Adverse effects of estrogen treatment: natural versus synthetic estrogens

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Abstract

The number of absolute contraindications is much greater for use of oral contraceptives than for estrogen replacement therapy (ERT). This is essentially because of the difference in the risk of vascular disease with the two types of treatment. Thus whilst natural estrogens may protect them from arterial disease, ethinylestradiol-containing formulations may be associated with an increased risk of myocardial infarction, particularly in smokers and with hypertension and thromboembolic diseases in young women. Moreover, they may cause benign liver tumors, while estradiol even in very high concentrations (e.g. during pregnancy) does not.

This difference is probably associated with the presence of the ethinyl group in ethinylestradiol which not only inhibits metabolism at C_{17}, but may inactivate irreversibly cytochrome P_{450} enzymes and thus may influence many metabolic processess. The high potency of ethinylestradiol is reflected by its profound effect on many hepatic serum parameters, e.g. binding globulins, renin substrate or hemostatic factors. Although ethinylestradiol may also exert beneficial effects on the cardiovascular system, e.g. increase in HDL, inhibition of LDL oxidation and vasodilatation, the changes in blood pressure and hemostasis may be deleterious in predisposed women.

Oral contraceptives contain ethinylestradiol because of the poor cycle control when natural estrogens are added to progestogens. This is probably due to the reduction of the local effect of estradiol on the endometrium by progestogens which stimulate degrading enzymes.

Introduction

The instructions for use of both oral contraceptives and estrogen replacement therapy (ERT) document an increased risk of various diseases during use of the drugs. The number of absolute contraindications with ovulation inhibitors is, however, much greater than for ERT (Table 1). Indeed it is likely that after the successful outcome of ongoing prospective studies, cardiovascular disease will become an indication for ERT rather than a contraindication. There is no doubt that the impact of the ethinylated estrogen used in oral contraceptives is much stronger than that of 'natural' estradiol. Moreover, the requirements for prescribing oral contraceptives are much more stringent than for ERT, as the 'pill' is generally used by healthy women without a therapeutic purpose. Some of the absolute contraindications for the 'pill', as listed in Table 1, are therefore only relative for ERT. In postmenopausal women suffering from liver disease and other metabolic disorders, transdermal application avoids the occurrence of an estrogen 'bolus', and consequently any impact on hepatic metabolism. It can be assumed that this method of estradiol therapy does not affect the organism more than endogenous estradiol. Consequently, ERT is possible or even recommended in women suffering from many severe diseases, provided that there is an appropriate indication for treatment.

Cardiovascular and venous diseases

The difference between ethinylestradiol (EE) and estradiol becomes obvious when the relative risk of vascular disease during treatment with oral contraceptives is compared with that of ERT (Table 2). While natural estrogens may protect from arterial disease even in women who smoke, EE-containing formulations may cause myocardial infarction, hypertension and thromboembolic disease in young women. Although EE, like estradiol and equine estrogens, is a potent antioxidant[1,2] and may exert a pronounced vasodilator effect on

Table 1 Absolute contraindications for oral contraceptives (OC) and ERT

Ethinylestradiol (OC)	*Estradiol (ERT)*
Acute or progressive liver disease	Acute venous thromboembolism
Gall-bladder disease	Breast cancer
Recurrent cholestatic jaundice	
Previous or current thrombosis	
Micro- or macroangiopathy	
Cardiovascular disease	
Diabetes mellitus with angiopathy	
Lupus erythematosus	
Hyperhomocystinuria	
Hormone-dependent neoplasia	
Severe hypertension	
Severe hypertriglyceridemia	

arteries, its powerful effect on coagulation factors, on platelets and perhaps on the endothelium may contribute to the development of arterial diseases such as hypertension or myocardial infarction (Table 3). In predisposed women, the vasoconstrictor effect on arteries of the progestogen component of the pill may enhance vasospasms at the site of endothelial lesions, and, under the influence of a procoagulatory state induced by EE, may cause the development of ischemic events.

Some of the most striking differences between EE and estradiol are the changes in the level and activity of several coagulation factors. A cross-over study with postmenopausal women revealed a much greater shift to hypercoagulation by treatment with only 10 μg EE than with 2 mg estradiol (Table 4)[3]. The low EE dose caused a significant increase in factor VII, factor VIII and von Willebrand factor, while 2 mg estradiol had no influence. As EE might also exert a more pronounced action on platelet function than estradiol, the relatively high incidence of three cases of deep vein thrombosis observed in 25

Table 2 Relative risk of venous and arterial diseases during treatment with oral contraceptives (OC) and estrogen replacement therapy (ERT) as compared with untreated women

Disease	*OC*	*ERT*
Cardiovascular disease (total)	1.5	0.5
Myocardial infarction (total)	3.3	0.5
Myocardial infarction(non-smoker)	1.0	0.5
Myocardial infarction (smoker)	3.5	0.6
Myocardial infarction (heavy smoker)	20.0	0.8
Stroke (total)	1.4	1.0
Subarachnoidal hemorrhage (heavy smoker)	10.0	—
Deep venous thromboembolism	4.0	2.5

Table 3 Influence of ethinylestradiol, and orally and transdermally applied estradiol on lipid metabolism, vessel wall and hemostasis. HDL, high-density lipoprotein; VLDL, very low-density lipoprotein; LDL, low-density lipoprotein

Parameter	*Ethinylestradiol*	*Oral estradiol*	*Transdermal estradiol*
Lipid metabolism	strong	moderate	weak
HDL-cholesterol	increase	increase	no change
triglycerides	increase	increase	no change
VLDL/LDL turnover	increase	increase	no change (?)
LDL-cholesterol	decrease	decrease	no change (?)
LDL oxidation	inhibition	inhibition	inhibition
Vasodilatation	increase	increase	increase
Blood pressure	increase	decrease	decrease
Hemostasis parameters	strong	weak	none
Platelet aggregation	?	?	?
Endothelium	?	?	?

Table 4 Cross-over study of effect of 10 μg ethinylestradiol (EE) or 2 mg estradiol valerate (E_2) on various hemostasis parameters: treatment of 24 postmenopausal women for 6 weeks[3]. vW, von Willebrand

Parameter	*10 μg EE*	*2 mg E_2*
Fibrinogen	—	—
Factor VII (antigen)	+ 13%**	—
Factor II-VII-X complex	—	—
Factor VIII (activity)	+ 17%*	—
vW factor (antigen)	+ 17%*	—
Antithrombin III	− 14%**	− 9%**
β-Thromboglobulin	+ 94%*	+ 44%
Platelet factor 4	+ 100%	+ 50%

*$p < 0.05$; **$p < 0.01$

postmenopausal women within 3 months of treatment with 20 μg EE may be explained[4]. The development of venous thromboembolism may be facilitated by the vasodilator effect of estrogens in veins which may contribute to the occurrence of stasis there, and also by the lack of constrictor effects by progestogens, which may also increase distensibility and capacitance. When conjugated estrogens or estradiol are given in ERT, the incidence of venous thromboembolism is reported to be very low (three to five per 10 000 postmenopausal women[5,6]). This discrepancy justifies the recommendation not to use EE for ERT, even at low dosages.

Effect on hepatic function

As a result of powerful hormonal and pharmacological effects on the liver, EE may cause morphological alterations in hepatocytes, increase the activity of transaminases and induce intrahepatic cholestasis[7–9]. The latter is dependent on the EE dose, and appears to be associated with a certain predisposition. It may be mediated by a change in lipid composition of hepatocyte membranes, resulting in altered membrane fluidity. In contrast to EE, natural estrogens have no harmful effects on hepatic function. Benign liver tumors may be induced by treatment with oral contraceptives in a dose- and time-dependent manner, while estradiol even in very high concentrations (e.g. during pregnancy) has no influence[10].

On the other hand, the increased occurrence of gall-bladder disease during oral contraception, which is due to an estrogen-induced change in the composition of bile, may also be observed in women on ERT. As it occurs only during the first years of treatment, predisposing factors in women may play a role.

Some other side-effects which mostly occur transitorily during both ERT and oral contraception, e.g. fluid retention, mastalgia and nausea, appear to reflect a direct local hormone effect resulting in an increase

in plasma volume and capillary permeability, or a disturbance of gastrointestinal function.

Mechanism of action

As for the adverse effects, the reason for the difference between EE and natural estrogens is not well understood, but is clearly associated with the existence of the ethinyl group at position 17α of the EE molecule. There are two alternative mechanisms by which EE may cause adverse effects which differ from those of natural estrogens: first, in certain tissues or organs EE may exert a much stronger hormonal effect than natural estrogens because its local inactivation is slowed down; and second, the reactive intermediate produced by oxidative activation of the ethinyl group may cause pharmacological effects by interaction with enzymes, membranes and other physiologically important structures or compounds[11,12].

The predominant pathway of estradiol metabolism is the oxidative transformation into estrone catalyzed by the 17β-hydroxysteroid dehydrogenase. Estrone shows only weak estrogenic activity, but can be transformed back to estradiol by this enzyme. High serum concentrations of estrone and estrone sulfate may however serve as a circulating, hormonally inert reserve for the formation of estradiol. By inhibiting the oxidation of the 17β-hydroxy group, the ethinyl group prevents the rapid inactivation of EE in the intestinal tract and liver during the first liver passage, resulting in an increase of bioavailability from 3% (estradiol) to 38–48% (EE) after oral application[11]. Moreover, the lack of possible retransformation of an estrone-like metabolite results in different pharmacokinetics. While EE shows a rapid decline in serum concentration after reaching the maximum, the estradiol levels remain elevated through 10 or more hours after oral application. The retarded metabolism of EE enables a marked reduction of the EE dose contained in oral contraceptives, but the hormonal and pharmacological potential of these formulations, which exceeds that of a 100-fold dose of estradiol, clearly demonstrates that low dosage is of limited value.

The binding affinity of EE does not markedly differ from that of estradiol, and the peak serum levels reached after intake of 30 μg EE or 2 mg estradiol are similar. Consequently, a higher effect of EE in certain tissues must be associated with a slower local metabolism. Part of the adverse effects induced by EE appear to be based on the existence of the ethinyl group. The ethinyl group is able to inactivate cytochrome P_{450}-dependent enzymes irreversibly after oxidative activation of the triple bond[12]. Cytochrome P_{450} is ubiquitous in the liver and the vessels and every other tissue, and is involved in most metabolic processes. At high local concentrations, ethinylated steroids may cause

profound metabolic changes and may contribute to the development of complications[11].

Potency of natural and synthetic estrogens

The pharmacological properties of the various estrogens are responsible for the fact that EE affects various serum parameters, particularly those of hepatic origin, much more strongly than conjugated estrogens and estradiol (Table 5). As after oral administration the estrogen levels during the first liver passage are much higher than after parenteral application; hepatic effects are particularly enhanced if the bioavailability is high. Therefore, the potency of EE is much higher with regard to hepatic parameters than with regard to the peripheral or clinical effects, and the ratio between hepatic and clinical effects is much higher during use of EE than that of natural estrogens (Table 6). This is exemplified by the actions of the estrogens on serum-binding globulins, renin substrate or hemostatic parameters (Tables 4 and 5)[13–18]. While transdermally applied estradiol has

Table 5 Effect of different estrogens at various doses on serum concentrations of sex hormone-binding globulin (SHBG), corticosteroid-binding globulin (CBG) and renin substrate

Estrogen	*SHBG*	*CBG*	*Renin substrate*
Estradiol transdermal, 100 µg	—	—	—
Estradiol oral, 1 mg	+ 60%	—	+ 85%
Estradiol oral, 2 mg	+ 120%	+ 20%	+ 180%
Conjugated estrogens, 0.30 mg	+ 50%	—	+ 50%
Conjugated estrogens, 0.63 mg	+ 80%	+ 20%	+ 100%
Conjugated estrogens, 1.25 mg	+ 120%	+ 50%	+ 250%
Equilin sulfate, 0.15 mg	+ 20%	—	+ 25%
Equilin sulfate, 0.30 mg	+ 45%	—	+ 45%
Equilin sulfate, 0.60 mg	+ 100%	+ 30%	+ 70%
Ethinylestradiol, 5 µg	+ 100%	—	+ 100%
Ethinylestradiol, 10 µg	+ 200%	—	+ 150%
Ethinylestradiol, 20 µg	+ 240%	+ 60%	+ 200%

Table 6 Relative potency of various estrogens with regard to clinical efficacy and effects on calcium excretion, and serum concentrations of follicle-stimulating hormone (FSH) high-density lipoprotein (HDL)-cholesterol, sex hormone-binding globulin (SHBG) and renin substrate (potency of estradiol = 1)

Estrogen	*Hot flushes*	*Vaginal epithelium*	*Urinary calcium*	*FSH*	*HDL-cholesterol*	*SHBG*	*Renin substrate*
Estradiol	1	1	1	1	1	1	1
Estriol	0.3	0.3	0.1	0.3	0.2	—	—
Estrone sulfate	—	0.9	0.9	0.9	—	0.9	1.5
Conjugated estrogens	1.2	1.5	2	1.1	1.5	3	5
Ethinylestradiol	120	150	40	120	400	500	350

Table 7 Effect of different estrogens on serum concentration of human growth hormone (hGH), insulin-like growth factor I (IGF-I), and growth hormone-binding protein (GHBP)[20]

Estrogen	*hGH*	*IGF-I*	*GHBP*
Estradiol transdermal, 100 µg	—	+ 40%	—
Estradiol valerate oral, 2 mg	+ 230%	− 20%	+ 110%
Conjugated estrogens, 1.25 mg	+ 300%	− 23%	+ 130%
Ethinylestradiol, 20 µg	+ 450%	− 30%	+ 300%

no influence, the effect of orally administered estrogens are dose-dependent. The results show that at clinically equivalent doses (1 mg and 2 mg estradiol vs. 0.625 mg and 1.25 mg conjugated equine estrogens vs. 10 and 20 µg ethinylestradiol) the hepatic effects of ethinylestradiol are disproportionally high, while those of conjugated estrogens are higher than those of estradiol (Tables 5 and 6). The improvement of hot flushes by treatment with ethinylestradiol has been shown to reach the maximal efficacy at a dose of 15 µg[19].

At clinically relevant doses there is also a stronger increase in the serum levels of human growth hormone (hGH) and growth hormone-binding protein (GHBP), and a more pronounced decrease in insulin-like growth factor (IGF-I) during treatment of postmenopausal women with EE than with natural estrogens. Transdermally applied estradiol does not affect hGH and GHBP, but increases IGF-I (Table 7)[20]. The clinical significance of these changes are not yet clear.

Contraception with estradiol-containing formulations?

The question remains, why all oral contraceptive preparations contain ethinylestradiol, but not estradiol. The reason is the insufficient cycle control when natural estrogens are combined with progestogens. In the absence of progestogens the proliferative effect of estradiol on endometrium is stronger than that of EE[21]; in the presence of progestogens, the local effect of estradiol in endometrial cells is, however, insufficient due to stimulation by progestogens of degrading enzymes like 17β-hydroxysteroid dehydrogenase and sulfotransferases[22]. Treatment of young women with combined formulations of estradiol with progestogens is therefore associated with a high rate of irregular bleeding and consequently a low acceptance. Moreover, EE enhances the contraceptive efficacy of the progestogen component of the pill not only by an impairment of gonadotropin secretion, but also by direct inhibition of follicular development and steroid synthesis[23].

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Discussion

Commenting on Professor Kuhl's finding that *oral* estriol is less effective for preventing hot flushes, Dr Ginsburg pointed out that giving estradiol vaginally is, however, highly effective, probably because this avoids the hepatic first pass. Estriol also has the advantage of not affecting the endometrium and may be unjustly neglected as replacement therapy. It would need to be given vaginally, but is then more effective in relieving hot flushes than normally thought. Agreeing, Professor Lippert observed that applying 0.5 mg estriol (or estradiol) vaginally produces serum levels of estriol (or estradiol) similar to those after taking 8 mg of the estrogen orally. Hence the marked vascular effects of small amounts applied vaginally. The effects of estriol on bone have, however, yet to be evaluated.

Responding to Professor Lippert who expressed reservations about women's willingness to apply vaginal cream every day, Dr Ginsburg said that she had also employed a sustained preparation in the form of a retained pessary. In her view, many women prefer to put in a pessary, and there is no reason why a practical one should not be developed to last for several weeks, at least. Professor Lippert was less sanguine, however. He stressed that the vaginal epithelium differs, varying in pH, secretions and absorptive properties – as shown by the unreliable absorption of prostaglandins when given vaginally to terminate pregnancy. He also queried the effect of daily estriol absorption from the

vagina, because it might begin to stimulate the endometrium, and therefore require the addition of a progestogen.

In Dr Ginsburg's experience, however, no endometrial changes could be observed by electron microscopy after over a year of vaginal estriol. Professor Kuhl replied that many women applying 0.5 or 1 mg of estriol vaginally for a longer period will eventually develop endometrial proliferation and perhaps hyperplasia. Dr Ginsburg disputed this.

Congratulating Professor Kuhl on his informative Table comparing the potencies of equal doses of estrogens in different ways – biochemically, or in the breast or endometrium – Dr Hardiman said that it was highly desirable to present clinical responses in the same way. Hot flushes, for example, would need a much higher dose of estriol than of estradiol for control. Clinically equivalent doses of estriol and estradiol could then be compared, with a view to eliminating unacceptable menopausal complaints causing adverse effects on the cardiovascular system or elsewhere.