Exogenous Oestrogen: The Female, Cardiovascular Disease and Exercise

K. Birch

Department of Exercise and Sport Sciences, Manchester Metropolitan University, Crewe and Alsager Faculty, Hassall Road, Alsager, Stoke-on-Trent, ST7 2HL, United Kingdom.

Key words: Hormone replacement therapy, menopause, menstrual cycle, oral contraceptive, osteoporosis.

1. INTRODUCTION

Genetically fixed and periodic, the female menstrual cycle is a natural phenomenon spanning the reproductive life of women from menarche (puberty) to the climacteric (menopause). Following menarche the cycle is characterized by episodic patterns of both gonadotropin (luteinizing hormone; LH: follicle stimulating hormone; FSH) secretion from the anterior pituitary and steroid hormone (progesterone and oestrogen) secretion from the ovaries, to promote follicular development, oocyte maturation and ovulation. The cessation of, in particular, oestrogen secretion during, and following the menopause has been associated with an increased risk of both osteoporosis and cardiovascular disease (CVD) in women. The consequent consumption of exogenous sources of oestrogen in the form of either hormone replacement therapy (HRT) or oral contraceptive preparations (OC) has led to questions concerning the efficacy of these products. The purpose of this paper is to provide an overview of the relationship between exogenous oestrogen consumption and cardiovascular disease, with special reference to the exercising female. The effects of OC and HRT upon the risk of osteoporosis can be found elsewhere in this book.

1.1. Sources of Exogenous Oestrogen

(a) Oral Contraceptives

Oral contraceptives are manufactured from the synthetic steroid hormones oestrogen and progesterone. The first combined oral contraceptive (COC) was developed in the 1950s from a potent orally active oestrogen - ethynylöestradiol (EE: 150μg) - and an orally active progestogen - norethynodrel (10 mg). The pills were taken for a 21-day period with a 7-day break (monophasic) but were found to initiate venous thrombo-embolism in some women. The concentration of the oestrogen components of the COC has since been progressively reduced to the now “low-dose COCs” - 20-35 μg EE. The progestogen component of COCs are classified as first generation (norethynodrel), second generation (levonorgestrel) and the newer third generation (desogestrel, gestodene and norgestimate) progestogens [1]. The dose of progesterone given, via the pill, can be changed once (biphasic) or twice (triphasic) during
each cycle. Progesterone only pills are available as norethisterone, norgestrel, lynoestrenol and ethynodiol diacetate (the latter two are metabolised to norethisterone in the body).

(b) Hormone Replacement Therapy

Whilst the COC is usually prescribed to prevent the occurrence of pregnancy, menopausal HRT is prescribed to relieve detrimental menopausal symptoms, for the prevention or treatment of osteoporosis and for the prevention of cardiovascular disease. Unlike the synthetic COC, HRT contains natural oestrogens which have less of the undesirable side effects. These oestrogens can be given orally, parenterally or vaginally. Oral preparations are the most popular and have different metabolic effects from parenteral or vaginal HRT due to “first-pass” hepatic metabolism. The oral preparations are (i) Conjugated equine oestrogens (CEO) - daily dose - 0.625 mg; (ii) Oestradiol - daily dose - 1 mg, converted to oestrone in the gut; (iii) Oestrone - daily dose - 1.5 mg; (iv) Oestriol - daily dose - 1-2 mg; and (v) Combinations - dose varies. The commercially available combined preparation in the UK is micronized oestradiol (2 mg) and norethisterone (1 mg) as a daily tablet. The parenteral oestrogens are (i) Transdermal oestradiol patches - 50 µg/24 h; (ii) Transdermal oestradiol gel - daily dose - 2.5 mg; and (iii) Subcutaneous oestradiol implants - 50 mg every 4-6 months. Vaginal preparations are again a choice of oestril, CEO or an oestradiol ring [2].

2. HORMONAL STATUS AND CARDIOVASCULAR DISEASE

There has been much debate as to the risks and benefits of both OC and HRT as prescribed drugs. Clinical events such as impaired liver function, depression, hypertension and thrombosis have, however, been significantly reduced with “low-dose” preparations. The effect of utilizing exogenous sources of reproductive hormones on the relative risk of CVD is an ongoing debate. Medical evidence has suggested for decades that, in western society, the death rate from coronary artery disease (CAD) is somewhat greater in men than in women between the ages of 25-55 years [3]. This difference in mortality rate narrows after the menopause, and the incidence of clinical manifestations of CVD in women increases significantly [4]. Evidence of this nature led to the belief that the hormone oestrogen has “cardioprotective” properties, and consequently that the use of OCs and HRT should be encouraged.

The informed decisions that medical personnel have to make in prescribing (or not) hormonal preparations, are based upon epidemiological evidence gained from retrospective and prospective studies. The Royal College of General Practitioners [5] reported that CVD was the largest single cause of mortality in women using OCs with a RR of 4.2 (95% CI, 2.3-7.7). Vessey et al. [6] found a similar, but non-significant increase in coronary heart disease (CHD) death rate in OC users from 17 family planning clinics in England and Wales (RR, 3.3, 95% CI, 0.9-17.9). The risk of fatal and nonfatal myocardial infarction (MI) with OC use was assessed by Mann and Inman [7]. In 72 cases and 190 controls under 45 years of age, the RR of nonfatal MI in current OC users was 3.1 after correction for other MI risk factors. Data from 207 fatal MI and 250 age matched living controls under 50 years of age, revealed a threefold increase in the risk of fatal MI among current users of OC (no allowance made for smoking). These observations were confirmed in a larger study in the USA [8] with a reported RR of 3.5 (95% CI, 2.2-5.5) for nonfatal MI in current OC users when corrected for confounding variables. This risk was elevated further in heavy smokers.
The Nurses' Health Study [9] included data from 121,700 female nurses registered in the USA. The study was prospective in nature, beginning in 1976 and followed up in 1978 and 1980. Multivariate analysis, controlled for confounding factors, revealed that the RR for the occurrence of an MI with current OC use was 1.8 (95% CI, 1.1-2.9). There was no association with duration of OC, or previous OC use. Amongst smokers with hypertension and currently OC users the RR was 19 (95% CI, 4.7-78). This increased to 170 (95% CI, 31-1,100) when hypertensive non-smoking OC users were compared with control subjects with none of the three risk factors. Post-mortem examinations in women who have died whilst using OC suggest that CHD is usually thromboembolic rather than atheromatous, and indeed in cynomolgus macaques, necropsy revealed thoracic and abdominal intimal plaque cross-sectional areas to be larger in control subjects, compared to those given OC tablets (50 µg EE and 500 µg norgestrel) [10].

More recent studies by The Transnational Research Group on Oral Contraceptives and the Health of Young Women [11,12] have considered the relative risk of both venous thromboembolism and MI in utilizing third generation OCs. In large international case-control studies, using stratified analysis and unconditional logistic regression adjusted for confounding risk variables, were compared the use of second and third generation OCs and no OC use. The RR for thromboembolism and MI respectively was: 3.2 (95% CI, 2.3-4.3) and 3.1 (1.5-6.3) for second generation products v no use; 4.8 (3.4-6.7) and 1.1 (0.4-3.4) for third generation products v no use; and 1.5 (1.1-2.1) and 0.36 (0.1-1.2) for third generation v second generation products. It would appear that the increased risk of venous thromboembolism associated with third generation OC use may be offset by the decreased risk of MI. Once again the risk of both conditions is increased further with additional smoking and obesity.

The Framingham study [13] reported that from 1234 post-menopausal women those who utilized oestrogen replacement over an eight-year examination period had a much greater risk of CHD (1.8) than non-users (corrected for confounding variables). These data, however, were reanalysed in 1987 [14] whereupon a non-significant adverse effect of oestrogen replacement amongst older women (60-69 years), and a non-significant protective effect amongst younger women (50-59 years) was found. The Nurses' Health Study reported RR of non-fatal MI or fatal CHD in any time users of HRT (CEO), compared with never users, as 0.5 (age adjusted; 95% CI, 0.3-0.8). In current users the RR was 0.3 (0.2-0.6) and in former users 0.7 (0.4-1.2). This compares favourably with the RR of 0.54 (95% CI, 0.29-0.79) for all-cause death in oestrogen users v non-users in the Lipid Research Clinics Program Follow-up study [15].

Henderson et al. [16] examined CHD risk factors and mortality rates in a prospective analysis of 8881 women from a retirement community in California. Women with a history of oestrogen use had an all-cause, age adjusted mortality of 22.5 per 1000 person years, compared to 28.7 amongst life time non-users (p < 0.0001). The mortality among current users was 18.2/1000 person years. It would appear that the use of HRT in non-smoking post-menopausal females has some cardioprotective benefits. The evidence, however, remains arguable and care must be taken in interpreting data collected mainly from white, middle-class, educated females. It would seem, however, that there are "cardioprotective" properties of oestrogen in third generation OC and HRT preparations, whilst second generation OCs tend towards a higher potency and thus a greater risk of CAD.
3. METABOLIC ACTIONS OF OESTROGEN AND PROGESTERONE

The mechanism behind the “cardioprotective” nature of some OCs and HRT has been assumed to be related to positive alterations in lipid profiles. Low concentrations of high density lipoproteins (HDL), high triglycerides and high low density lipoproteins (LDL) have been associated with an elevated risk of CVD [17]. The action of exogenous sex hormones serves to reverse this risk profile; however the net result of the hormonal product depends on the type and dosage of its components. Indeed, the observation from the Framingham Study [18] that low levels of HDL was also a powerful predictor of CHD, linked with the findings of increased CAD with increasing doses of progestins [19], led to the triphasic OC pills reducing the progestin component. The third generation pills have less of the negative effects of the progestins upon lipid parameters.

The oral administration of synthetic and natural oestrogens enhances triglyceride synthesis in the liver, whilst also increasing the synthesis of Apolipoprotein B (apoB) [20]. This results in an elevated concentration of very low density lipoprotein (VLDL) known to be associated with CVD. Interestingly however, the VLDL particles produced via oestrogen consumption have been found to be the larger variant ("fluffy-puffy"), and consequently non-atherogenic [21]. Concurrent with the increase in VLDL synthesis is an oestrogen precipitated decrease in the percentage of VLDL particles converted into LDL [21]. This would appear to be related to an increased clearance of VLDL, rather than a slower conversion of intermediate density lipoprotein (IDL) to LDL [22]. Wolfe and Huff [23] reported that the addition of 75 μg of the progestogen, norgestrel to 1 mg oestradiol, prevented this increase in VLDL synthesis.

The increase in plasma HDL during oestrogen consumption is partly due to an enhanced rate of HDL constituent synthesis (with increased Apolipoprotein A1), and partly due to an inhibited liver lipase activity reducing the conversion of HDL₃ into HDL₂ [24]. The beneficial effects of the synthetic and natural oestrogens can be offset by the progestins, although this is more the case with nor-testosterone derived (e.g. levonorgestrel), rather than 17-hydroxy-progesterone derived (e.g. medroxy-progesterone acetate) products [25]. Cross-sectional studies have suggested that in post-menopausal oestrogen therapy the negative progestogen effects may be short term. Indeed, Barrett-Connor et al. [26] reported that women who had used combination therapy for longer than three years (opposed and unopposed by progestins) had HDL concentrations 11% greater than non-oestrogen users. Alterations in lipid profiles due to exogenous sex hormones do not occur with parenterally administered preparations.

In addition to alterations in the lipid profile of oestrogen users, there has been the question of whether OCs induce insulin resistance as a forerunner to CVD. Godsland et al. [27] examined insulin resistance via mathematic modelling of glucose and insulin concentrations during an intravenous glucose tolerance test. The authors reported a 30-40 % reduction in insulin sensitivity in those women using combined formulations containing 30-40 μg EE plus levonorgestrel, norethindrone or desogestrel. Norethindrone alone had no effect upon insulin resistance, indicating that the oestrogen component is primarily responsible. These results were also found with the use of “low-dose” triphasic and monophasic preparations [28,29]. An increased insulin response to a glucose load has been found with both oral and intravenous glucose tolerance tests [27].

Deterioration of glucose tolerance whilst utilizing oral combinations of the oestrogens and progestogens has been reported consistently [28,29], and is known to be associated with risk of CVD. Godsland et al. [27], Huey-Herng Sheu et al. [28] and Watanabe et al. [29] utilized
a minimal model method to examine metabolic parameters when consuming OCs. Each of the studies confirmed glucose intolerance, hyperinsulinaemia and insulin resistance. The glucose intolerance has been reported to be due to a reduction in insulin sensitivity that is not appropriately compensated by an increase in pancreatic β-cell function. This is attenuated by a decreased glucose sensitivity. Counter-regulatory hormones may also be implicated in insulin resistance in OC users. Oestrogens are known to increase plasma free cortisol and growth hormone [30]. It may be that the suppression of hepatic gluconeogenesis in response to glucose is impaired with elevated cortisol levels [31]. The mechanism behind the increased insulin resistance in OC users has yet to be finalized. Furthermore, more evidence is needed to establish the effect of the natural oestrogens used in HRT.

4. IMPLICATIONS FOR EXERCISE (& HEALTH)

Given that the sex hormones have the potential to affect glucose metabolism, it is perhaps feasible to predict alterations in exercise metabolism in OC users. The effects of HRT upon metabolism are less clear as the oestrogenic component is a natural oestrogen, and thus less potent. The effects of natural oestrogens upon exercise metabolism during the menstrual cycle tend to depend upon nutritional status [32]. McNeill and Mozingo [33] exercised 11 nonathletes at three points throughout their menstrual cycles before, and following two cycles of OC use. They reported an increased oxygen consumption at standardized cycle ergometer workloads with OC use and hypothesised a consequent switch towards triglyceride dependence. Bonen et al. [34] examined 15 nulliparous women, 7 OC users and 8 non-users, during treadmill walking at 40 and 85 % maximal oxygen uptake. During heavy exercise glucose concentrations increased significantly in both groups; however, the glucose concentrations in the OC group were significantly lower than in the control group (p < 0.05). Although the patterns and concentrations of FFA response were not significantly different between the two groups, the absolute FFA concentration in the OC group, during the 30 min of mild exercise, was significantly higher (p < 0.05). The insulin response did not differ between groups but was, however, persistently lower in the follicular phase of the menstrual cycle and the non-use phase of OC use. Growth hormone (hGH) was also seen to be elevated in the OC use phase during mild exercise when compared to the non-use phase and with the control group. These findings were supported by Bemben et al. [35]; however, these are the only two research groups that have reported lower glucose levels in OC users than non-users. The majority of research contends that glucose levels are higher in OC users, regardless of exercise mode [36].

It is a common belief that an increased concentration of FFA means that more of the substrate is being utilized by exercising muscle, and that greater availability may inhibit carbohydrate metabolism. Furthermore, oestrogen therapy in ovariectomized rats stimulated FFA oxidation and reduced glucose oxidation during exercise (indicated from the appearance of $^{14}$CO$_2$ from $[^{14}$C]palmitate and $[^{14}$C]glucose) [37]. It would appear that FFA metabolism is thus, enhanced during mild exercise in OC users. Lactate accumulation during heavy exercise serves to reduce the concentration of FFA by stimulating the reesterification of FFA, and there is thus a greater reliance on carbohydrate metabolism [34].

Bonen et al. [34] reported no increase in the cortisol response to exercise in their OC group. They suggested that this is due to the suppressive effects of OCs upon the
hypothalamic pituitary adrenal axis. Consequently the reduction in ACTH observed in OC users [38] prevents the cortisol synthesis and release that normally occurs during exercise. Blunted cortisol responses should lead to a reduction in hepatic gluconeogenesis, and thus a reduction in blood glucose. This was not the case in Bonen and co-workers’ study leading them to conclude that the alterations observed in cortisol concentrations during exercise were not significant in relation to glucose mobilization or utilization. Bunt [36], however, reported elevated cortisol and human growth hormone (hGH) during exercise in OC users, both of which are known to impair hepatic gluconeogenesis suppression [31] leading to an increased glucose concentration.

The effect of OCs on carbohydrate metabolism is still a contentious issue. It appears that oestrogen acts to inhibit gluconeogenesis and glycogenolysis whilst enhancing lipid metabolism during mild exercise. The mechanism for these changes may be from direct effects upon the liver, muscle and adipose tissue, or indirect effects via alterations in the concentrations of insulin, glucagon, cortisol and hGH. Exogenous oestrogen, and the elevated oestrogen concentration seen during exercise [34], may increase the insulin:glucagon ratio leading to insulin insensitivity and glucose intolerance. The elevation in insulin, hGH and cortisol in OC users at rest may continue into exercise and result in impaired hepatic gluconeogenesis, and the preferential utilization of lipid substrates. Investigations into these parameters are hampered by differing types of OC preparations, length of OC use, subject nutritional status and level of fitness and flaws in experimental controls. Nonetheless, it is safe to assume that carbohydrate metabolism is subtly altered by both natural and exogenous oestrogen; the effect of this upon physical performance, however, is minimal.

Exercise is an integral part of health, the beneficial effects of which aid to decrease the risk of CVD. In non-smoking, non-obese women the potential “cardioprotective” benefits of exercise and the natural oestrogens (pre and post-menopausal) are overwhelming. In a society where CVD is one of the most expensive and biggest killers of the twentieth century, the promotion of “cardioprotective” health is paramount. That is not to say that OCs do not have their cancerous and thromboembolic risk, and that HRT does not carry its own risks; but with careful education and prescription oestrogen replacement may be “the single most important cardiovascular therapy of this century” (Dr John Stevenson, The Daily Mail, August 27, 1996, p 5).

REFERENCES

**Discussion: Exogenous Oestrogen: The Female, Cardiovascular Disease and Exercise**

**J.P. Clarys:**
Are there adverse effects on blood pressure?

**K. Birch:**
In the case of oral contraceptives, there tends to be a minimal increase in most people who are asymptomatic to begin with. It tends to be brought about by an oestrogen-enhanced increase in plasma renin activity. In HRT users, that is not the case and, although there is an increase in renin, the molecules of renin tend to be of high molecular weight and those types of renin molecules are seen in normotensive people.

**M. Orme:**
We are now seeing an interesting situation where women who have been taking one of the newer oral contraceptive steroids and who suffer from a venous thrombosis are suing their doctor in spite of the fact that these newer drugs are less likely to cause a cardiovascular event than the older drugs. So you would need to be a soothsayer par excellence to predict for the individual patient the end result. In a very few women a clot may be caused but in others protection against cardiovascular disease will occur. This will cause many management problems for doctors.

**K. Birch:**
I think that it is definitely an ethical problem we have got to consider. And certainly places in England like the National Osteoporosis Society and other societies such as the British Health Foundation, are taking this very seriously and targeting their education very much at young athletes. Young athletes who are hypoestrogenic for a long time have an increased risk of cardiovascular disease and also of decreased bone mineral density. Which type of pill to take is indeed a medical question.

**A.D. Martin:**
Overall, the studies that look at mortality show positive net effect in terms of longevity with the use of these replacement therapies. So as far how you decide which particular individual is going to benefit and which does not: that is a clinical decision.

**F. Brouns:**
There is a rapid development linked to epidemiological studies from Japan which showed that people who have a high consumption of soy (which is rich in isoflavones) have a reduced risk of cardiovascular disease, breast cancer and osteoporosis. I just wonder if anybody is aware of differences in bone mineral density in the athletic population of Japan vs Western countries.

**A.D. Martin:**
I have not seen any study that looks at athletes from Japan or even from China, but it would be very interesting.
F. Brouns:
What do you think in terms of osteoporosis prevention in amenorrheic athletes? Would there be a role for these type of phytoestrogens as "replacement therapy"?

K. Birch:
I believe so. There is a lot of argument in the medical world about whether HRT should be removed in post-menopausal women and that the vasomotor symptoms be treated by diet and various minerals. It tends to be an argument that is ongoing.

A.J.M. Wagenmakers:
I believe you suggested that there is an increased reliance on fat as fuel when these women on oral oestrogens are exercising at low intensity. Is there a difference in the oxidative capacity of the muscle or is something changing at the supply side, that is the rate of lipolysis in adipose tissue or muscle?

K. Birch:
The evidence is equivocal but most people would state that it is a growth hormone and cortisol effect directly upon suppressing gluconeogenesis and glycogenolysis. And also, when these women begin to exercise they tend to be hyperinsulinemic as well, so metabolism tends towards the free fatty acid-glucose cycle acid and glycogen-sparing.