Percutaneous 17ß-estradiol replacement therapy in hypertensive postmenopausal women

M.C. Osório-Wender[1], D. Vitola[3] and P.M. Spritzer[1,2]

[1]Unidade de Endocrinologia Ginecológica, Hospital de Clínicas de Porto Alegre, [2]Departamento de Fisiologia, Universidade Federal do Rio Grande do Sul, and [3]Instituto de Cardiologia do Rio Grande do Sul, Porto Alegre, RS, Brasil

Abstract

Correspondence

P.M. Spritzer
Departamento de Fisiologia
Universidade Federal do Rio Grande
do Sul
Rua Sarmento Leite, 500
90050-170 Porto Alegre, RS
Brasil
Fax: 55 (051) 226-7191

The present study evaluated the short-term effects of percutaneous 17ß-estradiol on blood pressure, metabolic profile and hormonal levels in postmenopausal women with systemic arterial hypertension. After a wash-out period of 15 days, 10 hypertensive patients were treated with guanabenz acetate to control blood pressure, followed by 17ß-estradiol in the form of hydroalcoholic gel administered for 21 of 28 days of each cycle, for 3 cycles. Patients were evaluated before, during and 2 months after estrogen administration. Systolic and diastolic blood pressure or heart rate did not present any significant change in any patient when compared to those periods with the antihypertensive drug only (pretreatment period and 60 days after estrogen therapy was discontinued). Plasma biological markers of hepatic estrogenic action (plasma renin activity, antithrombin III, triglycerides, total cholesterol and lipoproteins) also remained unchanged during the study. Hormone treatment was effective, as indicated by the relief of menopausal symptoms, a decrease in FSH levels (73.48 ± 27.21 to 35.09 ± 20.44 IU/l, P<0.05), and an increase in estradiol levels (15.06 ± 8.76 to 78.7 ± 44.6 pg/ml, P<0.05). There was no effect on LH (18.0 ± 9.5 to 14.05 ± 8.28 IU/l). Hormone levels returned to previous values after estrogen treatment was discontinued. The data indicate that short-term percutaneous 17ß-estradiol replacement therapy, at the dose used, seems to be a safe hormone therapy for hypertensive menopausal women. Nevertheless, a controlled, prospective, randomized clinical assay with a larger number of subjects is needed to definitely establish both the beneficial and harmful effects of hormone replacement therapy in hypertensive women.

Introduction

Three major benefits derive from hormone replacement therapy (HRT) in menopausal women: a better quality of life due to relief of vasomotor symptoms (1) and treatment of urogenital atrophy (2), prevention and treatment of osteoporosis (3,4), and a decrease in mortality caused by cardiovascular disease (5-8).

The incidence of hypertension increases in postmenopausal women (9,10), which is probably related to the estrogen deficit typical of this period of life. On the other hand,

HRT using conjugated estrogens administered orally is related to the onset of hypertension in up to 5% of treated women (11). The renin-angiotensin-aldosterone system seems to be one of the mechanisms responsible for the association between higher blood pressure levels and the use of oral estrogen in some women (12). Previous studies evaluating blood pressure and HRT in normotensive women revealed that the use of a non-oral natural estrogen did not alter or even reduced blood pressure levels (13-15).

The aim of the present study was to evaluate the effectiveness of percutaneously administered 17ß-estradiol (17ß-E$_2$), as well as its metabolic and cardiovascular tolerance by postmenopausal women with blood pressure levels controlled by antihypertensive treatment.

Patients and Methods

Ten postmenopausal hypertensive women were selected among those seen at the Gynecological Endocrinology Unit of the Hospital de Clínicas de Porto Alegre (HCPA). The criteria for selection were as follows: natural menopause established at least one year before the beginning of the study or surgical menopause with estrogen and gonadotropin levels compatible with postmenopause; no use of drugs capable of affecting the hepatic metabolism or any treatment with hormones for six months before the study; normal gynecological examination, including palpation of the breasts, mammogram, cytology of the cervix, and histology of the endometrium; normal hepatic and renal function tests and no pathology other than hypertension; symptoms of estrogen deficit, and hypertension classified as slight to moderate in the absence of antihypertensive treatment (160/ 114 mmHg maximum, or higher blood pressure levels in the absence of hemorrhage, exudate, or papilledema upon fundoscopy).

In order to determine the presence of hypertension, the various antihypertensive treatments of the patients (diuretics, methyldopa or propranolol) were discontinued for a period of approximately 15 days (wash-out period) during which they underwent cardiologic evaluation. The 10 patients who fulfilled the criteria for inclusion were submitted to complete clinical examination, fundoscopy, electrocardiogram, and echocardiogram (uni- and bidimensional, using a Doppler-SSD 730 Aloka apparatus, according to the technique recommended by the American Society of Echocardiography).

Guanabenz acetate was used as the antihypertensive treatment at progressively higher doses for three to four weeks until blood pressure levels were normalized. Thereafter, the patients were kept on a fixed dose of this drug until the end of the study.

A single researcher using the same random-zero sphygmomanometer measured blood pressure levels and pulse rate weekly. After a rest period of 10 min, blood pressure and pulse rate were determined three times at 5-min intervals, first in the supine and then in the standing position. Patient weight was checked every 15 days, and the variable used was the body mass index (BMI = weight/ height^2).

The following serum concentrations were determined for all patients: estradiol, LH, FSH, plasma renin activity (PRA), aldosterone, fasting glucose levels and glucose levels 2 h after the ingestion of 75 g glucose, total cholesterol, high, low, and very low density lipoproteins (HDL-c, LDL-c and VLDL-c, respectively), and antithrombin III (A-III). Blood samples were collected at three different times: before hormone treatment, at the end of the second cycle using percutaneous 17ß-E$_2$, and 2 months after hormone treatment was discontinued, between 8:00 and 10:00 a.m., following a 12-h fast. The biochemical determinations were performed in the Biochemistry Laboratory of the HCPA by the colorimetric-enzymatic method using the 400 Roche Centrifichem System. A-III was determined in the Hemotherapy Unit of

the HCPA using the A-III chromogenic assay (Baxter Healthcare Corporation, Deerfield, IL). Hormone levels were determined at the Radioimmunoassay Laboratory of the HCPA using commercial radioimmunoassay kits (Serono, E_2-DPC, and PRA-Baxter for LH, FSH and aldosterone, respectively).

After blood pressure was controlled with the antihypertensive drug and samples had been collected for laboratory tests, patients were given 17ß-E_2 in the form of hydroalcoholic gel (Besins-Iscovesco Laboratory, Paris, France). The patients were instructed to apply 2.5 g of the gel (1.5 mg 17ß-E_2) to the skin of the abdomen, thighs and arms daily for 21 days, for 3 cycles of 28 days each. At the end of the second cycle blood samples were collected, and a second echocardiographic examination was performed during the third cycle. When the 3-month period of estrogen administration was completed, all patients with a uterus were submitted to hysteroscopy with a microcolpohysteroscope (model Hamou II), in addition to biopsy of the endometrium, and were treated with daily doses of 10 mg medroxyprogesterone acetate for 10 days.

The study design was a prospective study, and each patient was her own control. The data were analyzed by analysis of variance and the Student-Newman-Keuls test, with the level of significance set at P<0.05. The data are reported as means ± SD or median and range. The study was approved by the Ethics Committee of the Hospital de Clínicas and informed consent was obtained from each subject.

Results

The median age of the patients was 55 years (48-70 years), the median postmenopausal period was 7.5 years (2-23 years), and mean BMI was 28.8 kg/m^2 (SD ± 4.37). Eight of the 10 women had natural menopause and the other two had undergone sur-

gical menopause.

Figure 1 shows blood pressure levels during the study. With the antihypertensive treatment, blood pressure levels were controlled and were significantly lower than those during the period without treatment. The use of hormone therapy associated with the antihypertensive drug did not cause any significant change in blood pressure for any patient when compared to the periods with the antihypertensive drug only (pretreatment period and 60 days after estrogen therapy was discontinued).

Menopausal symptoms decreased during estradiol treatment as evaluated weekly by the Kupperman index. No adverse skin effect caused by the use of the gel was reported. Serum estradiol (E_2) levels during the pretreatment period were low (15.06 ± 8.76 pg/ml), as typically observed in postmenopausal women. During estrogen replacement therapy, E_2 rose to 78.7 ± 44.6 pg/ml (P<0.05), a value compatible with that of the follicular phase of normal young females, returning to postmenopausal levels two months after discontinuation of estrogen therapy (14.5 ± 6.07 pg/ml) (Table 1).

Gonadotropin levels at the initial evaluation were 73.48 ± 27.21 IU/l for FSH and 18.01 ± 9.56 IU/l for LH. With the use of percutaneous 17ß-E_2, these levels decreased
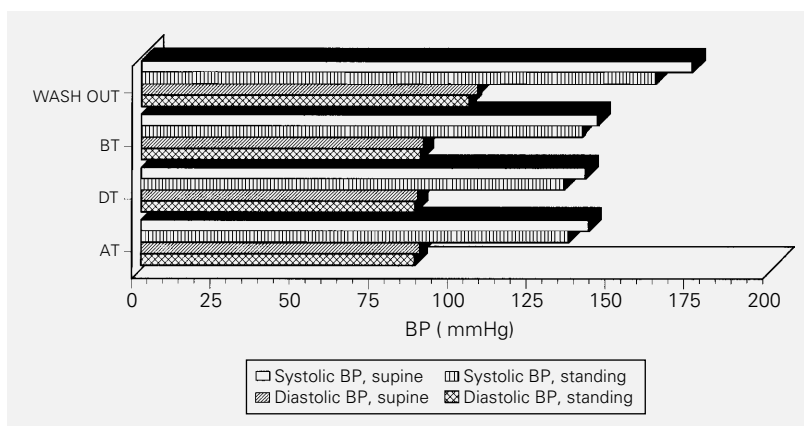

Figure 1 - Systolic and diastolic blood pressure (BP) levels during the study. WASH OUT, Without antihypertensive treatment; BT, before estrogen treatment; DT, during estrogen treatment; AT, 2 months after hormone treatment was discontinued.

to 35.09 ± 20.44 (P<0.05) and 14.05 ± 8.28 IU/l, respectively. Two months after discontinuing the use of estradiol, gonadotropin levels increased again, with FSH being 70.6 ± 29.05 IU/l (P<0.05) and LH 22.1 ± 16.39 IU/l (Table 1).

The effects of estradiol on BMI, glucose, PRA, aldosterone, and A-III are presented in

Table 1 - Hormonal profile of patients at the three periods studied (BT = before treatment, DT = during treatment, AT = two months after discontinuation of treatment).

Data are reported as individual values and as means ± SD for each period. *P<0.05 *vs* BT and AT (Student-Newman-Keuls test).

Patient	Estradiol (pg/ml)			FSH (IU/l)			LH (IU/l)		
	BT	DT	AT	BT	DT	AT	BT	DT	AT
1	16.8	117.0	9.0	79.5	27.0	62.0	17.3	7.4	16.6
2	15.5	28.0	9.0	71.5	45.0	65.0	9.5	11.9	11.0
3	10.0	50.0	23.0	33.3	22.5	30.0	5.9	5.6	7.4
4	17.3	180.0	12.0	79.5	45.0	65.0	12.0	5.0	11.8
5	6.5	75.0	9.0	98.5	52.0	60.0	22.1	28.3	61.0
6	9.0	70.0	25.0	118.5	75.0	120.0	34.3	19.5	37.5
7	36.0	94.0	15.0	68.0	20.0	75.0	26.0	12.0	27.0
8	21.0	39.0	10.0	67.0	42.0	80.0	17.0	19.0	21.2
9	7.5	49.0	13.0	29.0	16.0	35.0	7.5	7.3	10.0
10	11.0	85.4	20.0	90.0	6.4	114.0	28.5	24.5	17.6
$\bar{x}$	15.06	78.7*	14.5	73.48	35.09*	70.6	18.01	14.05	22.1
SD	8.76	44.6	6.07	27.21	20.44	29.05	9.56	8.28	16.39

Table 2 - Lack of effect of percutaneous 17ß-estradiol on body mass index (BMI), fasting glucose, plasma renin activity (PRA), aldosterone and plasma antithrombin III (A-III).

Data are reported as means ± SD for 10 women before treatment (BT), during treatment (DT) and two months after discontinuation of treatment (AT). Patients received 1.5 mg/day 17ß-estradiol percutaneously. There were no significant differences between groups (Student-Newman-Keuls test).

	BT	DT	AT
BMI (kg/m^2)	28.82 ± 4.37	28.56 ± 4.36	28.28 ± 4.25
Fasting glucose (mg/dl)	102.5 ± 16.63	101.0 ± 16.58	102.4 ± 14.88
Glucose after 2 h (mg/dl)	123.9 ± 30.66	123.9 ± 37.02	118.6 ± 29.75
PRA (ng ml^{-1} h^{-1})	0.53 ± 0.39	0.58 ± 0.56	0.71 ± 0.54
Aldosterone (ng/dl)	10.2 ± 3.24	11.3 ± 5.1	11.5 ± 4.9
A-III (%)	96.5 ± 8.5	95.0 ± 8.74	103.4 ± 11.35

Table 2. No statistically significant changes were observed in BMI or carbohydrate metabolism during the study. The mean values ± SD for PRA, aldosterone, and A-III did not reveal any statistically significant change during any period studied, and values were normal at all stages (Table 2).

The different parameters of the lipid profile were altered in most patients before any treatment. Total cholesterol values were high for all 10 patients, triglycerides were above normal levels in 7 patients, LDL-c and VLDL-c were abnormally high in 8 patients, and the HDL-c level was normal in only 4 patients. The mean values of total cholesterol and of the three lipoproteins were high during the three periods studied. However, no significant differences were observed between the three periods (Table 3).

Plasma renin levels did not change throughout the study; fundoscopy was characteristic of a slight hypertensive retinopathy in 7 patients, and normal in the other 3; the electrocardiographic exams of 6 patients were normal; there were signs of an overloaded left ventricle in 3 patients and of an overloaded left auricle in 1 patient (data not shown). Two echocardiograms were performed for each patient, with a mean interval of 4 months between exams (an initial exam and another one before discontinuation of estrogen therapy). The results always showed hypertrophy of the left ventricle and decreased compliance, compatible with hypertension. The echocardiographic evaluation performed during treatment with percutaneous 17ß-E_2 did not show any changes in parietal thickness or systolic function when compared to the initial exam (data not shown).

At the beginning of the study, a biopsy of the endometrium obtained by suction ruled out the presence of any pathology in the 8 women with a uterus, revealing atrophic endometria in 6 patients and proliferative endometria in the other 2.

Hysteroscopy supplemented with an endometrial biopsy performed in the patients at

Table 3 - Lipid profile of patients receiving 17ß-estradiol percutaneously.

Data are reported as individual values and as means ± SD. The Student-Newman-Kuels test showed no statistically significant difference between the mean values of the variables analyzed at periods BT (before treatment), DT (during treatment) and AT (two months after discontinuation of treatment).

Patient	Total cholesterol (mg/dl)			HDL-c (mg/dl)			LDL-c (mg/dl)			VLDL-c (mg/dl)			Triglycerides (mg/dl)		
	BT	DT	AT	BT	DT	AT	BT	DT	AT	BT	DT	AT	BT	DT	AT
1	246	242	198	39	41	85	163	136	77	44	65	36	222	323	182
2	333	241	304	65	67	57	139	220	193	28	27	54	140	118	268
3	342	316	295	49	45	48	267	232	165	50	39	72	243	195	362
4	204	202	171	60	60	52	115	126	102	19	18	17	95	88	86
5	291	280	291	58	60	28	187	172	194	51	54	28	254	148	141
6	281	217	272	56	48	69	186	144	145	39	25	58	194	123	289
7	287	305	273	43	48	45	190	225	200	31	32	28	156	161	152
8	265	257	265	47	65	69	171	144	169	46	48	27	229	239	236
9	276	251	264	45	43	35	97	98	125	107	101	104	538	483	521
10	334	344	291	59	47	54	198	222	153	72	55	84	360	273	418
$\bar{x}$	285.9	265.5	262.4	52.1	52.4	54.2	181.3	171.9	152.3	48.7	46.4	50.8	243.5	225.1	265.5
SD	42.91	45.09	43.65	8.61	9.59	16.92	50.58	49.06	40.97	25.16	24.41	28.69	126.5	117.7	136.2

the end of the estrogen administration period did not reveal any hyperplastic changes in any case. Endometrial histology after hormone therapy revealed proliferative endometria in 4 women and atrophic endometria in the other 4. At the end of the study, the 8 patients with a uterus were instructed to take 10 mg medroxyprogesterone acetate every day for 10 days. Half of them had slight deprivation bleeding and the other half did not bleed.

Discussion

The effectiveness of percutaneous 17ß-E_2 observed in the present study through the relief of menopausal symptoms, the increase in serum estradiol levels and decrease in gonadotropin levels confirmed our preliminary data (16) and the results obtained by other authors who used the same route of estradiol administration (17,18).

In women in the reproductive period, estrogen secreted by the ovary is first released into the systemic circulation and then reaches the liver, already at physiological concentrations. On the other hand, it is known that the high initial levels of estrogen in the liver following oral administration may cause considerable changes in hepatic metabolism. Many of the negative side effects of estrogen replacement therapy derive from changes in the synthesis of liver proteins that result from first-passage metabolism (19,20).

Recent studies using non-orally administered estrogens have shown a smaller incidence of these side effects, thus confirming the importance of avoiding supraphysiological hepatic concentrations of this steroid, particularly in patients who are hypertensive or at the risk of suffering thromboembolism (19,20). In the present study we observed that, during the hormone treatment, the plasma levels of liver proteins considered to be specific markers of estrogen action (PRA, A-III, lipids, and lipoproteins) remained stable, showing that the percutaneous administration of the drug did not alter the estrogen-dependent hepatic metabolism.

A-III is the main physiological inhibitor

of coagulation and can be significantly reduced by orally administered estrogen therapy (21). In the present study A-III levels remained unchanged, reinforcing the advantage of using this mode of drug administration for those patients whose coagulation factors must not be altered.

Hypertension can occur or become exacerbated in women who are on estrogen replacement therapy, probably because of changes in the renin-angiotensin-aldosterone system. Under physiological conditions, the concentration of the renin substrate represents a constraint in the system. The oral administration of estrogen stimulates the hepatic synthesis of this protein, causing an increase in the levels of angiotensin I and the secretion of aldosterone. Therefore, a significant increase in renin substrate levels may lead to a state that, together with other predisposing factors, could enhance or start the development of hypertension in susceptible women (22). In the group of patients studied, with a record of hypertension prior to menopause, the use of percutaneous 17ß-E_2 did not induce modifications either in the levels of PRA and aldosterone or in the echocardiographic measurements. Moreover, blood pressure levels, controlled by the antihypertensive treatment, remained stable throughout the hormone therapy as well as after it was discontinued. Only few studies have been carried out to evaluate HRT in hypertensive menopausal women (23). Lip et al. (23) did not use a wash-out period in order to determine whether the patients actually were hypertensive, or use the same antihypertensive drug for all patients, nor did they describe types, doses, and modes of administration of HRT.

Endometrial evaluation of our patients by hysteroscopy with a biopsy performed after the estrogen therapy revealed no hyperplastic transformations. This confirmed our expectations, since previous studies carried out to assess the risk of endometrial hyperplasia due to the exclusive use of estrogen (with no opposing progestogen) have shown that an average period of 8 to 12 months of estrogen therapy was required to bring about a hyperplastic transformation (24). The 4 patients who presented proliferative endometria at the end of the study had deprivation vaginal bleeding after the use of medroxyprogesterone acetate. The patients who still had an atrophic endometrium even after estrogen therapy did not present vaginal bleeding after using progestogen.

The data obtained in the present study indicate that percutaneous 17ß-E_2, at the dose used, was effective both in correcting menopausal symptoms and in increasing serum E_2 while reducing the levels of gonadotropins during hormone therapy. The non-oral administration of the steroid, by avoiding the first hepatic passage of the molecule, prevented the stimulation of liver protein synthesis responsible for undesirable side effects. The present results indicate good cardiovascular tolerance for this modality of hormone therapy. Furthermore, the data suggest that short-term percutaneous 17ß-E_2, at the dose used, seems to be a safe hormone therapy for hypertensive menopausal women. Nevertheless, a controlled, prospective, randomized clinical assay with a larger number of subjects is needed to definitely establish both the beneficial and harmful effects of HRT in hypertensive women.

Acknowledgments

References

1. Steingold KA, Laufer L & Chetkowski RJ (1985). Treatment of hot flashes with transdermal estradiol administration. *Journal of Clinical Endocrinology and Metabolism*, 61: 627-632.

2. Bathia NN, Bergman A & Karam MM (1989). Effects of estrogen on urethral function in women with urinary incontinence. *American Journal of Obstetrics and Gynecology*, 160: 176-181.

3. Lindsay R, Hart DM & Clark DM (1984). The minimum effective dose of estrogen for prevention of postmenopausal bone loss. *Obstetrics and Gynecology*, 63: 759-763.

4. Christiansen C & Riis BJ (1990). 17ß-Estradiol and continuous norethisterone: a unique treatment for established osteoporosis in elderly women. *Journal of Clinical Endocrinology and Metabolism*, 71: 836-841.

5. Bush TL, Barret-Connor E & Cowan LD (1987). Cardiovascular mortality and contraceptive use of estrogen in women: results from the Lipid Research Clinics Program Follow-up Study. *Circulation*, 75: 1102-1119.

6. Stampfer MJ, Colditz GA, Willet WC, Manson JE, Rosner B, Speizer FE & Hennekens CH (1991). Postmenopausal estrogen therapy and cardiovascular disease: ten year follow-up from the Nurse's Health Study. *New England Journal of Medicine*, 325: 756-762.

7. Petitti DB, Perlman JA & Sidnei S (1987). Noncontraceptive estrogens and mortality: long-term follow-up of women in the Walnut Creek study. *Obstetrics and Gynecology*, 70: 289-293.

8. Henderson BE, Paganini-Hill A & Ross RK (1991). Decreased mortality in users of estrogen replacement therapy. *Archives of Internal Medicine*, 151: 75-78.

9. Kornhauser C, Malacara JM, Donato F & Botello D (1994). High prevalence of arterial hypertension in women over 50 years of age in the city of Leon, Guanajuato. *Revista de Investigacion Clinica*, 46: 287-294.

10. Staessen J, Bulpitt CJ, Fagard R, Lijnen P & Amery A (1989). The influence of menopause on blood pressure. *Journal of Hypertension*, 1: 361-364.

11. Lobo RA (1987). Different types of estrogens and progestogens. *Obstetrics and Gynecology Clinics of North America*, 14: 143-167.

12. Ganten D, Takahashi S, Lindpainter K & Mullins J (1991). Genetic basis of hypertension. The renin-angiotensin paradigm. *Hypertension*, 18 (Suppl III): 109-114.

13. Hassager C, Strom V, Guyene TT & Christiansen C (1987). The long-term effect of oral and percutaneous estradiol on plasma renin substrate and blood pressure. *Circulation*, 76: 753-758.

14. Von Eiff AW, Plotz EJ, Beck KJ & Czernik A (1971). The effects of estrogens and progestins on blood pressure regulation of normotensive women. *American Journal of Obstetrics and Gynecology*, 4: 31-47.

15. Osório MC, Vitola D & Spritzer PM (1992). Gel de estradiol 17ß no tratamento de pacientes pós-menopáusicas hipertensas. *Arquivos Brasileiros de Endocrinologia e Metabolismo*, 36: 40-43.

16. Wren BG, Brown LB & Routledge DA (1982). Differential clinical response to oestrogens after menopause. *Medical Journal of Australia*, 2: 329-332.

17. Philippe E, Faguer A, Charpin C, Loubière R, Mascarel A, Leduc F, Dupin Ph, Hemet J, Vauzelle JL, Bigel P, Bapin M, Pagès A, Lenne Y, Laguillaumie B, De Lignières B & Gillet JY (1993). L'endomètre sous traitement hormonal substitutif de la menopause par estradiol percutané et progestérone micronisée à faible dose. *Pathologica*, 85: 465-487.

18. Gillet JV, Faguer B, Andre G, Magnin G, De Lignières B & Philippe E (1994). Recherche d'un traitement hormonal substitutif "sans règles" avec la progesterone micronisée orale. *Journal de Gynecologie, Obstetrique et Biologie de la Reproduction*, 23: 407-412.

19. Holst J, Cajander S, Carlstrom K, Damber MG & von Shoultz B (1983). A comparison of liver protein induction in postmenopausal women during oral and percutaneous oestrogen replacement therapy. *British Journal of Obstetrics and Gynaecology*, 90: 355-360.

20. De Lignières B, Basdevant A, Thomas G, Thalabard JC, Bodadr CM, Conard J, Guyenne TT, Mairon N, Corvel P, Guy-Grand B, Mauvais-Jarvis P & Sitruk-Ware R (1986). Biological effects of estradiol-17ß in post-menopausal women: oral versus percutaneous administration. *Journal of Clinical Endocrinology and Metabolism*, 62: 536-541.

21. De Lignières B, Conard J, Samama M, Basdevant A & Guy-Grand B (1983). Differential AT III response to oral and parenteral administration of 17ß-estradiol. *Thrombosis and Haemostasis*, 49: 245.

22. Lobo RA (1990). Cardiovascular implications of estrogen replacement therapy. *Obstetrics and Gynecology*, 75 (Suppl 4): 18s-25s.

23. Lip GYH, Beevers M, Churchill D & Beevers DG (1994). Hormone replacement therapy and blood pressure in hypertensive women. *Journal of Human Hypertension*, 8: 491-494.

24. Clisham PR, Ceddars MI, Greendale G, Fu YS, Gambone J & Judd HL (1992). Long-term transdermal estradiol therapy: effects on endometrial histology and bleeding patterns. *Obstetrics and Gynecology*, 79: 196-201.