A U T O R Z Y Z A P R O S Z E N I

Oral *versus* non-oral hormone replacement therapy: How important is the route of administration?

Doustna i parenteralna hormonalna terapia zastępcza: jakie znaczenie ma droga podania?

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Summary

Although there are differences in the pharmacokinetic profiles of oral and non-oral routes of administration the clinical relevance of these differences remains to be determined. Likewise, there are differences in the metabolic and haemostatic effects of different routes of administration of oestrogen but these may have clinical relevance. For some parameters, such as lipids and lipoproteins, glucose and insulin metabolism, there are greater benefits from oral administration; for others, particularly haemostatic changes and effects on CRP, there are advantages from transdermal administration. For the potential benefits of HRT on CHD, these differences probably have less impact than the effect of the dose of hormones used and the lowest effective should be prescribed.

Irrespective of dose, certain small sub-groups of patients should be specifically treated with an oral regimen eg those with lipid and lipoprotein abnormalities and impaired glucose tolerance whereas others should be treated with a transdermal regimen eg those with a personal or relevant family history of venous thrombosis. However, the vast majority of patients possess none of these risk factors and for them it will come down to personal preference. The availability of different combinations and doses of hormones, as well as different routes of administration, allows HRT to be tailored to the individual and there are few women for whom a suitable form of HRT cannot be found. Although data are lacking we believe it unwise to believe that fully transdermal combination therapy will not impact on risk of incident breast cancer. Based on current evidence transdermal HRT may also cause more irregular and breakthrough bleeding with sequential and continuous therapies than oral counterparts .

Key words: **menopauze – metabolism** / **menopause – drug effects** / / **hormone replacement therapy – adverse effects** / / **dydrogesterone – therapeutic use** / **estradiol – therapeutic use** /

Streszczenie

Zmiany w efekcie metabolicznym i hemostatycznym w wyniku różnej drogi podania estrogenów mogą mieć znaczenie kliniczne. Profil farmakokinetyczny po podaniu doustnym może być odmienny niż po podaniu leku inną drogą, należy jednak określić znaczenie kliniczne tej różnicy.

Parametry biochemiczne, takie jak stężenie lipidów i lipoprotein, glukozy oraz metabolizm insuliny, wykazują korzystniejszy profil po podaniu doustnym; lecz dla innych parametrów, szczególnie w zakresie hemostazy i wpływu na CRP, większe korzyści istnieją z podania przezskórnego.

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Korzystny wpływ hormonalnej terapii zastępczej na CHD w mniejszym stopniu zależy od drogi podania leku, natomiast duże znaczenie ma dawka hormonu, który powinien być przepisany w najmniejszej skutecznej ilości.
Niezależnie od dawki, pewna, niewielka grupa pacjentek powinna być leczona drogą doustną. Są to kobiety z zaburzeniami lipidowymi i lipoproteinowymi oraz z nieprawidłową tolerancją glukozy. Terapię przezskórną powinno się natomiast zalecać kobiet z rodzinnym występowaniem lub z przebytą zakrzepicą żylną. Jakkolwiek większość pacjentek nie posiada czynników ryzyka i dlatego wybór drogi podania leku zależy od ich osobistych preferencji.
Dostępność różnych kombinacji i dawek hormonów, a także różne drogi podania leku, pozwalają na indywidualne dostosowanie hormonalnej terapii zastępczej, tak iż niewiele jest kobiet, dla których nie można znaleźć odpowiedniego preparatu.
Chociaż brakuje jeszcze danych, uważamy że nie ma wystarczających przesłanek, aby stwierdzić, że przezskórna złożona terapia nie ma wpływu na ryzyko raka piersi. W oparciu o dotychczasowe dowody naukowe, przezskórna hormonalna terapia zastępcza, zarówno sekwencyjna jak i ciągła, może częściej powodować nieprawidłowe krwawienia niż jej doustne odpowiedniki.

Słowa kluczowe: **menopauza / menopauza – powikłania / menopauza – wpływ środków chemicznych / terapia hormonalna zastępcza / terapia hormonalna zastępcza – przeciwwskazania / terapia hormonalna zastępcza – stosowanie leczenia / / terapia hormonalna zastępcza – działanie szkodliwe /**

Introduction

The development in the late 1970's / early 1980's of non-oral forms of *hormone replacement therapy* (HRT), such as percutaneous gels and transdermal patches, soon led to valid discussion as to whether these had advantages over oral HRT. Unfortunately, competing commercial interests rapidly reduced this healthy scientific debate to a controversy, and with selective use of the literature oral HRT could be made to appear to have more favourable effects than non-oral HRT, or vice-versa. Not surprisingly, the average clinician became completely confused.

Periodically over the last 25 years this controversy has resurfaced. It has recently reappeared following the publication of the *Women's Health Initiative* (WHI) results with oral therapy. These were not as favourable as expected. Therefore, the manufacturers of the non-oral treatments have attempted to distance their products from the WHI results on the basis that non-oral HRT is somehow different and safer than oral treatment. But is this justified?

We have more then 60 years of combined research experience with HRT and have worked on the development of oral, transdermal and percutaneous treatments from the middle 1970s. This manuscript expresses our views on the current status of the debate on the safety and efficacy of oral versus non-oral HRT.

Physiology and Pharmacology

The demonstration that oestradiol could be absorbed through the skin and into plasma in amounts sufficient to alleviate oestrogen deficiency symptoms from percutaneous gels (Whitehead et al., 1979) and transdermal patches (Schenkel et al., 1982) led to a detailed pharmacokinetic and pharmacodynamic evaluation of these different routes of administration. Later research included buccal, sub-lingual and intranasal administration.There is a very comprehensive recent review of this topic [1].

Because only percutaneous and transdermal routes have gained widespread patient acceptance, only these will be considered here. Compared to oral HRT, transdermal oestradiol was shown to produce a more physiological oestradiol/oestrone ratio and lower doses could be administered because of the avoidance of the "first-pass" hepatic metabolism. However, even to this day, we do not know whether the differences in the oestradiol/oestrone ratio between non-oral and oral forms of HRT, and the higher plasma oestrone sulphate and sex hormone binding globulin (SHBG) levels achieved with oral therapy have meaningful clinical implications with regard to beneficial oestrogenic effects and side-effects.

It should be remembered that the liver metabolises more than 98% of circulating oestradiol and that the entire blood volume, 5 litres, passes through the liver every minute. Thus, any form of HRT must have a hepatic impact if given in therapeutic doses. If the same type of oestrogen is given orally and non-orally in comparable doses, then any difference in hepatic metabolism eg lipid or coagulation status, between the routes of administration will be due to the "first pass" effect seen only with oral administration.

The principal issue regarding oral and non-oral HRT is the possible different effects on arterial and venous disease risk. These will now be considered in detail.

HRT effects on metabolic risk factors for coronary heart disease (CHD)

There are many metabolic changes that accompany the use of HRT, and these vary with the doses of steroids used, the types of preparations (both oestrogens and progestogens), and the route of administration.

Oestrogen lowers total cholesterol, regardless of type of steroid or route of administration, and this effect is maintained in the long term whilst on treatment [2]. This reduction in cholesterol results primarily from a decrease in the potentially atherogenic low density lipoprotein (LDL) cholesterol concentrations due to an up-regulation of apoB100 receptors. Oral oestrogen is more effective than transdermal oestrogen in this respect [3].

Oral HRT may increase the proportion of small dense LDL particles [4], but it also increases their clearance from the circulation [5].

Thus, their shortened residence time in the circulation should reduce the likelihood of their retention in the arterial wall. Transdermal oestradiol does not decrease LDL particle size [6], but it is not known if it improves LDL particle clearance. Small dense LDL particles may be more susceptible to oxidative damage, leading to foam cell production and the generation of atheroma, but somewhat contradictory studies have shown that both oral and transdermal oestrogen helps protect LDL against oxidative damage [7, 8].

Oral oestrogen also improves the postprandial clearance of potentially atherogenic lipoprotein remnants [9], which again will help towards the prevention of atheroma. It is not known whether transdermal oestradiol has this effect. Oral oestrogen lowers the levels of lipoprotein (a), another lipoprotein risk marker for CHD, whereas transdermal oestradiol alone has no effect [3].

The addition of androgenic progestogens appears to lower lipoprotein (a) and this effect is seen with both oral and transdermal HRT. Orally administered oestrogen increases high density lipoprotein (HDL) cholesterol, and particularly the HDL_2 subfraction which is thought to protect against atherosclerosis development primarily through reverse cholesterol transport. Transdermal oestradiol appears to have a much lesser effect on increasing HDL cholesterol than oral oestrogen [3].

The type and route of administration of oestrogen also determines its effects on triglycerides. Oestrogens primarily affect endogenous triglyceride concentrations. Conjugated equine oestrogens cause an increase in triglycerides [3, 10], due to the hepatic first-pass effect of this steroid. This may well be exaggerated with this preparation because the equine component appears to have a prolonged cellular retention time. Orally administered oestradiol has a similar but smaller effect on raising triglycerides, whereas transdermal oestradiol causes a reduction in triglycerides [3, 10].

Progestogens have differing effects on lipids and lipoproteins, depending on their androgenicity and perhaps on their overall dosage [11].

The addition of progestogens to oestrogen therapy has no adverse effect in terms of LDL reduction, since, although they increase LDL production, they also increase its clearance. Androgenic progestogens, such as norgestrel and to a lesser extent medroxyprogesterone acetate (MPA), reverse the HDL-raising effect of oestrogen [10] because they increase hepatic lipase activity. In contrast, certain non-androgenic progestogens, such as dydrogesterone, have little negative impact on oestrogen-induced increases in HDL and HDL_2 [12].

Testosterone-derived progestogens, such as levonorgestrel and norethisterone acetate (NETA), decrease triglyceride levels by reducing secretion of very-low-density lipoprotein (VLDL). C-21 progestogens do not prevent the increase in triglycerides induced by oral oestrogens. Thus, combined oestrogen-progestogen HRT may lead to an increase in HDL but at the expense of an increase in triglycerides, or lead to a decrease in triglycerides but at the expense of a decrease, or no increase, in HDL.

Which change is more important in terms of CHD benefit remains unknown but, when all these changes in lipids and lipoproteins are considered together, the various changes seen with most HRT combinations are likely to be beneficial overall.

Oestrogen also affects glucose and insulin metabolism. Oral administration of oestradiol to postmenopausal women brings changes in glucose and insulin concentrations suggestive of an improvement in insulin resistance, whereas transdermal oestradiol is fairly neutral in its effects [13]. Progestogen addition may modify the effects of oestrogen on glucose and insulin metabolism, depending on the type of progestogen used. Testosterone-derived progestogens, such as norgestrel, may increase insulin resistance [14].

NETA given orally may also have a negative effect [13], but when given transdermally it has little impact [14]. Non-androgenic progestogens such as dydrogesterone have little adverse effect [15], although MPA has unwanted effects.

In certain clinical situations, such as dyslipidaemia or diabetes, some HRT regimens will be potentially more beneficial than others. Thus, oral oestrogens have a superior effect to transdermal oestradiol in terms of reducing LDL and increasing HDL, whilst transdermal oestradiol is superior in terms of reducing triglycerides. Oral oestradiol is effective in improving insulin sensitivity, whereas transdermal has less effect.

Oral HRT has been shown in two large randomised trials to reduce the incidence of diabetes in postmenopausal women [16, 17], whereas there are only data from a small observational study to show such an effect with transdermal oestradiol [18].

Oral HRT has the effect of preventing or reversing the menopausal deposition of central fat [19], whereas transdermal HRT does not [20]. Abdominal obesity is associated with increased circulating levels of leptin and resistin, and decreased levels of adiponectin and ghrelin. Oral HRT appears to have little effect on adiponectin and leptin levels [21, 22], but increases ghrelin levels [23]. The effects of transdermal oestradiol on adipocytokines are unknown.

Oestrogen affects coagulation and fibrinolysis, increasing both pro-coagulant and fibrinolytic activity. The effects of oral HRT on haemostasis are somewhat complex [24, 25]. There is a reduction in certain pro-coagulant factors linked with atheroma development, such as fibrinogen and factor VII, but also a reduction in anti-coagulant factors such as antithrombin. Similar changes are seen with transdermal HRT [6].

It is likely that the initiation of oral oestrogen therapy causes a transient imbalance between coagulation and fibrinolysis, thereby causing a short-term increase in thromboembolism risk, which disappears as these processes gradually readjust and come back into a balance. This would explain the epidemiological observations of an increase in both arterial and venous disease risk in the 6-12 months after the initiation of therapy with a decrease thereafter. However, dosage is also likely to be important. Oral oestrogen appears to increase coagulation activation in a dose-dependent manner. A recent study of low dose oral HRT (oestradiol 1mg and NETA 0.5mg) did not show any adverse changes in coagulation activation [26]. The non-oral administration of oestrogen may limit or even avoid this adverse effect [27]. Progestogens are probably fairly neutral in their effects on haemostasis.

HRT effects influencing vascular function

The vasodilatory effect of oestrogen may be due in part to an acute oestrogen receptor-dependent effect on the nitric oxide synthase (NOS) pathway, which leads to increased levels of endothelial nitric oxide synthase (eNOS) [28], and increased production of the potent vasodilator nitric oxide (NO). NO is involved in regulation of blood pressure, platelet function, inhibition of vascular smooth-muscle proliferation and expression of adhesion molecules. Oestradiol increases NO production, as measured by circulating surrogates. Some studies have suggested a superior effect of oral over transdermal oestradiol in this respect [29], but others have shown the opposite [30], whilst yet others have shown no difference [31]. When vascular endothelial function has been measured, oral oestradiol has been shown to have either a greater [32] or similar [33] beneficial effect to transdermal oestradiol. Similarly, both oral and transdermal HRT have been shown to lower the levels of the cell adhesion molecules E-selectin and vascular cell adhesion molecule-1 (VCAM-1) in postmenopausal women [6, 34].

Elevated levels of C-reactive protein (CRP) are associated with increased CHD risk [35], and HRT has an effect on these levels. Oral HRT has been shown to increase CRP concentrations, whereas transdermal HRT appears to have no effect [36]. However, the significance of this increase in CRP is unclear, as it is associated with decreases in other vascular inflammatory markers [37].

Arterial function may also be affected by oestrogen via changes in the renin-angiotensin-aldosterone system. Because of the hepatic first-pass effect, it has been postulated that oral oestrogen might increase renin substrate activity and aldosterone concentrations, thereby adversely affecting blood pressure. Such an effect would not be expected with transdermal oestradiol. However, oral oestradiol does not increase aldosterone levels [38, 39]. Both oral and transdermal HRT have been shown to reduce circulating angiotensin-1 converting enzyme (ACE) activity [6, 40], with a greater effect being seen with oral administration. Small falls in blood pressure are seen with both oral and transdermal HRT.

Clinical studies of HRT and CHD

Many observational studies have consistently shown that postmenopausal HRT use is associated with a reduction in CHD of around 40%. Analyses from the *Nurses' Health Study* have shown that HRT use is effective for both primary and secondary prevention of CHD [41, 42]. The observational data relate virtually entirely to oral therapy, with no epidemiological data on transdermal therapy as yet available.

Randomised trials using clinical endpoints, however, for CHD have not shown an overall benefit. The HERS trial [43] of oral HRT (conjugated equine oestrogens 0.625mg and MPA 2.5mg) for the secondary prevention of CHD showed a significant trend towards reduction in events, but this was after an initial increase in events with HRT – the pattern of early harm followed by later benefit. Exactly the same pattern was seen in the large primary prevention trial using the same oral HRT, the *Women's Health Initiative* (WHI), again with a significant trend towards reduction but an early transient increase in events [44].

It has been argued that the early harm was due to an inappropriately high starting dose of HRT for the age of the women participating in the study. This could have led to transient increases in coagulation activation and adverse vascular remodelling, thereby causing an early increase in events [45]. Could a different route of administration have avoided this? The small Papworth HRT atherosclerosis study (PHASE) was a randomised secondary prevention trial of transdermal oestradiol with or without the addition of transdermal NETA, and showed exactly the same pattern of early harm followed by possible later reduction, and no overall benefit [46]. However, the dose used, oestradiol 80μg daily, was again excessive for the age of the patients. Thus, it appears that there is no difference in CHD outcomes whether HRT is given orally or transdermally. The more important factor thus appears to be the dose. The effects of HRT in the younger women (50-59 years) in the WHI oestrogen-alone trial produced a significant reduction in CHD events for the composite endpoint of myocardial infarction, death and coronary interventions, probably because for these women the dose of HRT was appropriate. Older women need lower doses to avoid early harm, and it is of interest that in two secondary prevention trials where lower starting doses were used, there was no early increase in coronary events [26, 47]

Compliance

Entering the terms "compliance with hormone therapy, hormone replacement therapy or oestrogen therapy" into the database of the *US National Library of Medicine* and the *National Institutes of Health* (containing over 16 million citations) produces just under 240 references for papers published between 1991 and 2006.

The first and most important conclusion is that there is no really large scale, long-term, randomised, prospective trial comparing quality of life issues, compliance or continuance between oral and non-oral regimens.

The largest prospective study with quality of life as a primary endpoint [48] was of four months duration and involved 74 postmenopausal women randomly assigned to conjugated equine oestrogens 0.625mg/day or transdermal oestradiol 50mcg with sequential MPA 10mg/day added for 12 days each cycle. No treatment differences were observed for a variety of domains measured by a Menopause Specific Quality of Life questionnaire. A twelve month placebo-controlled study of 60 postmenopausal women with coronary artery disease randomised to transdermal oestradiol 50mcg or conjugated equine oestrogen 0.625mg/day with both groups again receiving sequential MPA reported an overall improvement in mood and cognitive function with both treatments with a similar increase in quality of life measures (ref. 156).

The first Kaiser Permanante study report from Northern California was a retrospective database search for prescription use in women with an intact uterus in a managed health care programme [49]. A statistically significant difference in the continuation rate was observed, with more drop-outs in the transdermal group applying a 50mcg oestradiol patch compared to the oral group receiving conjugated equine oestrogens 0.625mg/day (RR=2.6, 95% confidence interval 1.8 to 3.8). Both groups also took MPA sequentially.

A subsequent paper [50] included hysterectomised women and increased the sample size to 4,458 subjects. This is to date the largest study comparing oral and non-oral treatments. It was again observed that women starting treatment with oral HRT, conjugated equine oestrogens 0.625mg/day, were less likely to discontinue therapy compared to those starting treatment with transdermal oestradiol 50mcg/day (RR=1.5, 95% confidence interval 1.3-1.8). This difference was found in both hysterectomised and non-hysterectomised women.

Perrone et al [51] compared continuous/combined oral and transdermal treatments with sequential oral and transdermal therapies using oestradiol 50mcg and conjugated equine oestrogen 0.625mg/day. MPA was the progestogen which was added either sequentially or continuously. There were approximately 25 patients in each treatment group and after two years the drop-out rates were similar between the four groups, ranging between 31 and 39%. Whilst there were fewer bleeding problems in the groups receiving continuous/combined treatments in year two, the dropout rate was higher because the continuous progestogen appeared to cause more breast tenderness. There were no differences in continuance between the oral and transdermal groups.

The effects of low-dose HRT using conjugated equine oestrogens 0.3mg/day orally and transdermal oestradiol 25mcg have been reviewed It was concluded that these low doses are effective in controlling symptoms [52] and reducing bone loss [53].

Finally, just two studies have compared oral therapy with a different form of non-oral therapy, namely percutaneous gel. In a prospective, randomised, open study of 885 women followed for two years, Serfety et al. [54] reported that a fixed-dose of oral oestradiol valerate and sequential MPA provided approximately the same continuance (around 75%) as a variable dose of percutaneous oestradiol gel, (Oestrogel, Laboratoires Besins-Iscovesco).

Hirvonen et al. [55] compared oral oestradiol valerate and sequential MPA with two doses of a different gel, (Sandrena, Organon Laboratories) and also observed similar continuance rates between the groups.

The Endometrium

It has been known for many years that the doses of oestradiol and oestrone-based preparations needed to control oestrogen deficiency symptoms effectively cause endometrial stimulation [56], and will increase the risk of endometrial hyperplasia and cancer in the long-term unless opposed by a progestogen at adequate dose and duration [57].

For many years it was believed that oestrone was more carcinogenic than oestradiol, because firstly postmenopausal women not receiving HRT who develop endometrial cancer tend to be overweight/obese and have a higher oestrone than oestradiol value in plasma (because of the peripheral conversion from androstenedione), and secondly because most of the early reports linking HRT to an excess risk of endometrial cancer were associated with conjugated equine oestrogens, which give rise in plasma principally to oestrone. However, even in the postmenopausal woman receiving an oestrone based preparation, the principal oestrogen within the nucleus of the epithelial endometrial cell is oestradiol [58].

The nuclear oestradiol/oestrone ratio is reduced by the addition of progestogen with consequent lowering of stimulation. This is one of the ways in which progestogens reduce the risk of hyperplasia and carcinoma [59]. Clinically, comparable therapeutic oestrogen doses are likely to carry a similar risk of endometrial cancer irrespective of the route of administration. Therefore the choice of preparation may depend upon other factors, such as regularity of bleeding (with sequential therapy), or lack of bleeding (with continuous/combined treatments).

Before commenting on bleeding further, it is stressed that there are no standard definitions to describe bleeding with HRT. Some of the definitions established by the *World Health Organization* to evaluate bleeding with hormonal contraception have been applied to HRT but, for the most part, inconsistencies in bleeding definitions have made data interpretation even more difficult. (For a full review of this problem see Archer and Pickar, 2002) [60]. Again, there are numerous papers in the literature comprising small patient numbers and/or short durations of treatment. We have selected three papers to review. Unfortunately, there are no direct comparisons for treatments likely to be considered "first choice" in 2007.

In a prospective, randomised, double-blind, controlled, trial Johnson et al. [61] compared two oral continuous/combined treatments over 6 months in 438 early postmenopausal women. One group received oestradiol 1mg/day and NETA 0.5mg/day. The other half took conjugated equine oestrogens 0.625mg/day and MPA 2.5mg/day. The oestradiol/NETA regimen was associated with significantly less bleeding ($p<0.005$). No bleeding or spotting was reported in 59% and 68% of women during cycles 1-3 and 4-6, respectively. Comparable data for conjugated equine oestrogens and MPA were 60% and 62%, respectively.

Wyeth has introduced lower dose conjugated equine oestrogens regimens based on 0.45mg and 0.3mg/day, both with continuous MPA. Bleeding data for these lower dose regimens are available [62] but comparisons with the data of Johnson et al. [61] are difficult because of the different expression of results. "Cumulative no bleeding" was observed in 59% of women taking conjugated equine oestrogens 0.45mg and MPA 2.5mg and in 65% taking conjugated equine oestrogens 0.3mg and MPA 1.5mg over 13 cycles of treatment [62].

Ylikorkala and Rozenberg [63] studied patients receiving fully transdermal therapy based on oestradiol 50µg/day. Allocation to transdermal NETA, either sequentially or continuously, was random. Both sequential and continuous NETA regimens were given at one of two doses, 170mcg/day or 350mcg/day. Over 90% of subjects bled with sequential therapy. The results were expressed for three monthly phases (quarters). The median number of days of bleeding per quarter varied over the study period but no clear pattern of change emerged. It was about 3 days less with the lower dose of NETA, (12-17 days) compared to the higher dose (16-19 days). The continuous data were expressed on an intention-to-treat analysis of subjects starting treatment in each quarter. This is again different from the other papers considered here. Amenorrhea was reported by around 35% of women during the first quarter, by around 47% during the fourth quarter

(end of year one), and by approximately 57% by the eighth quarter at the end of two years. Our interpretation is that transdermal continuous/combined regimens are associated with more bleeding than the oral regimens.

Breast Status

Incident Breast Cancer

Because of the prevalence, large scale studies (thousands of women) are required to determine whether oestrogens influence incident breast cancer risk. Randomised controlled trials have been performed with oral therapy but no comparable data are available for transdermal treatment. However, it would be most unwise to assume that non-oral routes will not impact on breast cancer risk. "Absence of evidence" must not be confused with "evidence of absence".

The Womens Health Initiative reported that a continuous regimen of conjugated equine estrogens, 0.625mg/day and MPA 2.5mg/day, increased the risk of incident breast cancer after a mean of 5.2 years. There were 8,506 active users and 8,102 women in the placebo group. The hazard ratio (HR) was 1.26 (nominal 95% confidence interval 1.00-1.59) Thus, the absolute risk was increased from 30 per 10,000 person years to 38 per 10,000 person years. *(Writing Group for the Womens Health Initiative Study,* 2002) [64]. There was no increase in risk in women traditionally considered at high risk eg those with a family history. At the time of publication there had been 5 deaths due to breast cancer, 3 in the active group and 2 in the placebo users.

After a mean of 7.1 years of treatment with conjugated equine estrogens alone, 0.625mg/ day, in hysterectomised women the HR for incident breast cancer was reduced at 0.8.(95% confidence interval 0.62-1.04). This reduction was not significant (P=0.9). There were 5,310 active users and 5,429 placebo-users (Stefanick et al., 2006). The precise reason for the differences between the results is not known but one explanation would be that the progestogen, MPA, is responsible for the increase in risk observed with combined therapy. Whether other progestogens have similar effects is not known. *The Million Women Study,* an observational study, reported similar increases in risk of incident breast cancer with all commonly prescribed progestogens eg NETA, norgestrel, and MPA [65].

This study, however, has various methodological deficiencies and has been critiqued [66]. These include relying on patient recall for details of treatment, and only recording current treatment. No details of past use were collected.

We consider this a major error when it is known that 45% of women will have changed their form of HRT at least once during the first 2-3 years of therapy. We consider the data from the *Million Women Study* unreliable.

Breast Density

This is an area of much confusion. Breast density is dependent upon many factors including age, body mass index, nulliparity and age at first pregnancy. Additionally, a recent study of twins reported that the heritable percentage of the density-risk relationship was approximately 65%, ie about two-thirds of the risk was genetically conferred [67].

In postmenopausal women not using HRT it is well recognised that the more dense the breast the greater the risk of breast cancer. With oral HRT it is widely reported that the greatest increases in density are observed with continuous combined treatments, then sequential therapies and the smallest increases occur with oestrogen-alone. These data have been extensively reviewed [68, 69].

However, what is not clear is whether those women showing the greatest changes in breast density with HRT are those who go onto develop the disease.

The changes in density with non-oral treatments are much less well studied: indeed, we can find only two reports in the literature with transdermal therapy. Lundstrom et al. (2001) [70] reported that in 55 women receiving transdermal oestradiol 50mcg/day an increase in mammographic density was seen in 2%. With oral oestriol 2mg/day an increase was seen in 6%. Finally, Harvey et al. (2005) [38, 39] compared fully transdermal therapy based upon 50mcg/day of oestradiol with a continuous combined oral HRT of oestradiol 2mg/day and NETA 1mg/day. Four percent of women using the transdermal treatment had a significant increase in mammographic breast density compared to 16% with oral HRT. The authors concluded that transdermal HRT has a lower incidence of increased mammographic density. Our concern is that this study did not compare oestrogen preparations of equal potency and we would like to see the study repeated using oestradiol 50mcg/day compared with oral oestradiol 1mg/day, and preferably without a progestogen because of possible confounding by this hormone.

Most importantly, though, is the need to show that changes in mammographic breast density with HRT accurately predict those women at an increase in cancer risk. Whilst we can follow the pathway of increased breast density potentially signifying harm with oestrogen/progestogen HRT which increases incident breast cancer, we cannot follow this logic with oestrogen alone. This treatment increases density yet the controlled data report a 20% reduction in cancer risk!

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PRACE ORYGINALNE
położnictwo

The evaluation of selected indices of apoptosis in placentas from pregnancies complicated by fetal growth restriction

Zachowanie sie wybranych parametrów oceny apoptozy w łożyskach pochodzących z ciąż powikłanych hipotrofią wewnątrzmaciczną.

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Abstract

Background: *Fetal growth restriction is related to a high rate of prematurity and mortality. In cases of unknown origin utero-placental circulation changes are the main factor which is due to the changes in blood vessels. The understanding of the mechanism may help in further prevention of FGR.*

Material and methods: *The expression of bcl-2 and bax in normal pregnancies and complicated by FGR were compared. The study was conducted in 2005-2006 at The Medical University of Lodz – HRP Unit and The Kopernik Hospital – Lodz.*

Bcl-2 and bax were estimated using an immunohistochemical method. Bcl-2 was estimated in trophoblast, bax in decidua and trophoblast.

Results: *In a study group the mean value of bcl-2 in trophoblast was 37,04±10,51, in a control group the mean value was 65,74±6,97. The estimation of bax was done in trophoblast and decidua separately. In the group of FGR mean value of bax expression in trophoblast was 45,35±10,5. In decidua the mean bax expression value was 24,11±7,3. In controls in trophoblast the mean value was 12,53±7,54, in decidua the mean expression of bax was 6,63±2,24.*

Conclusion: *1. Apoptosis in trophoblast is lower in normal pregnancy than in FGR.*
2. Increased expression of pro-apoptotic proteins in placenta might be one of the reason for FGR development.

Key words: **apoptosis / bax / bcl-2 / fetal growth retardation – physiopathology / / pregnancy complications – pathology / pregnancy complications – physiopathology / placenta – pathology / trophoblasts – pathology /**

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