone acetate, 30 µg EE + 75 µg gestodene, 30 µg EE + 150 µg desogestrel and 20 µg EE + 150 µg desogestrel, some of which were carried out over 12 intake cycles, show that there is no connection between the serum levels of the contraceptive steroids and the occurrence of intermenstrual bleeding. This also applies to the individual average values determined over the long term, with which the large intra-individual fluctuations from day to day could be compensated for by frequent pharmacokinetic investigations (a total of 12 times for each test person) (89). Intermenstrual bleeding has occurred in women with high or low levels of EE or progestin; the ratio between EE and progestin levels, which is also variable, was not relevant to the occurrence of spotting or breakthrough bleeding. The large intra-individual fluctuations in the serum concentration of the contraceptive steroids may play an etiological role. It is conceivable that a sudden sharp drop in serum levels from one day to the next could lead to spotting and breakthrough bleeding, whether the serum levels were high or low before the drop. After all, missing a pill that causes a sudden drop in steroid levels increases the rate of bleeding between periods by a factor of 13 to 16 (90). Bleeding between periods also occurs more frequently in the event of interactions with medications that increase the breakdown of contraceptive steroids through enzyme induction in the liver and can cause a drop in steroid levels (91).

Our investigations, in which the cycle behavior was precisely registered by daily entries in a cycle calendar, showed that with all preparations, the bleeding rate between periods (almost exclusively spotting) was around 50% in the first cycle and decreased to 5 to 10% in the following cycles. The preparation with 20 µg did not differ from those with a higher EE dose. This corresponds to the findings of other investigators (92–96). Interesting was the fact that in a cross-over study with the combinations 20 µg EE + 150 µg desogestrel and 30 µg EE + 150 µg desogestrel, which was carried out with 18 women, of the 9 women with intermenstrual bleeding, no fewer than 7 had irregular bleeding with both preparations registered in the first cycle – an indication of a predisposition.

In general, the prevailing notion is that supplements containing 50 µg EE have better cycle control than supplements containing 30 µg EE. This is not the case, as systematically conducted controlled studies have shown. As early as 1965, Pincus reported frequent intermenstrual bleeding at the beginning of taking high-dose ovulation inhibitors. With a preparation containing 100 µg mestranol + 2.5 mg norethynodrel alone, the rate of breakthrough bleeding in the first cycle was 28.3% (97). In investigations with combinations of 50 or 80 µg EE with 2.5 mg norethisterone acetate, 0.5 mg norgestrel or 2 mg megestrol acetate, Goldzieh et al. (98) found an average intermenstrual bleeding rate between 27% and 44% for the preparations with 50 µg EE and between 5% and 26% for those with 80 µg EE in the first 6 cycles. The only combination that had a low intermenstrual bleeding rate of 5% contained 80 µg EE + 0.5 mg norgestrel – an indication of the importance of a strong progestin component for cycle control.

The view of better cycle control with high-dose ovulation inhibitors can be explained by the fact that corresponding experience was gained in field studies, mainly with so-called conversions from a high-dose to a new, lower-dose preparation. Since these women were in a stable phase after long-term use of a high-dose ovulation inhibitor, and the change resulted in a temporary rate of bleeding between periods due to the adjustment that was taking place, the impression arose that the new, lower-dose preparation had poorer cycle control. At this point it is forgotten if intermenstrual bleeding occurred at the beginning of taking the high-dose preparation. Incidentally, the manufacturer's information about intermenstrual bleeding rates of 20 to 30% in the first cycle is based on the extremely imprecise recording of side effects in the so-called field studies (usually through global retrospective surveys at longer intervals).

If the intermenstrual bleeding is precisely registered, combinations with 50 µg EE do not differ from those with a low EE dose. This is consistent with the endocrine biochemistry of the endometrium. The higher-dose preparations, which according to the 5th Zurich Recommendation (15) can be prescribed for additional indications (above all persistent intermenstrual bleeding with combination preparations), mean the two-phase preparations (sequential preparations), which in the first phase are EE in a dose of 50 µg contain. Due to the strong proliferation of the endometrium while taking the 7 pure estrogen tablets, a stable cycle behavior can usually be achieved. They can also occasionally be used successfully for depressive moods that occur with combination preparations.

Functional ovarian cysts

The suppression of gonadotropin secretion by oral contraceptives is a time-dependent process, so that relatively normal LH and FSH concentrations are still found during the first week of administration (99, 100). During this time, the follicular maturation, which can already begin in the seven-day tablet-free interval between pill cycles, is not completely suppressed in some women. Although the growing follicles do not reach maturity because their development is disturbed, functional cysts can develop, but these almost always regress in the following cycle (101). They tend to occur when the first pill is started on day 5 of the cycle (102) or when a pill is missed (101). In recent years there has been a suspicion that the protection afforded by the pill against the development of functional ovarian cysts is less with the low-dose preparations than with the higher-dose ones. Since many of these reports are based on sonographic examinations, it is difficult to differentiate between growing follicles. However, there are indications based on laparoscopically verified findings that the incidence of functional ovarian cysts is considerably higher, at least under treatment with three-stage preparations, than with monophasic ones (101, 103, 104). This can be explained by less suppression of follicular development during the first phase, when the progestin dose is relatively low (102). A certain follicle activity can also be determined during the intake of sequential preparations. In contrast, the low-dose monophasic combinations with a potent progestin may provide protection similar to that of anti-ovulation drugs with 50 µg EE or more (103, 105–107). Although rare, functional ovarian cysts also occur under treatment with high-dose combination drugs (108–110), but the large prospective studies consistently confirm a 40–90% reduction in ovarian cysts (17, 107), with the Oxford study Family Planning Association from 1987 (107) recorded largely low-dose preparations. Also, the number of hospitalizations for functional ovarian cysts in the US did not change between 1979 and 1986, although the proportion of women taking three-step preparations increased to 3 million over this period (111). Accordingly, the use of high-dose combination preparations with an EE content of 50 µg cannot be justified with regard to an allegedly lower risk of functional ovarian cysts.

Drug interactions

The many reports of interactions between different drugs and contraceptive steroids relate primarily to intermenstrual bleeding, but also to pregnancies due to contraceptive failure. Some drugs can increase hepatic inactivation through enzyme induction, leading to a decrease in EE and/or progestogen (91, 112). For example, when rifampicin and an ovulation inhibitor are administered at the same time, the progestogen level can drop by an average of 42% due to the increased metabolism, although the individual differences are very large. In some women there is no change at all, while in others, for example, norethisterone levels drop by 70% (112, 113). The drop in steroid levels is all the greater, the higher the individual serum concentration was previously. The EE level can also fall with a similarly large fluctuation range of between 9% and 78%. For both components, the average half-life is halved. Similar to the serum levels of contraceptive steroids, large individual differences can also be found in drug interactions. Accordingly, the measure of temporarily using high-dose ovulation inhibitors during treatment with such drugs represents a major uncertainty factor; a higher dose may be unnecessary if appreciable enzyme induction does not occur; it may be correct if the drop induced is offset by the higher-dose drug; and it may not be sufficient when the enzyme induction is very strong; in such cases, a false sense of security is feigned, which can result in an unwanted pregnancy. Since – as already mentioned – the progestin component is primarily responsible for the contraceptive effect, it would be more important to increase the progestin effect and not to increase the EE dose. For the same reasons, a temporary destruction of the intestinal flora during treatment with antibiotics cannot actually be held responsible for pregnancy, unless the drug also causes enzyme induction. The failure of the enterohepatic circulation only affects the EE, but not the gestagen, so that the EE level can only drop, possibly leading to intermenstrual bleeding. Therefore, if drug therapy is necessary while taking hormonal contraceptives, which may jeopardize contraceptive safety, additional or alternative contraceptive measures are recommended. Since the individual reactions of the patients cannot be predicted, a possible conception cannot be reliably ruled out, even if the dose of contraceptive steroids is increased.

Conclusion

On the basis of the available knowledge it can be assumed that the pharmacological effects and the side effects of ethinylestradiol and thus the health risk are all the greater, the higher the dose. Accordingly, preparations with the lowest possible estrogen dose should be used for oral contraception. Since combination products with 50 µg ethinyl estradiol have no advantages over those with 35 µg or less – provided a suitable progestin component is present – there is no indication for higher-dose combination products. An exception are two-phase preparations, which can be prescribed if there is an additional indication (e.g. persistent poor cycle control with low-dose combination preparations without an organic cause).

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