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Absorption and Metabolic Effects of Different Types of Estrogens and Progestogens

*Rogerio A. Lobo, M.D.**

In this review, the absorption of estrogens and progestogens will be discussed. This will be followed by a consideration of the metabolic effects of these steroids. The emphasis of this article will be on how absorption and metabolism of these hormones affect clinical aspects of sex hormone replacement therapy. While several areas will be covered in more detail in other articles of this issue, an inclusion of data on lipid metabolism, coagulation, and hypertension will be pertinent to this discussion. In this context, differences between classes of estrogens and progestogens will be emphasized, specifically with respect to administration by different routes.

ESTROGEN PHARMACOLOGY

In the menopause, a dramatic decline in estradiol production occurs because estradiol is the primary product of the developing follicle. This decrease in estradiol levels begins in the perimenopause as follicular development decreases and heralds an increase in circulating levels of follicle-stimulating hormone (FSH), which may be elevated for many months before the last menstrual period.[53] Estrone is the predominant estrogen of the menopause and is responsible for the circulating estradiol during this time.[18] The ratio of estradiol to estrone is therefore reversed from that of the normal menstrual cycle and is less than 1.

The primary source of estradiol is via the aromatization of androstenedione, with the normal conversion rate being approximately 1.5 per cent. This source is influenced by conditions that increase the production of androstenedione (for example, stress) as well as factors that increase aromatization such as obesity and age.[1,20] To a lesser

*Associate Professor of Obstetrics and Gynecology, University of Southern California School of Medicine, and Chief of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Los Angeles County/University of Southern California Medical Center, Los Angeles, California

An important observation pertinent to our understanding of estrogen replacement and its metabolism is the finding that the predominant estrogen in the cytoplasm and nucleus is estradiol even if estrone is the predominant circulating estrogen (Fig. 3).[26,61] The finding that progestogen treatment lowers this ratio of estradiol to estrone in the endometrial cell[26] favors the concept that 17β-dehydrogenase activity plays the dominant role in modulating the biologic effects of estrogen replacement therapy. Thus, the metabolism and interconversion of estrogens in the circulation, which are subject to splanchnic and renal clearance and other factors, appear to be dissociated from the effects in the cells of target tissues.

Recent data on estrogen metabolism have suggested that smoking significantly reduces bioavailable estrogen concentrations. This occurs in postmenopausal women whether or not they are receiving estrogen replacement.[25] A proposed mechanism for these findings has been suggested[38] and is related to a proportionate increase in the rate of A-ring (2-hydroxylation) metabolism.

ESTROGEN ADMINISTRATION

Three separate classes of estrogen are used for estrogen replacement therapy. Native estrogens constitute the first group and include estradiol and estrone; estriol is used primarily in Europe. The second group comprises conjugated equine estrogens, which although considered "natural" include equine estrogens, primarily equilin sulfate. The third group is made up of synthetic estrogens: primarily ethinyl estradiol, quinesterol (an ester of ethinyl estradiol), and diethylstilbestrol.

Estrone is not well absorbed orally and is usually administered as estrone sulfate. Estradiol, although not usually absorbed well, results in good systemic estrogen levels if micronized. However, any estrogen administered orally is converted primarily to estrone. This is because of the first pass effect of estrogens through the liver and portal circulation. Through this passage, there is as much as 30 per cent reduction in bioavailable estrogens.[7] Rapid conjugation is the major mechanism for this and is also the major metabolic fate of estriol oral administration. The principal estrogen conjugate after oral administration of either estrone or estradiol is estrone-3-glucuronide. In serum, basal levels of estrone-3-glucuronide range from 3 to 5 nmol per L but only increase after oral administration.[7] Regardless of whether estradiol (estradiol valerate) or estrone sulfate is administered orally, estrone-3-glucuronide rises in the circulation to levels averaging 10 to 15 nmol per L. This glucuronidation of estrogen inactivation can increase with certain types of medication, specifically with drugs used in treatment of epilepsy. After systemic (nonoral) routes of estrogen replacement therapy, however, estrone-3-glucuronide levels do not rise (Fig. 4).

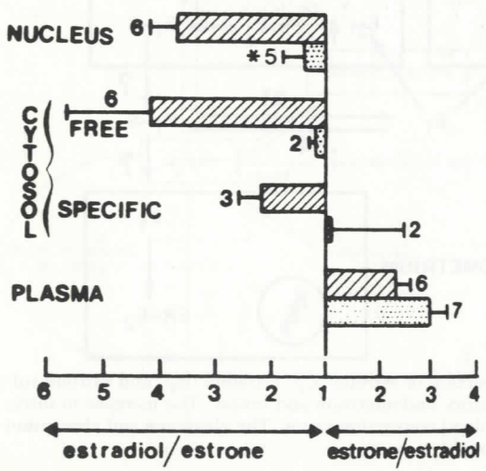

Figure 3. Intracellular and plasma ratios of estradiol and estrone after oral estrogen (*striped bars*) and estrogen and progestogen (*dotted bars*). (*From* King RJB, Dyer G, Collins WP, et al: Intracellular estradiol, estrone, and estrogen receptor levels in endometria from postmenopausal women receiving estrogens/progestins. J Steroid Biochem 13:377, 1980; with permission.)

As stated earlier, estrone is usually administered as the conjugate (estrone sulfate) because of its superior absorption. However, whether estrone sulfate is administered orally or as an estradiol conjugate (estradiol valerate), the kinetics of estrone entering the circulation as the predominant estrogen are the same (Fig. 5).[2] Peak levels of estrone occur approximately 4 hours after a dose and plateau over the next 2 hours. Levels of estrone sulfate increase to about 20 nmol per L or 7 ng per ml; estrone levels plateau at around 200 pg per ml after 1.5 mg of piperazine estrone sulfate (Fig. 6). Serum estradiol levels are always much lower than estrone after oral administration. The kinetics of oral piperazine estrone sulfate administration are similar when doses are increased from 1 to 3 mg.

From these and other data, the half-life for estrone sulfate ad-

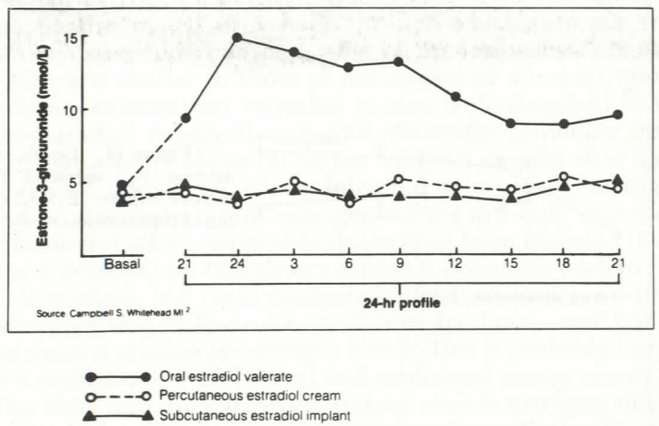

Figure 4. Levels of estrone-3-glucuronide after oral estradiol valerate, percutaneous estradiol cream and a subcutaneous estradiol implant.

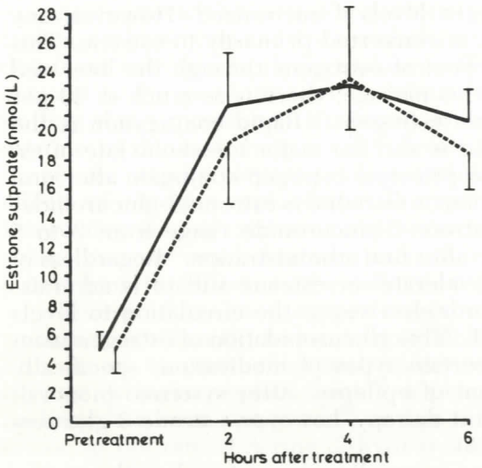

Figure 5. Estrone sulfate after piperazine: estrone sulfate (*dashed line*) and estradiol valerate (*solid line*). (*From* Anderson ABM, Sklovsky E, Sayers L, et al: Comparison of serum oestrogen concentrations in postmenopausal women taking oestrone sulphate and oestradiol. Br Med J 1:140, 1978; with permission.)

ministration has been estimated to be 12 hours. However, this half-life estimation in the circulation does not necessarily reflect events in peripheral tissues, which involve other conversion ratios and differing nuclear retention times for the different estrogens. Table 1 summarizes the levels of serum estrone and estradiol achieved after several different doses of oral estrogen, compiled from several

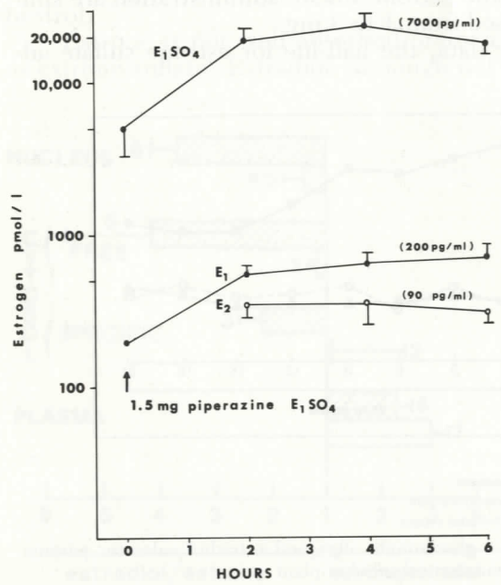

Figure 6. Levels of serum estrone (E_1), estradiol (E_2), and estrone sulfate (E_1SO_4) after 1.5 mg of piperazine estrone sulfate.

Table 1. *Approximate Serum Estrone and Estradiol Levels after Various Doses and Types of Oral Estrogen Replacement*

	ESTRONE (PG/ML)	ESTRADIOL (PG/ML)
Conjugated equine estrogen		
0.3 mg	76	19
0.625 mg	153	40
1.25 mg	200	60
Piperazine estrone sulfate		
0.6 mg	125	34
1.2 mg	200	42
Micronized estradiol		
1 mg	150	40
2 mg	250	60
Estradiol valerate		
1 mg	160	50
2 mg	300	60

sources,[12,29,40,65] Because sampling regimens have not been rigorous after dosing, these approximations (Table 1) pertain to average values expected 12 hours after ingestion.

NONORAL ABSORPTION OF ESTROGEN

Apart from the usual oral route of administration, estrogen is efficiently absorbed from the vagina, nasal mucosa, sublingually, and through the skin and subcutaneous fat. Different from oral administration, however, these systemic routes are not subject to first pass metabolism. Therefore, if estradiol is administered, estradiol levels exceed those of estrone.

Vaginal estrogen absorption is extremely efficient but is largely affected by the matrix or vehicle through which estrogen is delivered. When suspended in saline, the pharmacodynamics of estrogen absorption are similar to those of intramuscular administration.[52] In tablet form, micronized estradiol is also well absorbed.[35] Vaginal rings of estradiol release this steroid efficiently, achieving sustained levels of estradiol of about 60 pg per ml for 3 months after an initial burst effect.[60] However, when delivered as a cream, estrogen absorption is attenuated, and estrogen values are only one fourth of values achieved after comparable doses have been ingested (Fig. 7).[35]

The intranasal route delivers estrogen extremely well to the systemic circulation, but rapid dissipation of values occurs as with intramuscular injection.[48] The sublingual route has been used[6] but results in substantial variation in estrogen levels. This is probably because in reality a combination of the oral and sublingual routes occurs.

The skin and subcutaneous tissues absorb estrogen efficiently. As an estradiol pellet, an implant placed underneath the skin delivers steady levels of estradiol for 5 to 6 months.[30] Estradiol levels exceed

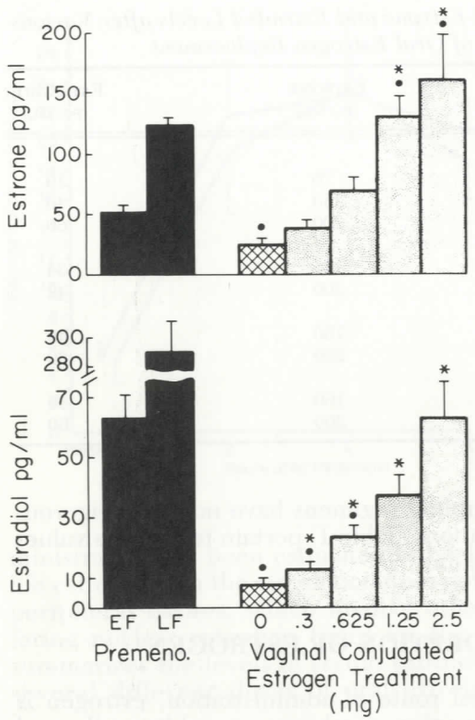

Figure 7. The mean (±S.E.) levels of estrone and estradiol observed in the two groups of subjects. EF = early follicular phase; LF = late follicular phase. ● = values significantly different ($P < 0.05$) from premenopausal values. (*From* Mandel FP, Geola FL, Meldrum DR, et al: Biological effects of various doses of vaginally administered conjugated equine estrogens in postmenopausal women. J Clin Endocrinol Metab 57:133, 1983; with permission.)

those of estrone and range from 60 pg per ml with 25 mg, to 80 to 100 pg per ml with 50 mg and 150 pg per ml with 100 mg.[30,39,57,63]

Percutaneous estradiol delivery is available in Europe as an ointment (Oestragel).[61,68] Application every other day is carried out over a wide surface area (up to 500 cm^2) of the lower abdomen and thighs. Generally, 1.5 or 3 mg of estradiol in 5 gm of cream or ointment is administered. Although clearly estradiol increases and exceeds estrone in the circulation, absorption of estradiol is extremely variable. Characteristic of this route of administration is that peak levels may be sustained for several hours. Alternate day treatment has been found to be effective (Fig. 8).[68]

The other transdermal method currently available in the United States is Estraderm. As an estradiol patch, available in 0.05 and 0.1 mg, estradiol is delivered efficiently with serum estradiol levels ranging from 40 to 80 pg per ml.[8,27,47] The patch is replaced every 3 days (Fig. 9). As demonstrated in the figure, physiologic levels of estradiol are delivered with this method. However, there is fluctuation in estrogen levels, and absolute steady state is not easily accomplished, particularly because of the need to replace the system every 3 days.

PLASMA STEROID AND PROTEIN HORMONE PROFILES

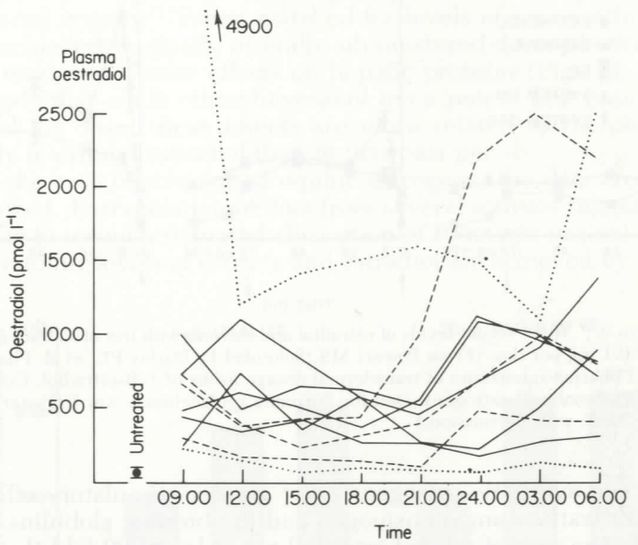

Figure 8. Plasma estradiol: Pretreatment and during Oestragel therapy. *Solid line:* 5 gm every night; *dashed line:* 5 gm alternate nights (applied on study night); *dotted line:* 5 gm alternate nights (none applied study night). (*From* Whitehead MI, Townsend PT, Kitchin Y, et al: Plasma steroid and protein hormone profiles in postmenopausal women following topical administration of oestradiol 17β. *In* Mauvais-Jarvis P, Vickers CFH, Wepierre J (eds): Percutaneous Absorption of Steroids. London, Academic Press, p. 231, 1980; with permission.)

ESTROGEN BY THE ORAL ROUTE

The oral route remains the most common way estrogen is administered. However, a characteristic of this route that needs to be further emphasized is the hepatic effect of rapid first pass. Estrogen is delivered as a bolus to the portal system, and inactivation of the ingested dose occurs as evidenced by conversion to conjugates, specifically estrone-3-glucuronide (see Fig. 4). In turn, hepatic proteins are stimulated, and some of these including clotting factors and renin substrate (RS) post a theoretical cardiovascular risk for the postmenopausal woman ingesting estrogens.

Earlier studies by us and others[15,37] have demonstrated a dose-related increase in hepatic globulin levels after oral administration of estrogen. However, a highly significant effect is also related to the type of estrogen administered, be it a native, equine, or synthetic.

Table 2[37] depicts the changes in various hepatic globulins after various estrogens have been ingested. On an equivalent weight basis,

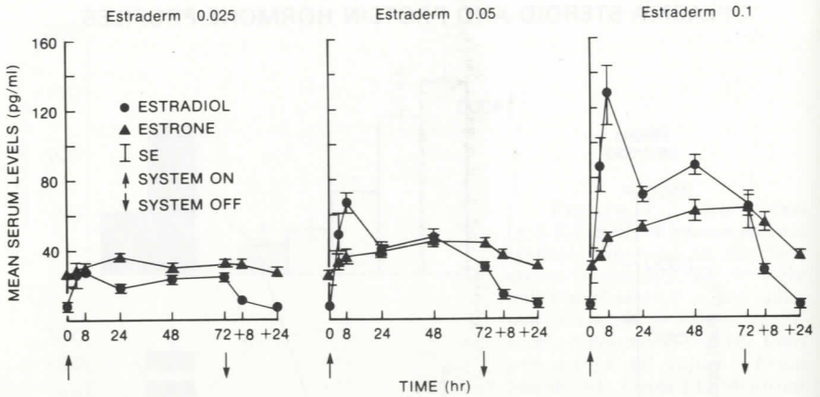

Figure 9. Mean serum levels of estradiol and estrone with use of Estraderm 0.025, 0.05, and 0.1 mg per day. (*From* Powers MS, Schenkel L, Darley PE, et al: Pharmacokinetics and pharmacodynamics of transdermal dosage forms of 17β-estradiol: Comparison with conventional oral estrogens used for hormone replacement. Am J Obstet Gynecol 152:1099, 1985; with permission.)

equine and synthetic estrogens exert greater stimulatory effects on renin substrate or angiotensinogen and the binding globulins. These effects in the case of ethinyl estradiol are at least 200-fold that of the native estrogens.[34,37] While the degree of FSH suppression is also related to the type of estrogen ingested, these changes are far less pronounced than the hepatic effects.

At least three important questions are raised by these data. First, is the greater potency of equine and synthetic estrogens purely related to their ability to stimulate hepatic globulins via the first pass effect? Second, what is the clinical significance or relevance of elevated hepatic globulin levels? Third, are other hepatic products such as lipoproteins similarly affected as the consequence of rapid first pass? The latter two questions are particularly relevant clinically and will be discussed in a separate section below.

Table 2. *Relative Potency According to Four Parameters of Estrogenicity*

	Serum FSH	Serum CBG-BC	Serum SHBG-BC	Serum Angiotensinogen
Piperazine estrone sulfate	1.1	1.0	1.0	1.0
Micronized estradiol	1.3	1.9	1.0	0.7
Conjugated estrogens	1.4	2.5	3.2	3.5
Diethylstilbestrol	3.8	70	28	13
Ethinyl estradiol	(80–200)*	(1,000)*	614	232

(From Mashchak CA, Lobo RA, Dozono-Takano R, et al: Comparison of pharmacodynamic properties of various estrogen formulations. Am J Obstet Gynecol 144:511–518, 1982, with permission.)

CBG-BC: Corticosteroid binding–globulin binding capacity.

SHBG-BC: Sex hormone–binding globulin binding capacity.

To determine whether an intrinsic property of ethinyl estradiol explains its stimulatory hepatic effect, ethinyl estradiol was administered to postmenopausal women vaginally in order to bypass the hepatic-portal system.[17] When matched for levels of serum ethinyl estradiol achieved, vaginally or orally administered doses of ethinyl estradiol rendered similar effects on hepatic proteins (Fig. 10). These data imply that while ethinyl estradiol has a potent first pass effect, matched for dose, these effects are more related to the chemical property of ethinyl estradiol than to first pass per se.

In the case of conjugated equine estrogens, the data are somewhat mixed. Extrapolation of data from several sources suggests that given the four-fold attenuated absorption of Premarin vaginal cream, when systemic levels of estrone and estradiol are achieved by 2.5 mg

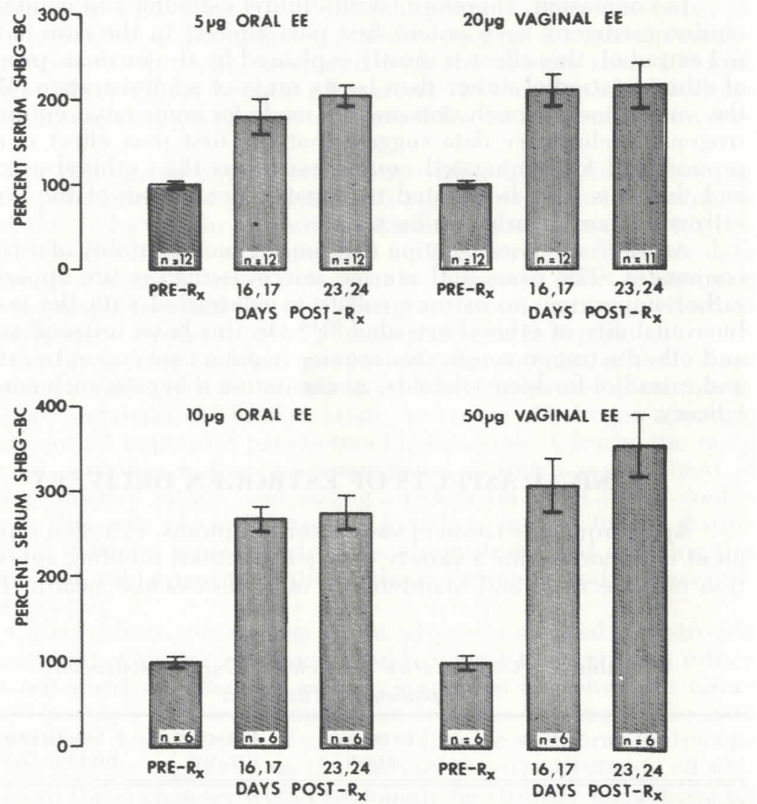

Figure 10. Mean (± S.E.) binding capacity of serum sex hormone–binding globulin in percentage of pretreatment (PRE-R_x) levels prior to and 16 and 17 as well as 23 and 24 days following daily oral or vaginal administration (POST-R_x) of 5 and 20 or 10 and 50 μg of ethinyl estradiol (EE), respectively, in postmenopausal women. (*From* Goebelsmann U, Mashchak CA, Mishell DR Jr: Comparison of hepatic impact of oral and vaginal administration of ethinyl estradiol. Am J Obstet Gynecol 151:868, 1985; with permission.)

of vaginal cream, hepatic effects are noted, yet still less than that of the comparable oral dose (0.625 mg) (Table 3).

Although these data suggest a greater first pass effect for conjugated equine estrogens than can be ascribed merely to this form of estrogen, we must realize that conjugated equine estrogens are a mixture of estrogens. The inability to measure and assess separately the potency of the equine estrogens has limited our ability to make definitive conclusions on this issue. Nevertheless, we have attempted recently to assess separately the potency of equilin sulfate, the major equine constituent of conjugated equine estrogens.[31] These data suggest that oral equilin sulfate is two- to four-fold more stimulatory to hepatic globulins than native estrogens on a weight basis and at least two-fold more potent than conjugated equine estrogens, of which 25 per cent is made up of equilin sulfate.

In conclusion, therefore, both ethinyl estradiol and conjugated equine estrogens have potent first pass effects. In the case of ethinyl estradiol, this effect is mostly explained by the intrinsic property of ethinyl estradiol rather than by its route of administration. While the same general conclusion may be made for conjugated equine estrogens, preliminary data suggest that the first pass effect is more pronounced for conjugated equine estrogens than ethinyl estradiol and that this may be related to hepatic metabolism of the equine estrogens, particularly equilin sulfate.

An alternative explanation rests on the bioavailability of estrogen conjugates. The brain and uterine microvasculature are apparently rather impervious to estrone sulfate as contrasted with the greater bioavailability of ethinyl estradiol.[59,64] On this basis, estrone sulfate and other estrogen conjugates require hepatic conversion to estrone and estradiol for bioavailability, necessitating a hepatic influence for efficacy.

CLINICAL ASPECTS OF ESTROGEN DELIVERY

Apart from alleviation of vasomotor symptoms, estrogen replacement is important for a variety of other functions inluding conservation of bone mass and maintenance of cardiovascular health. Pertinent to this review will be how various estrogens and their routes of administration affect some of these parameters.

Table 3. *Comparative Potencies of Current Estrogen Replacement Therapies*

	Estradiol (pg/ml)	Estrone (pg/ml)	Sex Hormone–Binding Globulin
Oral			
Conjugated estrogens			
0.6 mg	40	150	75
Vaginal			
Conjugated estrogen cream			
1.25 mg	35	120	0–10
2.5 mg	65	170	No change

Although somewhat crude, the biochemical parameters most used to assess postmenopausal bone resorption are fasting urinary calcium/creatinine and hydroxyproline/creatinine ratios. While many estrogens, even in small doses, decrease the calcium/creatinine ratio,[29] suggesting an inhibition of bone resorption, the different classes of estrogens have different potencies on bone resorption compared with their hepatic effects. In this regard, it requires 10 μg of ethinyl estradiol to significantly suppress the calcium/creatinine ratio, whereas doses from 0.3 to 0.625 mg of estrone sulfate are sufficient. Clinically, while conservation of bone mass has been established with approximately 20 μg per day of mestranol (which is converted to ethinyl estradiol), only 0.625 mg of conjugated equine estrogens is needed. This 30- to 100-fold potency difference between ethinyl estradiol and conjugated equine estrogens for calcium/creatinine ratios needs to be compared with the greater than 200-fold changes observed for hepatic parameters. In the case of ethinyl estradiol, these changes are not influenced by the route of administration.

For conjugated equine estrogens, while equilin sulfate has potent hepatic effects, it requires 0.625 mg of this equine estrogen to equal the reduction in calcium/creatinine ratios observed with the same dose (0.625 mg) of conjugated equine estrogens.[31] These data confirm that there is less of a dose- or type-specific effect of estrogen on bone resportion and that this, being a systemic estrogen effect, is not influenced by the route of administration or first pass.

Cardiovascular health issues include the potential effects of estrogens on carbohydrate metabolism, blood pressure, thrombosis, and lipid metabolism. The dose, type, and route of estrogen administration are all important parameters for this topic. Clearly, the most relevant assertion is that postmenopausal estrogen replacement is cardioprotective rather than posing a risk factor.[21,49] Clinical confusion in this area of cardiovascular health is related to not distinguishing between types of estrogens administered and equating the use of "natural" estrogens with synthetic estrogens and oral contraceptives.

Carbohydrate metabolism is not adversely affected by estrogen replacement. Current evidence would suggest that estrogen either does not exert an effect or actually improves carbohydrate tolerance,[56] perhaps by stimulating insulin receptor binding.[55] The data suggesting a deterioration of glucose tolerance with oral contraceptive use may be explained on the basis of 19-norprogestogen effects. While all these changes would seemingly be strongly influenced by hepatic first pass, no data directly address this issue.

A common misconception is to suggest that all estrogens adversely affect blood pressure. Although oral contraceptives pose a risk in this regard, this is not the case for other types of estrogen replacement. The mechanism whereby estrogen has been thought to raise blood pressure is via a stimulation of renin substrate. However,

the level of renin substrate elevated by estrogen itself does not explain the occurrence of hypertension. Recent evidence suggests that a particular high-molecular weight moiety of renin substrate, which is stimulated by estrogen, may explain the occurrence of hypertension with the use of synthetic estrogens in oral contraceptives.[54] However, no well-controlled data support an overall increased risk of hypertension with "natural" estrogen use. Indeed several studies suggest the opposite. Evidence exists that native estrogens decrease blood pressure in both normo- and hypertensive postmenopausal women.[28,32,69] Clearly, this influence of estrogen on blood pressure is largely related to the type of estrogen administered. While synthetic estrogens, particularly ethinyl estradiol, pose the greatest risk because of the stimulatory effects of renin substrate, conjugated equine estrogens, although more stimulatory to renin substrate than native estrogens, pose minimal risk. In unusual patients (approximately 5 per cent), hypertension has been associated with use of conjugated equine estrogens. Although the mechanism for this unusual hypertensive response remains enigmatic, monitoring to detect its occurrence is essential. Furthermore, because it is plausible that elevation of renin substrate levels may play some role in this rare occurrence of hypertension, avoidance of conjugated equine estrogens and/or the oral route of administration seems prudent. Specifically, systemic native estradiol administration (by subcutaneous pellet, transdermal methods, or vaginally) may be recommended because these regimens have been found not to raise renin substrate levels.

A similar scenario may be drawn for the effects of estrogen on coagulation. Oral contraceptives increase the risk for thromboembolic phenomena. While this is thought to be related to the stimulation of hepatic coagulation factors with synthetic estrogens, no such increase occurs with native estrogen or moderate doses of conjugated equine estrogens.[3,4,42] Specifically, the alterations observed with ethinyl estradiol (30 μg per day) in one study[4] did not occur with placebo or estrone sulfate (3 mg per day) in a 12-month crossover design.

Taken together, these data are reassuring that moderate doses of native and conjugated equine estrogens do not exert a risk for thrombosis in postmenopausal replacement therapy. However, we have to be cognizant that just as unusual hypertensive responses are known to occur, some patients have a propensity (perhaps genetically predisposed) to have thrombotic occurrences. One of several such problems may result from familial deficiency of antithrombin III levels. Under these circumstances and with any significant history of thrombosis, the type and route of estrogen delivery need to be critically considered. Since clotting factors are hepatic in origin and since non-native estrogens exert more of a stimulatory effect, patients who are at risk for thrombosis should have estradiol administered by a nonoral route.

While non-native estrogens have a propensity to stimulate renin substrate and clotting factors, and these pose potential risks, it is

unclear as to what significance might be ascribed to the simulation of other globulins (sex hormone–binding globulins, transcortin, ceruloplasmin, and so on). To our knowledge, while these changes signify estrogen first pass effects and are good markers of this response, there are no known major health consequences associated with these changes.

Another factor of great impact is the estrogen effect on lipoproteins. As reviewed elsewhere, much of the cardioprotective effect of estrogen replacement has been ascribed to changes in high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol. Since lipoprotein packaging is hepatic in origin, it would appear that first pass effects of estrogen are beneficial in this context for cardiovascular health. Because estrogen stimulates HDL cholesterol levels (and specifically HDL_2 and the associated apolipoproteins A1 and A2) and lowers LDL cholesterol levels, oral estrogens appear to have an advantage over nonoral routes. This concept, however, needs to be examined further.

Indeed, preliminary evidence would suggest that there appears to be a type-specific stimulatory effect of estrogens on lipid metabolism, with synthetic estrogens having the most marked stimulatory effect. In the case of ethinyl estradiol, however, this stimulatory effect does not absolutely depend on its oral route of administration. Contrary to common belief, matched for ethinyl estradiol serum levels, oral and vaginal ethinyl estradiol were equipotent in their ability to increase plasma HDL cholesterol levels.[17] However, that 2.5 mg of vaginal conjugated equine estrogens did not change lipid parameters[35] while ingestion of 0.625 mg consistently results in changes suggests that the oral route is important for lipid effects with this class of estrogen. These observations are consistent with our recent data on equilin sulfate, where as little as 0.15 mg orally of this estrogen significantly raised HDL cholesterol levels.[31]

The importance of the oral route is particularly relevant for lipid metabolism when the less potent native estrogens are used systemically. To date, the transdermal system, despite achieving physiologic estradiol delivery, has not been associated with changes in lipid levels, at least in short-term studies. Nevertheless, this observation need not be absolute for systemic estradiol delivery. The use of the estradiol pellet, which also bypasses first pass effects, results in significant elevations in HDL cholesterol level,[30,51] even with a single 25-mg pellet. These observations suggest the following conclusions. Both the type (synthetic more than native) and the route (oral more than systemic) of estrogen administration are important for a beneficial "cardioprotective lipid profile." However, given that synthetic estrogens are always to be avoided and that the oral route is sometimes not preferred, assurance of an adequate physiologic level of estradiol is important. Given an adequate and sustained estradiol level over several months (as is characteristic of the estradiol pellet), HDL cholesterol levels may increase associated with lowering of LDL cholesterol levels.

THE PROGESTOGENS

The clinical use of progestogens is important to oppose estrogen effects on the endometrium. To this end, progestogen effects are antiestrogenic (decrease in receptor content and mitotic activity) and decrease the potency of estrogens by enzymes that aid in its intracellular effects (dehydrogenase, sulfurylase). As reviewed previously for estrogens, different classes of progestogens have different potencies and metabolic effects. Different from estrogen, however, is that these potencies have been far less well studied. The native progestogens are progesterone and 17-OH progesterone. There are two synthetic categories: one grouped as 19-norprogestogens (as used in oral contraceptives) and the other, the C21 compounds with a 17-acetoxy group (medroxyprogesterone acetate, megestrol acetate).

PHARMACOLOGY OF PROGESTOGENS

For practical purposes, native progesterone is the only compound with significant biologic function. Significant reduction in potency occurs with 17α-hydroxylation. However, in an esterified form, long-acting 17-OH progestogens are in clinical use as parenteral progestogens (17α-hydroxyprogesterone valerate and caproate).

Absorption of oral progesterone is inefficient. Rapid hepatic hydroxylation and conjugation (first pass effects) occur, resulting in increases in pregnanediol-3-glucuronide, the major urinary metabolite. Nevertheless, oral progesterone has been used with some efficacy in postmenopausal women[67] in whom a dose of 300 mg may result in 5 to 10 ng per ml in the systemic circulation. A more efficient means of ingesting progesterone is with a micronized product. Utrogestin, which is available from France, may be administered orally in 100 to 200 mg doses. When administered in divided doses (100 mg at 9 a.m. and 200 mg at 9 p.m.), peak serum progesterone levels of more than 10 ng per ml are encountered (Fig. 11).[46] These findings were associated with significant endometrial progestational activity.

Oral administration of native progesterone is nevertheless subject to first pass effects. Characteristic of these changes is the rapid conversion of progesterone to desoxycorticosterone, an effect that does not occur readily with the systemic route.[43,44] When equal doses of progesterone are administered orally and intramuscularly, despite a three-fold increase in serum levels with the intramuscular route, the ratio of desoxycorticosterone/progesterone was much higher than with the oral route (Fig. 12). These data, which confirm hepatic effects characteristic of first pass phenomena, are interesting but await clinical relevance. Perhaps these and similar changes with oral progestogens would help explain unusual hypertensive and metabolic responses in some women.

Native progesterone is well absorbed vaginally and rectally[41,66]

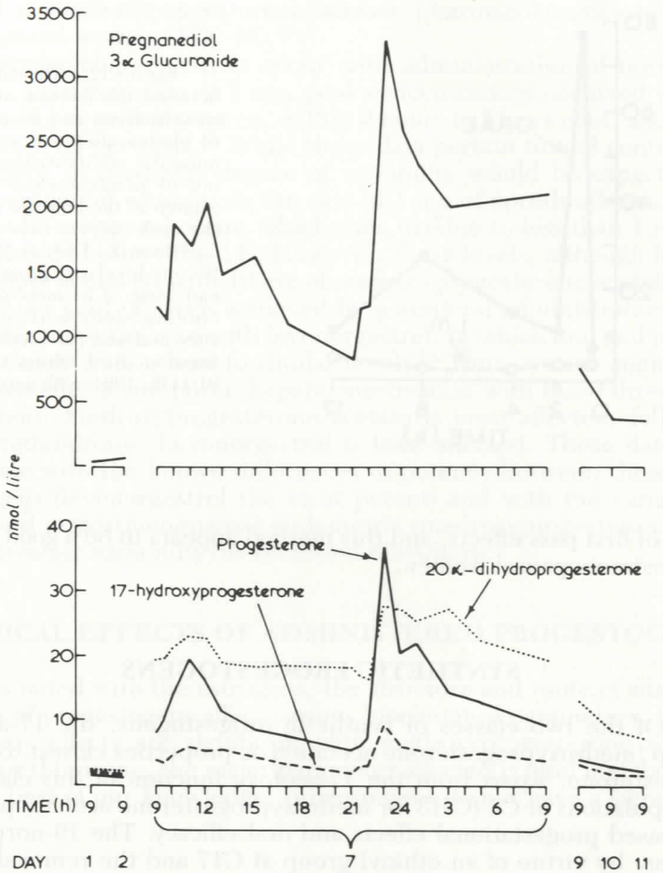

Figure 11. Mean concentrations of progesterone, pregnanediol 3α-glucuronide, 17-hydroxyprogesterone, and 20α-dihydroprogesterone in the peripheral plasma of postmenopausal women before, during, and after administration of oral progesterone. Pretreatment, days 1 and 2; after 5 days of treatment with 100 mg progesterone at 9 hours and 200 mg at 21 hours, day 7; and posttreatment, days 9 to 11. (*From* Padwick M, Endacott J, Matson C, et al: Absorption and metabolism of oral progesterone when administered twice daily. Fertil Steril 46:402, 1986; with permission.)

as well as nasally[58] but does not compare with the high levels achieved by the intramuscular route. These routes of administration afford much higher levels of progesterone than does the oral route, which is subject to first pass changes. It is for the levels of progesterone that may be achieved by nonoral routes that these methods are chosen for premenopausal women (who have the need to more closely mimic the normal luteal phase). To date, no adverse effects have been documented with the use of oral native progesterone in

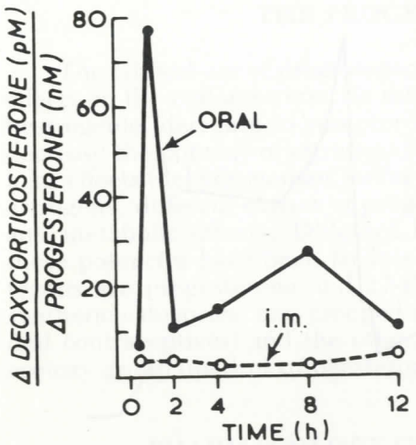

Figure 12. The mean ratio between the increase in deoxycorticosterone and progesterone in plasma after oral and intramuscular administration of 100 mg of progesterone in four women in the follicular phase of the cycle. (*From* Ottosson UB, Carlstrom K, Damber JE, et al: Serum levels of progesterone and some of its metabolites including deoxycorticosterone after oral and parenteral administration. Br J Obstet Gynaecol 91:1111, 1984; with permission.)

spite of first pass effects, and this method appears to be a good choice for postmenopausal women.

SYNTHETIC PROGESTOGENS

Of the two classes of synthetic progestogens, the 17-acetoxy group (medroxyprogesterone acetate) has properties closest to native progesterone. Apart from the 17-acetoxy function of this class, the manipulations at C6 (CH3 for medroxyprogesterone acetate) produce increased progestational effects and oral efficacy. The 19-norprogestogens, by virtue of an ethinyl group at C17 and the removal of the 19th carbon from C10, have increased progestational activity, oral efficacy, and reduced androgenic activity, even though this class is derived from testosterone. However, despite the C19 ethinyl group, which tends to nullify androgen action, characteristics of some members of this group (particularly norethindrone and levonorgestrel) are their androgenic side effects.

Oral absorption of these synthetic progestogens is variable. For this and other reasons, it has been difficult to ascribe potency ratios for these various progestogens. The most commonly used progestogens are medroxyprogesterone acetate, norethindrone, and levonorgestrel, with medroxyprogesterone acetate constituting the majority of prescriptions for postmenopausal patients in the United States.

Absorption of medroxyprogesterone acetate after a 10 mg oral dose is fairly rapid, reaching levels of 3 to 4 ng per ml within 1 to 4 hours, and declining to 0.3 to 0.6 ng per ml by 24 hours. However, these characteristics are variable, and major differences have been

noted in medroxyprogesterone acetate pharmacokinetics in postmenopausal women (Fig. 13).[11]

Similar characteristics occur with administration of norethindrone. After ingestion of 1 mg, peak concentrations occurred within 1 hr in 16 per cent of women, within 2 hours in 51 per cent, and after 2 hours in 33 per cent.[13] While these data pertain to oral contraceptive users, at least this degree of variability would be expected in postmenopausal women. In the case of 1 mg of norethindrone, peak levels of 5 ng per ml occur, which then decline to less than 1 ng per ml within 24 hours (Fig. 14). However, these levels, although higher than those achieved with 10 mg of medroxyprogesterone acetate, are still 60 per cent of levels achieved by parenteral administration.

This is not the case with levonorgestrel, in which oral and parenteral administration lead to similar levels.[23] Thus, we see significant first pass effects and portal-hepatic inactivation with these three progestogens. Medroxyprogesterone acetate is most affected, followed by norethindrone. Levonorgestrel is least affected. These data also correlate with the known differences in potency between these progestogens (levonorgestrel the most potent) and with the variability observed in postmenopausal endometria (medroxyprogesterone acetate, greatest variability) as reviewed elsewhere.

CLINICAL EFFECTS OF ADMINISTERED PROGESTOGENS

As noted with the estrogens, the structure and route of administration of progestogens affect various biochemical parameters. While first pass effects are significant with medroxyprogesterone acetate and norethindrone, the major parameter affected is lipid metabolism. To the best of our knowledge, progestogens do not have a significant

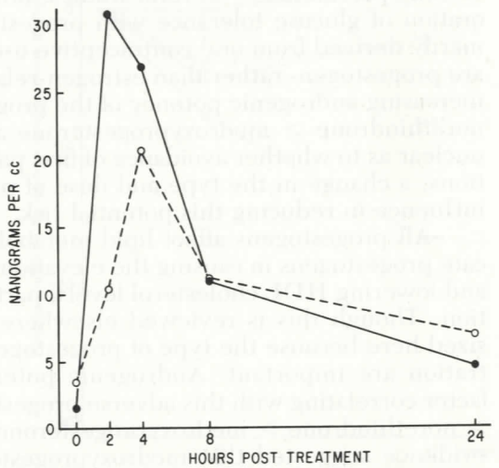

Figure 13. Plasma levels of medroxyprogesterone acetate after oral administration. (*From* Cornette JC, Kirton KT, Duncan GW: Measurement of medroxyprogesterone acetate by radioimmunoassay. J Clin Endocrinol Metab 33:459, 1971; with permission.)

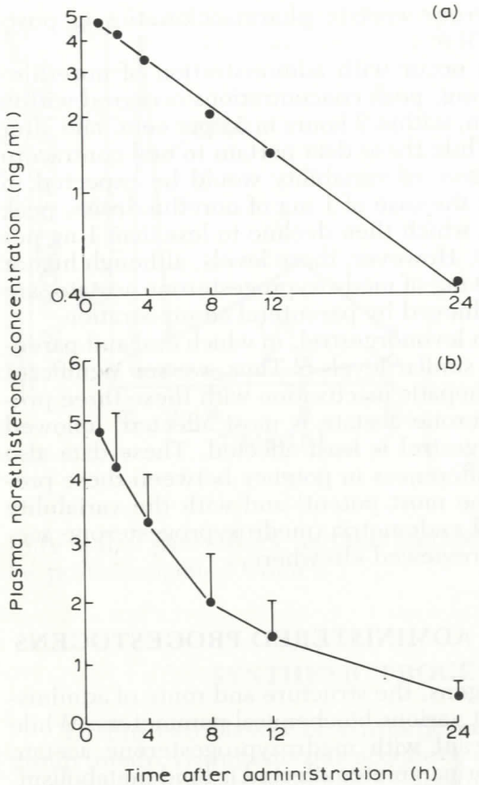

Figure 14. Plasma norethisterone concentrations in 18 Caucasian women after administration of 1 mg norethisterone orally. Mean values are shown with vertical bars denoting S.D. *a*, Semilogarithmic plot. *b*, Arithmetic plot. (*From* Fotherby K: Pharmacokinetics of progestational compounds. Maturitas 8:123, 1986; with permission.)

impact on binding globulins and appear to have negligible effects on clotting parameters.[10] Several studies, however, have noted a deterioration of glucose tolerance with progestogen use. These data, primarily derived from oral contraceptive use, suggest that these effects are progestogen- rather than estrogen-related and are associated with increasing androgenic potency of the progestogens (levonorgestrel > norethindrone > medroxyprogesterone acetate). Although it is yet unclear as to whether avoidance of first pass will affect these observations, a change in the type and dose of progestogen may have some influence in reducing this potential risk.

All progestogens affect lipid metabolism adversely. Data implicate progestogens in causing the elevations in LDL cholesterol levels and lowering HDL cholesterol levels, particularly the HDL_2 subfraction. Though this is reviewed elsewhere, these effects are emphasized here because the type of progestogen and its route of administration are important. Androgenic potency is again the principal factor correlating with this adverse progestogen effect (levonorgestrel > norethindrone > medroxyprogesterone acetate). Although earlier evidence suggested that medroxyprogesterone acetate (10 mg) was

devoid of such effects,[22] recent evidence[45] clearly suggests that medroxyprogesterone acetate lowers HDL and HDL_2 levels in postmenopausal women receiving sex steroid replacement (Fig. 15). This was not the case for native or natural progesterone, which to date appears to be devoid of harmful lipid effects.[45] Most significant among these observations is that even if progestogens (such as medroxyprogesterone acetate) cause only minor changes in lipoproteins, they clearly attenuate or prevent altogether the beneficial effects of estrogen replacement. Indeed if it can be shown that the estrogen-lipid effects are most responsible for the cardioprotective effect of estrogen use, the administration of any progestogen, other than progesterone, would not be appropriate.

Nevertheless, the dose of progestogen is important and may influence the impact of the route of delivery. Data from Whitehead and by us[16] suggest that the progestogen dose may be markedly reduced and still afford endometrial protection. This is clearly the case if the length of treatment is extended to 12 and 13 days. On this basis, ongoing studies have suggested that negligible lipid effects occur with 1 mg or less of norethindrone and 2.5 to 5 mg of medroxyprogesterone acetate, at least when administered only for 12 days. Studies of continuous daily dosing regimens await data analysis at the present time.

Another potential way to avoid some progestogen effects on lipid metabolism is to change from the oral to a systemic route. Earlier studies by us failed to demonstrate adverse effects with depo me-

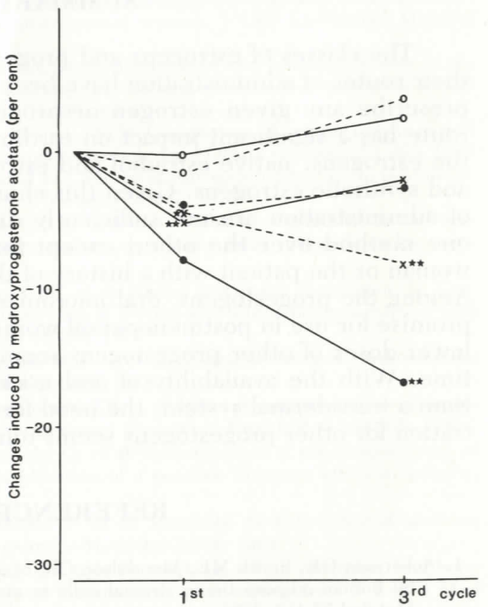

Figure 15. Percentage of change in mean total cholesterol and HDL-cholesterol, its subfractions, and apolipoproteins following the sequential addition of 5 mg of medroxyprogesterone acetate twice daily in 20 estrogen-primed postmenopausal women. Total cholesterol (x——x); HDL-cholesterol (x- - -x); subfraction 2 of HDL-cholesterol (●——●); subfraction 3 of HDL-cholesterol (○——○); apolipoprotein AI (●---●); apolipoprotein AII (○- - -○). *P < 0.05; **P < 0.01.

droxyprogesterone acetate on lipid parameters.[5] While other data are not as optimistic,[14] ongoing clinical studies using vaginal and subcutaneous implants of lower doses of norethindrone and dextronorgestrel have resulted in a reduction of changes in lipid metabolism as observed by the oral route.

While we have focused primarily on the potential harm of progestogens, this dose of sex steroids also has an impact on bone conservation. This systemic response does not appear to be influenced by different routes of administration. While native progesterone has not been adequately studied, both 17-acetoxy and 19-norprogestogens have efficacy. Medroxyprogesterone acetate is at least four times more potent than megestrol in reducing calcium/creatinine ratios,[33] and norethindrone appears more potent than levonorgestrel. Recent data also suggest an additional benefit of progestogens in increasing bone formation rather than just inhibiting bone resorption.

In conclusion, among the progestogens, oral micronized progesterone treatment appears to be the most convenient and attractive means of delivering progestogen to eliminate adverse endometrial stimulation. However, lower doses of ingested progestogens (medroxyprogesterone acetate and norethindrone) have benefit; lower doses of all the progestogens are being evaluated in nonoral delivery systems as well. On the horizon, for even greater convenience, the transdermal method of progesterone delivery (patch) is being investigated for clinical use.

SUMMARY

The classes of estrogens and progestogens currently in use and their routes of administration have been considered. The decision to prescribe any given estrogen or progestogen and by a particular route has a significant impact on cardiovascular risk factors. Among the estrogens, native estradiol and estrone are favored over equine and synthetic estrogens. Given this choice, oral and systemic routes of administration are not sufficiently different clinically to endorse one method over the other, except for the unusual hypertensive woman or the patient with a history of thromboembolic phenomena. Among the progestogens, oral micronized progesterone offers much promise for use in postmenopausal women. However, the oral use of lower doses of other progestogens seems appropriate at the present time. With the availability of oral micronized progesterone and in time a transdermal system, the need for alternate routes of administration for other progestogens seems unnecessary.

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Department of Obstetrics and Gynecology
University of Southern California Medical Center
Women's Hospital, Room 1M2
1240 North Mission Road
Los Angeles, California 90033