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Pharmacology of Hormone Replacement Therapy in Menopause

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1. Introduction

Menopause represents the final stage of the continuous process of reproductive aging in a woman's life, marking the end of her fertility. According to the World Health Organization (WHO), the natural menopause is defined as *the permanent cessation of menstruation resulting from the loss of ovarian follicular activity* (WHO Report, 1996). Preceded by endocrine and menstrual cycle changes described as "menopausal transition", natural menopause occurs at an average age of approximately 51 years, although a high inter-individual variability is supported by results from epidemiological studies. However, occurrence of menopause outside the estimated normal age interval (45-55 years) is associated with increased morbidity, either when a late or on the contrary, a premature cessation of menstruation appears. A late menopause implies a longer exposure to estrogens and a possible increased risk for breast (Colditz, 1993; Kelsey & Bernstein, 1996) and endometrial cancer (Dossus et al., 2010; McPherson et al., 1996) or for venous thromboembolism (Simon et al., 2006). On the other hand, women entering menopause earlier are facing a hypo-estrogenic state for a longer period compared to women undergoing normal menopause. That is the case for about 1% of women, which are confronted with the diagnosis of primary ovarian insufficiency (POI). POI is defined by the presence of amenorrhea associated with elevated follicle-stimulating hormone (FSH) levels in the menopausal range in women younger than 40 years (Bachelot et al., 2009). Women facing a premature cessation of the ovarian function were shown to be at increased risk for premature death, cardiovascular disease, neurologic disease, mood disorders, osteoporosis or psychosexual dysfunction (Shuster et al., 2010). As the main rationale for these disorders was linked to hormonal changes, maintaining a certain level of ovarian steroids for a given period of time arose as an essential condition for conserving life quality in women (Wilson, [1966]). Accentuated by the increasing life span, researches related to menopause and its treatment have provided scientific community with an increased body of data during the last decades. However, different aspects regarding the benefit/risk balance or the ideal doses and routes of administration of hormone replacement therapy (HRT) in menopausal women remain uncertain (Grodstein et al., 1997; Rossouw et al., 2002).

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In this context, our paper addresses various issues related to steroid hormone substitution, ranging from the basic pharmacology of sex steroids to their clinical use in HRT and subsequent benefits and risks.

2. Sex steroids

2.1 Natural oestrogens and progestogens

During a woman's reproductive lifetime, sex steroids (Oestrogens and Progestogens - the two main classes of female steroids) result mainly from the process of ovarian steroidogenesis and only small amounts are being secreted by the peripheral compartments (e.g. adrenals, adipose tissue). This characteristic is maintained until menopause, when subsequent to a decline in ovarian synthesis, sex steroid plasmatic levels rely only to the less significant amounts produced peripherally. In the particular case of pregnant women, the pivotal role for steroid secretion shifts from ovaries to placenta.

Ovarian secretion of sex steroids during reproductive age follows a monthly cyclic evolution under the control of pituitary gonadotropins (Figure 1A). This precise central control of the ovarian function depends on the coordinated pulsatile secretions of the hypothalamic GnRH (Bouligand et al., 2009) and of pituitary gonadotropins. The decrease in sex steroids levels in menopause abolishes the normal negative feedback at the hypothalamus and pituitary glands, resulting in an over-secretion of gonadotropins, especially FSH (Figure 1B). The pharmacological basis of hormone replacement therapy is to compensate the decrease of estradiol production by ovaries in order to limit the adverse events due to sex steroids deficiency.

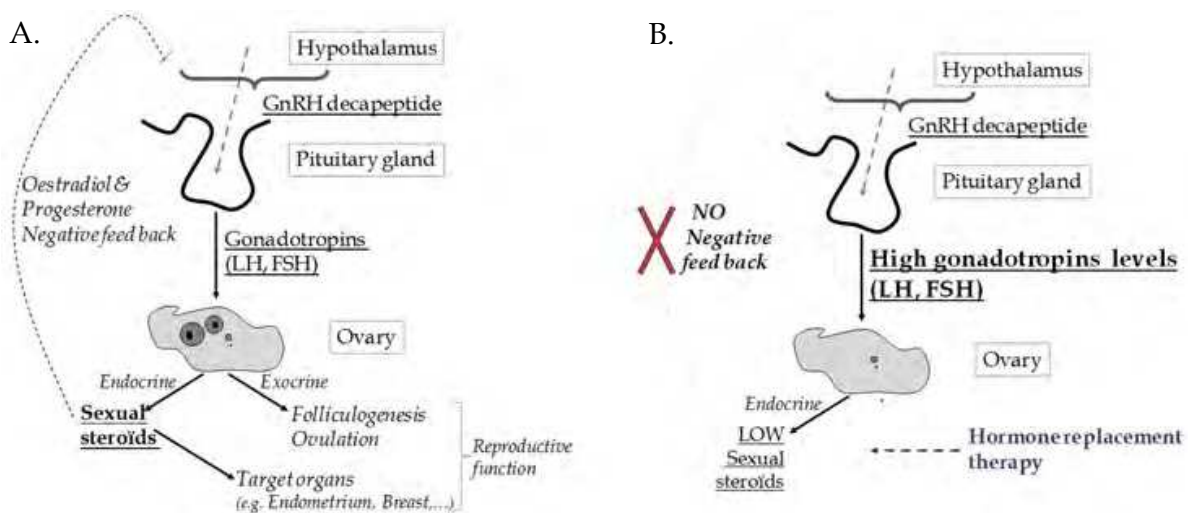


Fig. 1. The Hypothalamic-Pituitary-Gonadal (HPG) axis in women. A. Characteristics of HPG axis during the reproductive age. B. Changes in HPG axis following menopause.

Among the three forms of **natural circulating oestrogens** (i.e. estradiol, estriol and estrone, Figure 2), the main biological effect is exerted by estradiol, with a potency of approximately ten times that of estrone (Coldham et al., 1997; Van den Belt et al., 2004), while estriol exhibits the weakest estrogenic activity. In the second class of female sex steroids, **progesterone** represents the most important component, with significantly higher secreted levels than 17-hydroxyprogesterone, the other naturally occurring progestogen (Figure 2).

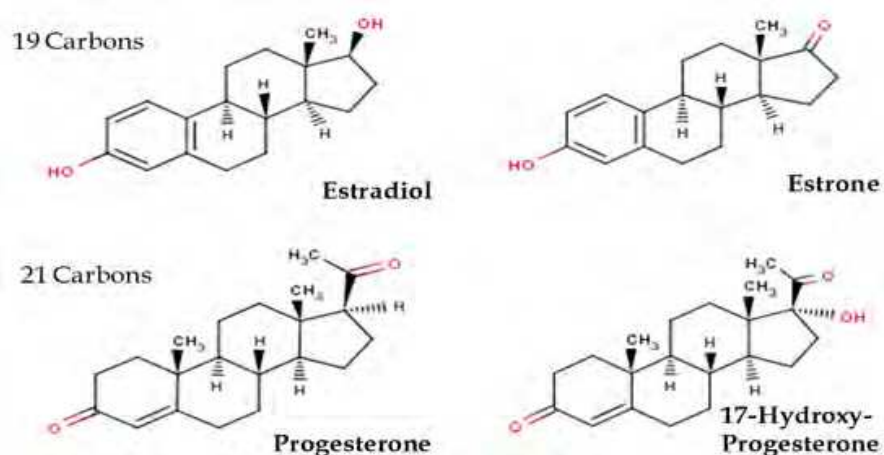
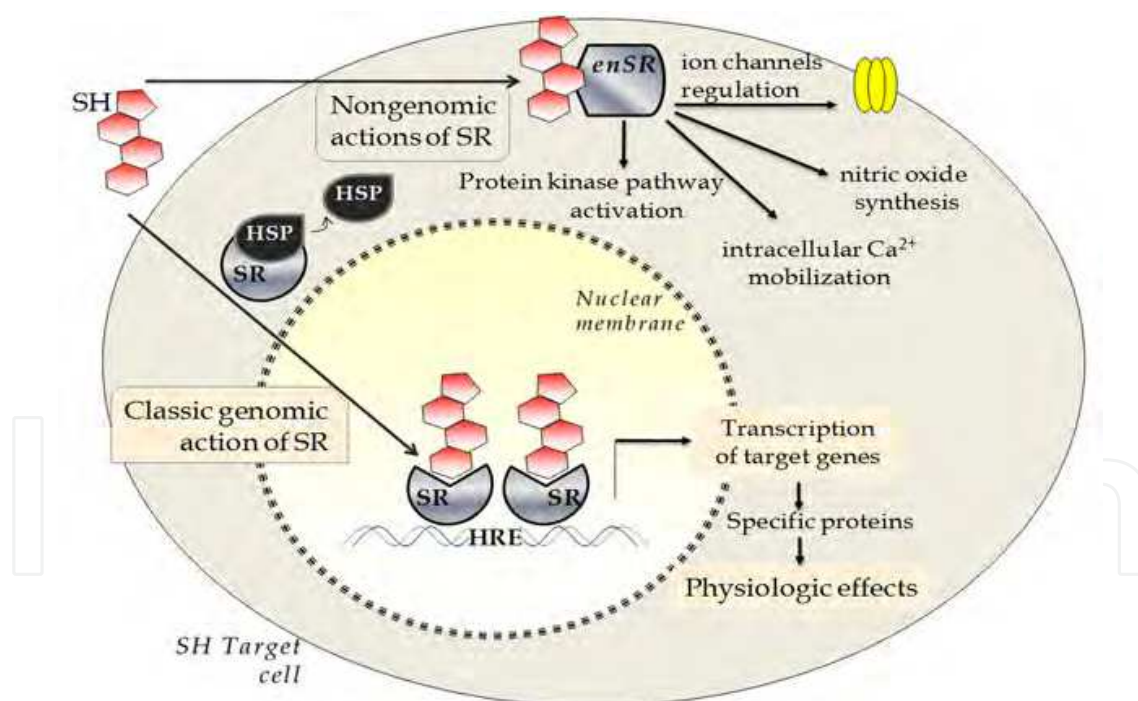


Fig. 2. Chemical Structure of Natural Sex Steroids

2.2 Mechanisms of action of sex steroids

The mechanisms by which oestrogen and progesterone exert their effects are complex (Figure 3A), and involve both classic pathways of hormone gene transcription through their cognate receptors, as well as “non-genomic” actions, the latter being characterized by significantly faster response rates (e.g. seconds, minutes).

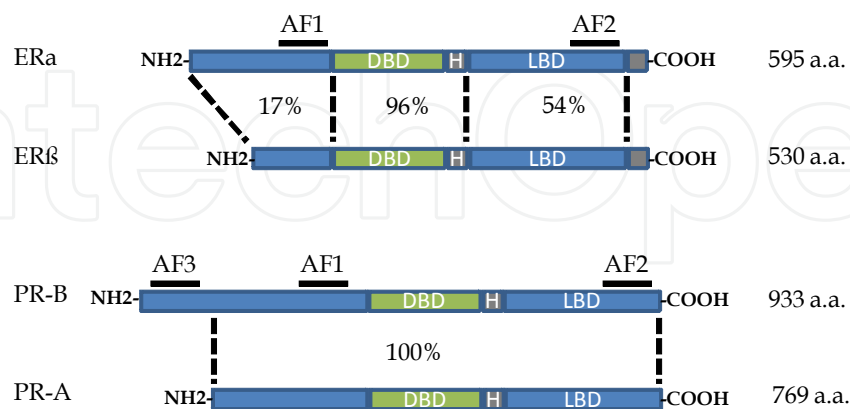


SH: steroid hormones (oestrogen, progesterone) ; SR: steroid receptor (ER, PR) ; enSR: extranuclear steroid receptors ; HSP: heat shock proteins ; HRE: hormone response elements.

Fig. 3.a. Sex steroids mechanism of action

Oestradiol and progesterone receptors (ERs and PRs respectively) belong to the large family of nuclear receptors (NRs), sharing several structural features (Loosfelt et al., 1986) and acting as transcriptional factors in a ligand dependent manner (For review, (Edwards, 2005).

Two major forms have been identified for each of the two types of ovarian steroid receptor, namely ER α and ER β (Kuiper et al., 1996; Walter et al., 1985), and PR-A and PR-B respectively (Conneely et al., 1989; Huckaby et al., 1987; Kastner et al., 1990; Khan et al., 2011) (Figure 3B).



LBD: ligand binding domain; DBD: DNA binding domain; AF: transcription activation domain (AF-1, AF-2, AF-3); H: Hinge region, a.a. : amino-acids. The percentages indicate the amino acid identity between domains of ER α and ER β and between A and B forms of PR.

Fig. 3.b. Domain structures of estrogen (ER) and progesterone (PR) receptors.

Most of ERs and PRs are constitutively localized in the nucleus in the absence of their ligands (Welshons et al., 1985), and nuclear localization signals have been described in the hinge region (Guiochon-Mantel et al., 1989; Picard et al., 1990). Due to their lipophilic nature, steroids will easily cross the cell membrane and bind to specific receptors, resulting in hormone-receptor complexes. Prior to ligand binding, receptors are inactive and associate protein complexes, among which the heat shock proteins (hsp) play important roles (e.g. hsp 90, hsp 70)(Pratt & Toft, 1997). But in the presence of their ligands, receptors undergo conformational changes with subsequent release of the associated protein complexes and bind to specific DNA sequences (hormone-response elements) from the promoter regions of target genes. The expression of target genes is thus modulated after interaction with various coregulators (Rosenfeld & Glass, 2001; Amazit et al., 2011). ERs and PRs bind DNA as dimers and have the ability to form both homodimers and heterodimers (ER α/β , PR A/B respectively)(Cowley et al., 1997; Leonhardt et al., 1998). Furthermore, the complexity of oestrogen and progesterone actions is enhanced by the growing body of evidence supporting the non-genomic mechanisms of steroid hormones action (Hammes & Levin, 2007; Levin, 2011; Losel & Wehling, 2003). These rapid effects may not be explained by the classic pathway and involve a variety of signalling events, such as the activation of various kinases, ion channels regulation and intracellular calcium mobilization or nitric oxide synthesis (Edwards, 2005; Madak-Erdogan et al., 2008). Responsible for generating these effects may be either membrane forms of classically ERs and PRs or alternative unrelated molecules (Wendler et al., 2010).

2.3 Physiological effects

Oestrogens and progestogens main effects concern the **reproductive organs**, initiating and supporting their development and functionality. Secondary sex characteristics are under the

close control of gonadal steroids. During the reproductive lifetime of a woman, oestrogens dictate the proliferation of the uterine endometrium and the development of endometrial glands, while progesterone promotes secretory changes of the endometrium, in a process of preparation of the ideal milieu for implantation of the fertilized ovum. In the **breast**, oestrogens promote the development of the stromal and ductal systems together with fat deposition at this level, and progesterone induces the development of the secretory units of the breast, causing alveolar cells to proliferate.

Although the reproductive system represents the principal target for sex steroids, their effects are far from being limited only to this system. **Bone health**, for instance, is greatly influenced by oestrogens levels, as they play an important role in the process of bone remodelling. Under their action, skeletal resorption is diminished due to a decreased osteoclastic activity and by consequence, bone formation is promoted. Furthermore, a **cardioprotective** role exerted by ovarian steroids was inferred due to the significantly lower rates of cardiovascular diseases manifested by women prior to menopause compared to men and the cancelation of these gender differences following menopause. Several **metabolic effects** are also described, oestrogens slightly increasing the metabolic rate, promoting deposition of the fat in subcutaneous tissue and changing lipoprotein profiles by increasing HDL and decreasing LDL cholesterol (Edwards, 2005; Guyton & Hall, c2006).

3. Menopause principal consequences

Given the multitude of physiological effects exerted by sex steroids in women, it is not surprising that the hormonal changes related to menopause have been linked to a wide spectrum of symptoms and disorders. The most frequent menopausal symptoms include vasomotor disorders (e.g. hot flashes, night sweats), urogenital atrophy (e.g. vaginal dryness, urinary symptoms), or psychological disturbances (e.g. sleep disturbances, forgetfulness, mood changes or depression), all of which may seriously impact on women's quality of life. Decreased oestrogen levels in menopause result in an altered bone structure with reduced bone mineral density (BMD) and increased risk for subsequent fractures. Postmenopausal women, compared to the premenopausal period, are also more prone to develop cardiovascular disease (CVD), which represents the leading cause of death in women. Furthermore, the increased risk of dementia and Alzheimer disease in postmenopausal women was also partially attributed to endogenous oestradiol depletion (Yaffe et al., 2007).

If the aforementioned effects are present in women undergoing natural menopause, the magnitude of these consequences is even higher in POI women and the dimension of each long-term effect may vary in relation to the exact cause of POI and to the rapidity of apparition of the oestrogen deficit (e.g. women undergoing surgical oophorectomy will face a sudden decrease in steroids levels compared to women experiencing a spontaneous POI) (Maclaran et al., 2010). All-cause mortality rates in women appear to be associated with age at menopause, women entering menopause before 40 years having mortality rates twice as the ones seen in the 50-54 years group (Snowdon et al., 1989). Studies on the cardiovascular risk in POI demonstrated that several risk factors for CVD are influenced by a premature occurrence of menopause (e.g. alteration of lipid profiles (Knauff et al., 2008), decreased insulin sensitivity (Corrigan et al., 2006) or the presence of metabolic syndrome (Eshtiaghi et

al., 2010)). Moreover, the impaired endothelial function found in women with POI, precursor of more severe vascular abnormalities, was improved by hormonal replacement, further supporting the role of steroids in normal cardiovascular function (Kalantaridou et al., 2004). POI patients present with low BMD, which seems to be greatly influenced by the accelerated bone loss during the first 4-5 years of menopause (Amarante et al., 2011; Anasti et al., 1998; Gallagher, 2007; Uygur et al., 2005; van Der Voort et al., 2003), and hence having an increased risk of fractures compared to their peers who underwent a physiological menopause. Finally, an increased risk for cognitive impairment, dementia and Parkinson disease, inversely proportional with age at menopause, was reported in premature menopausal women following oophorectomy (Rocca et al., 2007, 2008).

4. Hormone replacement therapy

4.1 Basis for the hormone replacement therapy in menopause

When an installed hormonal deficiency generates symptoms in an individual, disturbing its well-being, it is expected that by adjusting the deficit, an improvement or even an offset of the symptoms should be reached (Wilson, [1966]). That was the hypothesis guiding clinicians decisions about substitution of ovarian steroids in menopause. Hormone replacement therapy (HRT) has been a common practice during the last decades, being initially used for both treatment of symptoms and prevention of chronic medical conditions related to menopause (e.g. heart and bone diseases). But 2002, the year when the first results from a large randomized and placebo-controlled trial (the Women Health Initiative - WHI) were published, marked a major change in both clinicians and patients perception towards the use of HRT (Rossouw et al., 2002). Conducted with the aim of evaluating HRT major benefits and risks, WHI results contradicted previous observational studies and showed an increased risk for cardiovascular events together with that of breast cancer rates in the studied population. Even if this resulted in a significant reduction in the use of HRT worldwide (Hersh et al., 2004; Lagro-Janssen et al., 2010; MacLennan et al., 2004), it represented also the subject to some major controversies. One major debate is the legitimacy of applying these conclusions to all women, when most of the women concerned by HRT prescription belong to the 50-54 years age group while participants in the WHI study had an average age of 63 years and a high body mass index. Thus, following the release of the first WHI report, various studies intended to better evaluate the real risks and benefits associated with HRT were conducted. The resulting body of evidence has led to the necessity of periodic revision of the existing recommendations and statements in this field (North American Menopause Society (NAMS) position statement, 2010; Santen et al., 2010; Sturdee et al., 2011).

4.2 Current recommendations

Current recommendations specify that HRT use should be restricted mainly to moderate or severe menopausal symptoms alleviation. It should not be used as a mean of chronic disease prevention and it is advisable to restrict treatment administration to the shortest period and the lowest dosage possible to control symptoms effectively. Nevertheless, in selected cases, HRT may be used to treat or to reduce the risk of diseases (e.g. osteoporosis). This involves HRT use *in prevention of further bone loss and/or reduction of osteoporotic fracture in menopausal*

women when alternate therapies are not appropriate or cause side effects (NAMS position statement, 2010) or for women younger than 60 years, with an increased risk of fracture (Sturdee et al., 2011). In the particular case of women diagnosed with POI, HRT is recommended at least until the median age of natural menopause is reached (NAMS position statement, 2010).

4.3 Hormone replacement therapy regimens

4.3.1 Oestrogens and progestins in HRT

HRT comprises a variety of regimens, compounds, dosages and routes of administration. In most women, excepting hysterectomized patients, menopausal treatment requires preparations combining oestrogens with a progestin, the latter being used mainly to balance oestrogen's effects on the endometrium and to avoid endometrial hyperplasia and an increased risk of secondary carcinoma. This combination therapy may be administered either in a sequential cyclic regimen or in a continuous one. The sequential regimen involves the alternation of a pure oestrogenic period to an oestro-progestative one, leading to withdrawal bleeding when the progestin administration is discontinued. This regimen is commonly administered with a monthly cyclicity including at least 10 days of progestin treatment. Quarterly regimens are also available, involving progestin administration every 3 months, although in this case the risk for endometrial hyperplasia needs further evaluation. The continuous combined treatment implies the administration of both compounds on a daily basis and uses lower doses of progestin compared to the sequential regimen. This constitutes an option especially in older women not desiring a monthly withdrawal bleeding, even if uterine bleeding with unpredictable onset may not be excluded particularly during the first administrations (Doren, 2000; Ylikorkala & Rozenberg, 2000). Available formulations for the estrogens and progestins in HRT and their commonly used doses are listed in Table 1.

4.3.2 Other therapeutic options

Androgens are thought to play a role in maintaining a normal libido and sexual function in postmenopausal women and to potentially prevent the decline of bone quality, muscular force and cognitive function. Thus, after exclusion of other possible causes, androgen therapy represents an option for menopausal women with hypoactive sexual desire disorder undergoing concomitant oestrogen treatment, especially in those who have suffered a surgical menopause (Davis et al., 2008).

Tibolone is a synthetic compound with mixed oestrogenic, progestogenic and androgenic activities, representing an alternative to conventional HRT (Lazovic et al., 2008). It represents an efficient option for vasomotor symptoms alleviation or prevention of BMD loss in menopausal women (Gallagher et al., 2001; Swanson et al., 2006).

Another possible option in menopausal therapy refers to the **selective oestrogen receptor modulators (SERMs)**. These are pharmacologic agents characterised by variable oestrogen activity, acting as oestrogen agonists in some tissues while in other tissues they exert oestrogen antagonist effects. Examples of SERMs of interest in menopause treatment include raloxifene together with novel molecules like bazedoxifene, lasofoxifene or ospemifene.

Route	Oestrogens	Dosage
Oral	Conjugated estrogens (conjugated equine oestrogens)	0.625 mg
	Micronized 17 beta oestradiol	1, 2 mg
	Oestradiol valerate	1, 2 mg
	Estropipate (piperazine estrone sulphate)	0.75, 1.5, 3 mg
Transdermal	17 beta oestradiol (patch)	25, 37.5, 50, 75, 100 µg/day
	Oestradiol (gel)	1 mg/ 1g
Subcutaneous	Oestradiol (implant)	20, 50, 100 mg
Vaginal	Estriol (gel)	1mg/g
	Estradiol (tabs)	25µg
	Progestins	
Oral	Norethisterone acetate	0.5, 1 mg
	Medroxyprogesterone acetate	2.5, 5 mg
	Chlormadinone acetate	2, 5, 10 mg
	Drospirenone	2 mg
	Dydrogesterone	5, 10 mg
	Nomogestrol acetate	3.75, 5 mg
	Promegestone	0.125, 0.25, 0.5 mg
	Micronized progesterone	100, 200 mg
Transdermal	Levonorgestrel	7, 10µg/24h
Intrauterine	Levonorgestrel intrauterine device	20 µg/24h

Table 1. Commonly used oestrogens and progestins

4.4 Primary ovarian insufficiency: Particular requirements

Current publications highlight the lack of specifically designed HRT regimens for women with POI and the fact that existing observations from studies conducted on older women undergoing natural menopause should not be extrapolated to the much younger category of POI women. In the absence of a consensus regarding the ideal hormonal replacement regimen for women facing a premature cessation of the ovarian function, the oestro-progestative substitution commonly involves either HRT or combined oral contraceptive pills (COCP) prescription. Even if the use of the latter may be associated with a lower emotional impact for these patients, being perceived less as a treatment, it must be underlined that COCP standard preparations contain synthetic steroids in higher doses than the ones required for physiologic hormonal replacement in POI (Nelson et al., 2005). There is an urgent need to develop evidence-based guidelines relying on solid research in order to optimize the care of this group of women (Panay & Kalu, 2009).

4.5 Benefit versus risk of hormonal replacement therapy based 1 on the reviews of clinical studies

Despite the wide agreement that hormonal substitution remains the most effective option for the alleviation of menopausal symptoms, a careful evaluation of the benefit-risk balance is however essential prior to prescribing a HRT regimen because of its associated risks (Santen et al., 2010). The principal benefits and risks related to HRT in the light of recent evidences are further discussed in this paragraph.

The **cardiovascular events** represent the first cause of mortality in postmenopausal women and constituted a major subject of controversy regarding the use of HRT, an uncertainty accentuated by the discrepant results between randomised controlled trials (RCTs) (Hulley et al., 1998; Rossouw et al., 2002; Vickers et al., 2007) and observational studies (Bush et al., 1987; Grodstein et al., 1997; Stampfer et al., 1991). Initially, as expected from the physiological functions of oestrogens, several observational studies suggested a protective role of HRT on the cardiovascular system. Contrary to these observations, the WHI, a randomised, placebo-controlled trial, failed to validate the cardioprotective effect of HRT. The primary outcome of this study was related to the effects of menopausal substitution on the cardiovascular function and breast cancer risk, participants receiving either conjugated equine estrogens (CEE) alone (0.625mg/day) if hysterectomised (Anderson et al., 2004) or 0.625mg/day CEE in combination with 2.5mg/day medroxyprogesterone acetate (MPA) if they presented with an intact uterus (Rossouw et al., 2002). In an attempt to explain the disparity between these results the "timing hypothesis" arose as a possible answer, supported by differences between women enrolled in this study and those participating in observational studies (Grodstein et al., 2003). Thus, while the former included women more than a decade away from the onset of menopause, in the latter HRT was usually initiated shortly after menopause. Animal studies supported this hypothesis and demonstrated that the positive cardiovascular effects of hormonal substitution are inversely correlated with the delay of initiating the treatment (Clarkson, 2007). Several analysis, including some of the WHI subgroup data, tested the timing hypothesis and showed a trends towards a decreased risk in women younger and closer to menopause (Rossouw et al., 2007; Salpeter et al., 2006). Trials addressing specifically the effects of HRT in younger women (e.g. Kronos EarlyEstrogen Prevention Study (KEEPS) (Harman et al., 2005), Early Versus Late Intervention Trial With Estradiol (ELITE, NCT00114517) are currently under way and their results will probably shed a better light on these controversial facts.

Venous thromboembolism (VTE) is one of the major harmful effects of hormone therapy use among postmenopausal women (Olie et al., 2010). A recent meta-analysis on the risk of VTE in women using HRT indicated an increased risk by twofold to threefold when oral oestrogens were administrated (the combined relative risk (RR) from both trials and observational studies of 1.9 and confidence interval (CI) of 1.3 to 2.3, with a higher risk within the first year of treatment (Canonica, Plu-Bureau et al., 2008). When VTE risk was analysed in women receiving transdermal oestrogen, there was a combined RR of 1.0 (CI, 0.9 - 1.1). The impact of the route of administration on VTE risk and the recent pharmacogenetic studies providing support for the implication of the first pass effect in these different outcomes are detailed in chapter 5.

Musculoskeletal effects. Both observational studies (Cauley et al., 1995; Grodstein, Stampfer et al., 1999; Kiel et al., 1987) and RCTs (Cauley et al., 2003; Jackson et al., 2006; Lindsay et al., 2005) have proven HRT efficacy in reducing bone loss in menopausal women. Additionally, this positive effect appears to be present even when lower doses of oestrogen are used (Lindsay et al., 2005). However, rapidly after its discontinuation the protective effect on BMD is no longer evident. A recent study, evaluating hip fracture incidence after HRT cessation in a large cohort of 80,955 postmenopausal women, reported a significantly increased risk of hip fracture within only two years following HRT cessation compared to women who continued using HRT (Karim et al., 2011).

HRT and cancer risks. There is a large body of studies investigating the association between HRT and the risk for various types of cancer, primarily those hormone-dependent and particularly **breast cancer**. Breast cancer was one of the reasons for the premature discontinuation after 5.2 years of follow-up of the arm receiving combined HRT in the WHI trial, as the increased risk in breast cancer exceeded the stopping boundary for this adverse effect (RR 1.26; 95% CI 1.00-1.59) (Rossouw et al., 2002). Contrary to these findings, in the oestrogen-only group the relative risk was inferior compared to the control group (RR 0.77, 95% CI 0.57-1.06) (Anderson et al., 2004), suggesting that in addition to oestrogen, progestins have also a role in breast cancer pathophysiology. The risk of developing breast cancer increases with longer duration of HRT use (Beral, 2003; Fournier et al., 2008). One meta-analysis assessing the impact of HRT on the risk of invasive breast cancer in epidemiological studies and RCTs reported an increased annual risk for breast cancer varying between 0-9% in the case of E+P regimens and 0-3% in oestrogen-only administration (Greiser et al., 2005).

Although the risk of CHD was reported to increase when HRT is started a long time after the onset of menopause, the reverse situation seems to apply in the case of breast cancer. Data from the WHI trial supported this so called "gap time hypothesis" and reported an increased risk for breast cancer when HRT is started less than 5 years after the onset of menopause in both E (with a RR of 1.12 versus 0.58 when HRT was initiated less than 5 and respectively more than 5 years from menopause in women without a prior HRT use, or a relative risk (RR) of 1.00 versus 0.77 in women with prior HRT use) and E+P arms (with a RR of 1.77 versus 0.99 when HRT was initiated less than 5 and respectively more than 5 years from menopause in women without a prior HRT use, or a RR of 2.06 versus 1.30 in women with prior HRT use) (Prentice et al., 2009). The fact that ER positive breast tumours in postmenopausal women, but not in premenopausal ones, respond to treatment with high-dose oestrogen further supports this hypothesis and suggests that the decline in oestrogen levels associated with menopause may sensitize breast cancer cells to the proapoptotic effects of estrogen (Taylor & Manson, 2011).

Endometrial cancer (EC) constitutes another adverse effect linked to HRT use. The most common form of EC, the endometrioid (type I) variant, is generally hormonally responsive and women with an unbalanced oestrogen exposure are at increased risk for this form of EC. No risk increase was reported in women using a continuous combined HRT regimen, while the use of sequential HRT resulted in different risk profiles according to the duration of treatment (Jaakkola et al., 2011). Thus, when used for less than 5 years, the sequential E+P regimen showed a decreased risk for EC (RR 0.67, 95% CI 0.52-0.86), while continuing treatment after 5 years resulted in an increased risk for EC (RR 1.11,

95%CI 0.87-1.41 for the 5-10 years interval and RR 1.38, 95%CI 1.15-1.66 for an use exceeding 10 years).

Several studies reported an increased risk for **ovarian cancer** in women using HRT (Beral et al., 2007; Morch et al., 2009), with a stronger association in the case of unopposed oestrogen administration (Hildebrand et al., 2010). However, due to the small excess risk, the overall benefit-risk balance in HRT appears not to be significantly influenced by these results (Taylor & Manson, 2011).

Colorectal cancer. Observational studies have suggested an association between the use of HRT and a reduced incidence in colorectal cancer (Grodstein, Newcomb et al., 1999), an observation also validated by data from the E+P arm from the WHI trial (Chlebowski et al., 2004). However, despite a reduced overall rate, poor prognosis forms of colon cancer were diagnosed more frequently in women receiving HRT than in the placebo group. In contrast to the group receiving E+P, the reduced incidence of colorectal cancer was not found in the oestrogen-alone arm of WHI (Ritenbaugh et al., 2008). The relation between colorectal cancer and hormone exposure is further complicated by recent evidences suggesting that a greater endogenous estrogen exposure may increase the risk of colorectal cancer in postmenopausal women (Clendenen et al., 2009; Zervoudakis et al., 2011).

Finally, results from several studies comprising those of WHI (Chlebowski et al., 2009) have led to the inclusion of **lung cancer** on the list of potential adverse effects of HRT, although a neutral effect of HRT on lung cancer risk (Ayeni & Robinson, 2009) or even lower risks (Rodriguez et al., 2008) have been reported by others. Post-hoc analysis of WHI showed that even if the incidence of lung cancer in women using HRT did not increase, the number of death from lung cancer was significantly higher (in particular deaths from non-small-cell lung cancer) in women receiving combined HRT (Chlebowski et al., 2009), contrary to the use of oestrogen alone where the death rates were similar to the control group (Chlebowski et al., 2010).

The effect of HRT on a variety of conditions (e.g. mood disturbances, neurocognitive impairment, gallbladder disease, immune disorders, etc) have also been investigated. However, as either current evidences are insufficient or their impact on the overall benefit-risk balance is not significant, we will not detail them.

Particularities of the HRT benefit-risk balance in POI patients. Available results from studies evaluating HRT effects, especially its risks, do not address particularly the population of POI patients, but rather there is a tendency to apply to this group an extrapolation of findings from natural menopause, although there are evident differences in the HRT benefit-risk ratio between the two populations.

Cardiovascular and breast cancer risks, the two main adverse effects related to HRT use, need a special consideration in the context of women diagnosed with POI. First, the "timing hypothesis" for cardiovascular effects of HRT suggest a clear trend towards cardiovascular benefits in young women using HRT and hence, it is possible that the benefits in the younger POI patients might be even greater (Panay & Fenton, 2008). Secondly, the breast cancer risk profile differs in women undergoing a premature menopause compared to the general population. A younger age at menopause is protective against breast cancer regardless of whether the menopause was natural or surgical (Hulka & Moorman, 2008).

Thus, POI patients should be informed that results from reports on HRT associated breast cancer do not necessarily apply to their case, in which treatment is intended to provide the hormones that should be physiologically present at their age (Maclaran & Panay, 2011).

These particularities of the HRT risk profile in women facing a premature cessation of the ovarian function, together with the beneficial bone effects (Farquhar et al., 2009), support the current recommendations regarding the need for HRT substitution until the average age of natural menopause (Vujovic et al., 2010).

5. Pharmacology of hormone replacement therapy

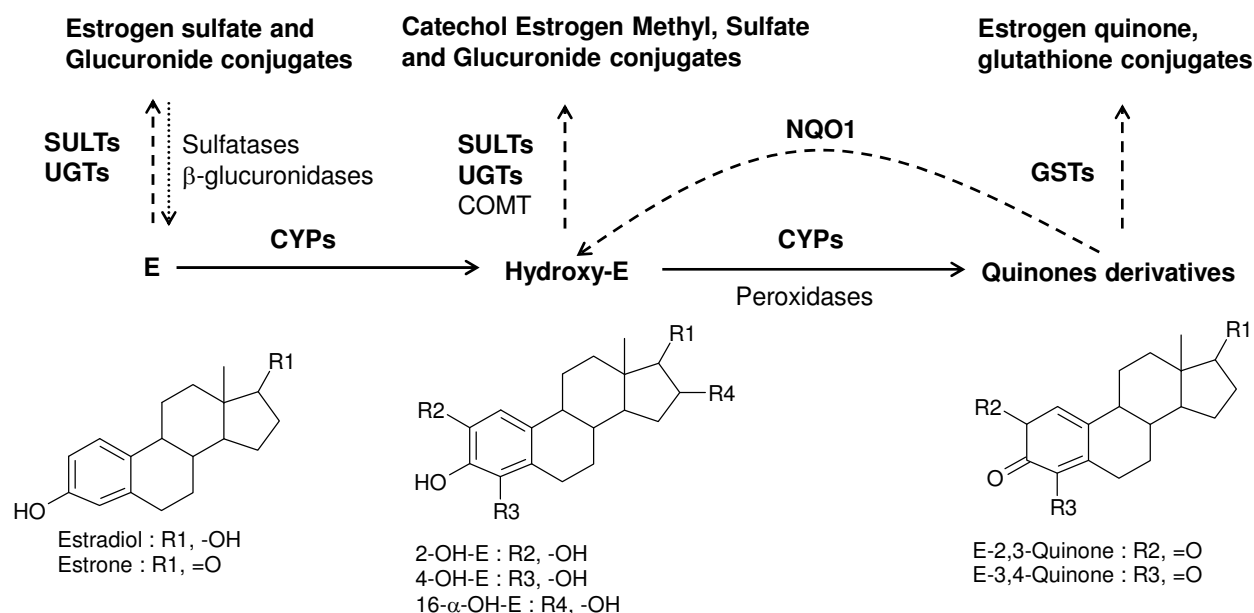
The pharmacology of hormone replacement therapy is of a particular interest given the complex benefit/risk balance and the importance of this treatment for women health. As illustrated in previous paragraphs, there is a wide diversity of drugs and protocols proposed for HRT. Our analysis will be limited to the pharmacology of the natural sex steroid 17 β -estradiol.

5.1 The route of oestradiol administration (oral versus transdermal) highlights the hepatic first pass effect

Oral oestradiol is commonly used by women receiving HRT, being seen as a convenient and inexpensive option. In turn, following oral administration, oestradiol is subject to the first-pass effect, a term that encompasses the metabolic changes underwent by a drug before it reaches systemic circulation. This results in the use of higher doses of oestradiol (~ 1,5 mg/day) compared to parenteral routes (patch ~ 50 μ g/24h). Moreover, subsequent to the various metabolic changes suffered by oestrogens once absorbed in the intestinal tract, a specific profile of oestradiol metabolites and oestrogen-dependent serum parameters with particular pathophysiological implications will appear, widely different from what is observed after the use of transdermal oestradiol where the first-pass effect is avoided.

The oestradiol metabolism pathway (Raftogianis et al., 2000) is outlined in Figure 4. Rapidly after the intestinal absorption, part of oral oestradiol is converted to oestrone, a reversible reaction catalysed by 17 β -hydroxysteroid-dehydrogenase (HSD), and the conversion may continue towards their inactive conjugates (i.e. sulfates and glucuronides). Subsequent to this process, the oestrone/ oestradiol ratio resulting from oral administration is significantly higher (approximately 5:1) than the one observed following transdermal administration (approximately 1:1, which is similar to the physiologic ratio found in premenopausal women)(Kuhl, 2005). Contrary to the aforementioned transformations, further phase I reactions (oxidation reactions catalysed by cytochrome P450 (CYP) enzymes) are no more reversible. The final steps in oestrogen metabolism involve the process of detoxification under the action of phase II enzymes.

The first pass effect of oestradiol results in various biological consequences (De Lignieres et al., 1986). For instance, a well known effect attributed to hepatic first pass is the decrease of IGF-1 after oral oestradiol, whereas no significant change was observed with transdermal oestrogens (Sonnet et al., 2007). Furthermore, an increased synthesis of blood coagulation factors (Caine et al., 1992) and resistance to activated protein C (Oger et al., 2003) constitute another important consequences which are directly implicated in VTE pathophysiology, one of the major adverse events of oral oestrogens.



Various isoforms of cytochromes P450s (CYP3A, CYP1A and CYP1B families) activate estrogens during phase-1 metabolism. Oxidative metabolites, such as hydroxyestradiol and quinone derivatives, are conjugated by various phase-2 enzymes. The expression of several of these enzymes (SULTs, UGTs, GSTs and NQO1) is regulated by Nrf2. E: estradiol or estrone; CYPs: cytochrome P450s; UGTs: UDP-glucuronosyltransferase; COMT: catechol-o-methyltransferase; GSTs: glutathione S-transferases; NQO1: NAD(P)H dehydrogenase, quinone 1. Phase-1 metabolism is represented by horizontal arrows. Phase-2 metabolism is represented by vertical arrows (dashed).

Fig. 4. Oestrogens hepatic metabolism

5.2 Pharmacokinetic of oral *versus* transdermal oestrogens

The pharmacokinetics of exogenous estrogens is complex and most efficacy studies of transdermal *versus* oral oestrogens have not included the measurement of oestrogen concentrations. The oral route of oestradiol administration is easy and convenient, however the hormone is extensively metabolized in the gut and the liver leading to first-pass effect and, as previously mentioned, to a high estrone/oestradiol ratio (Kuhl, 2005). On the other hand, transdermal 17 β -oestradiol is well absorbed through the epidermis and produces higher parent oestrogen serum concentrations and lower metabolites ratios because it bypasses the liver. Moreover, owing to a very low bioavailability [0.1 – 12%] of oral micronized 17 β -oestradiol (O'Connell, 1995), higher doses are needed for the oral route compared to transdermal administration (O'Connell, 1995; Powers et al., 1985).

Pharmacokinetic profiles of transdermal and oral oestradiol are very different with oral administration producing fluctuant concentrations compared to the more constant levels achieved with transdermal formulations (Kopper et al., 2009). Interestingly, there is no pharmacokinetic/pharmacodynamic relationship between serum levels and positive effects of oestradiol treatment. It has been clearly shown that serum level after transdermal oestradiol does not predict the outcome when treating hot flushes (Steingold et al., 1985). The precise oestradiol and estrone concentrations required to prevent bone loss and

cardiovascular disease after either oral or transdermal oestrogen administration are also unknown (O'Connell, 1995).

5.3 Venous thromboembolism risk and HRT

As previously mentioned, VTE represents one of the main adverse effects of HRT in postmenopausal women (Canonico, Plu-Bureau et al., 2008; Cushman et al., 2004). Yet, while oral oestrogen was associated with a significantly increased risk for VTE, this was not observed in women treated with transdermal oestrogen (Canonico et al., 2010; Canonico et al., 2007; Olie et al., 2010; Scarabin et al., 2003; Straczek et al., 2005). An explanation for the distinct VTE risk profile following the two routes of administration involves the first-pass effect of oestrogen. This was shown to affect the synthesis of various oestrogen-dependent hepatic serum factors (Kuhl, 2005), including coagulation and fibrinolysis factors, resulting in blood coagulation activation (Scarabin et al., 1997; Vehkavaara et al., 2001), increased thrombin generation (Scarabin et al., 2011) or induction of resistance to activated protein C (Hemelaar et al., 2006; Oger et al., 2003). However, the precise mechanisms by which these changes occur are still unclear.

5.4 Pharmacogenetics: Genetics factors predisposing to venous thromboembolism (VTE) after oral oestradiol

Straczek et al. investigated the impact of the route of oestrogen administration on the association between a prothrombotic mutation (factor V Leiden or prothrombin G20210A mutation) and VTE risk. This study confirms the increase risk of VTE due to oral 17 β -oestradiol in women presenting a genetic predisposition to VTE (Straczek et al., 2005). On the other hand, we have recently suggested that the hepatic metabolism of oestrogen may modulate the risk of VTE either through an increased phase I metabolism or through a decreased phase II metabolism. To address this important question, we have tested genetic polymorphisms capable to modulate oestradiol phase I or phase II liver metabolism. These polymorphisms do not increase the risk of VTE in the absence of HRT. First, we have demonstrated that increased expression of CYP3A5, a phase I enzyme of particular interest in oestrogen liver metabolism, in women carrying the CYP3A5*1 allele, is associated with a higher risk of VTE during oral oestrogen administration (RR 14.5; CI 2.8 - 73.9), without observing the same interaction in women receiving transdermal oestrogen (Canonico, Bouaziz et al., 2008). Further, we have investigated the association between VTE and nuclear factor (erythroid-derived 2)-like 2 (NFE2L2) polymorphisms (Bouligand et al., 2011). NFE2L2 gene encodes for a transcription factor also known as Nrf2 (NF-E2 related factor 2), essential for both maintenance and induction of phase II metabolism (Thimmulappa et al., 2002). One functional polymorphism (rs6721961) from the promoter region of NFE2L2 was described to be associated with an impaired auto-induction of this transcription factor (Marzec et al., 2007). The presence of this polymorphism may subsequently alter the expression of phase II genes, including those essential for the detoxification of oestrogen metabolites (see Figure 5) (Raftogianis et al., 2000). Our post-hoc analysis of the ESTHER Study (Canonico et al., 2007; Scarabin et al., 2003; Straczek et al., 2005) demonstrated the association between VTE risk and the NFE2L2 polymorphism (i.e. rs672196) in oral oestrogen users (RR 17.9; CI 3.7 - 85.7).

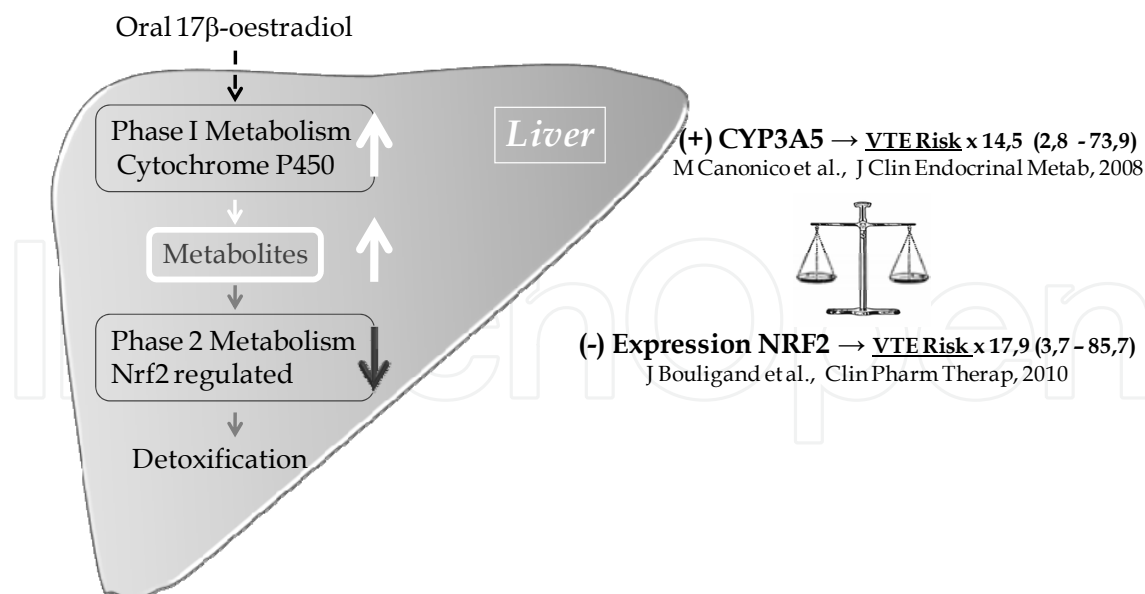


Fig. 5. Genetic polymorphisms modulating liver metabolism and first pass effect of oestrogens.

These pharmacogenetic studies provide new insights suggesting that liver metabolism of oestrogens may be implicated in the pathophysiology of VTE among women using HRT with oral oestrogen therapy. This original finding deserves further investigations in largest and independent series of women receiving oral 17β-oestradiol as well as other oestrogens with different metabolic pathways, not only to treat postmenopausal symptoms but also for contraception. Taking into account the proportion of women using exogenous hormone therapy, these new results may have important clinical implications to improve the stratification of thrombotic risk and identify new groups at high risk.

6. Conclusion

The increasing life expectancy observed during the last century, without an equivalent change in the average age of menopause, resulted in an increased number of women facing the effects of low ovarian steroids for a longer period of time. Thus, the high interest towards therapeutic options capable to alleviate menopausal symptoms and the extensive research in this field are not surprisingly. Despite the current controversies summarised here which encompass HRT use, further researches will likely improve therapeutic outcomes. In this context, pharmacogenetics studies play a key role in fulfilling the aim of providing patients with an individualised therapy which will reduce risks and improve benefits related to HRT.

7. References

- Amarante, F., Vilodre, L. C., Maturana, M. A. & Spritzer, P. M. (2011). Women with primary ovarian insufficiency have lower bone mineral density. *Braz J Med Biol Res*, Vol. 44, No. 1, (Jan 2011), pp. 78-83.

- Amazit, L., Roseau, A., Khan, J. A., Chauchereau, A., Tyagi, R. K., Loosfelt, H., Leclerc, P., Lombes, M. & Guiochon-Mantel, A. (2011). Ligand-dependent degradation of SRC-1 is pivotal for progesterone receptor transcriptional activity. *Mol Endocrinol*, Vol. 25, No. 3, (Mar 2011), pp. 394-408.
- Anasti, J. N., Kalantaridou, S. N., Kimzey, L. M., Defensor, R. A. & Nelson, L. M. (1998). Bone loss in young women with karyotypically normal spontaneous premature ovarian failure. *Obstet Gynecol*, Vol. 91, No. 1, (Jan 1998), pp. 12-15.
- Anderson, G. L., Limacher, M., Assaf, A. R., Bassford, T., Beresford, S. A., Black, H., Bonds, D., Brunner, R., Brzyski, R., Caan, B., Chlebowski, R., Curb, D., Gass, M., Hays, J., Heiss, G., Hendrix, S., Howard, B. V., Hsia, J., Hubbell, A., Jackson, R., Johnson, K. C., Judd, H., Kotchen, J. M., Kuller, L., LaCroix, A. Z., Lane, D., Langer, R. D., Lasser, N., Lewis, C. E., Manson, J., Margolis, K., Ockene, J., O'Sullivan, M. J., Phillips, L., Prentice, R. L., Ritenbaugh, C., Robbins, J., Rossouw, J. E., Sarto, G., Stefanick, M. L., Van Horn, L., Wactawski-Wende, J., Wallace, R. & Wassertheil-Smoller, S. (2004). Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*, Vol. 291, No. 14, (Apr 2004), pp. 1701-1712.
- Ayeni, O. & Robinson, A. (2009). Hormone replacement therapy and outcomes for women with non-small-cell lung cancer: can an association be confirmed? *Curr Oncol*, Vol. 16, No. 3, (May 2009), pp. 21-25.
- Bachelot, A., Rouxel, A., Massin, N., Dulon, J., Courtillot, C., Matuchansky, C., Badachi, Y., Fortin, A., Paniel, B., Lecuru, F., Lefrere-Belda, M. A., Constancis, E., Thibault, E., Meduri, G., Guiochon-Mantel, A., Misrahi, M., Kuttann, F. & Touraine, P. (2009). Phenotyping and genetic studies of 357 consecutive patients presenting with premature ovarian failure. *Eur J Endocrinol*, Vol. 161, No. 1, (Jul 2009), pp. 179-187.
- Beral, V. (2003). Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet*, Vol. 362, No. 9382, (Aug 2003), pp. 419-427.
- Beral, V., Bull, D., Green, J. & Reeves, G. (2007). Ovarian cancer and hormone replacement therapy in the Million Women Study. *Lancet*, Vol. 369, No. 9574, (May 2007), pp. 1703-1710.
- Bouligand, J., Cabaret, O., Canonico, M., Verstuyft, C., Dubert, L., Becquemont, L., Guiochon-Mantel, A. & Scarabin, P. Y. (2011). Effect of NFE2L2 genetic polymorphism on the association between oral estrogen therapy and the risk of venous thromboembolism in postmenopausal women. *Clin Pharmacol Ther*, Vol. 89, No. 1, (Jan 2011), pp. 60-64.
- Bouligand, J., Ghervan, C., Tello, J. A., Brailly-Tabard, S., Salenave, S., Chanson, P., Lombes, M., Millar, R. P., Guiochon-Mantel, A. & Young, J. (2009). Isolated familial hypogonadotropic hypogonadism and a GNRH1 mutation. *N Engl J Med*, Vol. 360, No. 26, (Jun 2009), pp. 2742-2748.
- Bush, T. L., Barrett-Connor, E., Cowan, L. D., Criqui, M. H., Wallace, R. B., Suchindran, C. M., Tyroler, H. A. & Rifkind, B. M. (1987). Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the Lipid Research Clinics Program Follow-up Study. *Circulation*, Vol. 75, No. 6, (Jun 1987), pp. 1102-1109.
- Caine, Y. G., Bauer, K. A., Barzegar, S., ten Cate, H., Sacks, F. M., Walsh, B. W., Schiff, I. & Rosenberg, R. D. (1992). Coagulation activation following estrogen administration to postmenopausal women. *Thromb Haemost*, Vol. 68, No. 4, (Oct 1992), pp. 392-395.

- Canonico, M., Bouaziz, E., Carcaillon, L., Verstuyft, C., Guiochon-Mantel, A., Becquemont, L. & Scarabin, P. Y. (2008). Synergism between oral estrogen therapy and cytochrome P450 3A5*1 allele on the risk of venous thromboembolism among postmenopausal women. *J Clin Endocrinol Metab*, Vol. 93, No. 8, (Aug 2008), pp. 3082-3087.
- Canonico, M., Fournier, A., Carcaillon, L., Olie, V., Plu-Bureau, G., Oger, E., Mesrine, S., Boutron-Ruault, M. C., Clavel-Chapelon, F. & Scarabin, P. Y. (2010). Postmenopausal hormone therapy and risk of idiopathic venous thromboembolism: results from the E3N cohort study. *Arterioscler Thromb Vasc Biol*, Vol. 30, No. 2, (Feb 2010), pp. 340-345.
- Canonico, M., Oger, E., Plu-Bureau, G., Conard, J., Meyer, G., Levesque, H., Trillot, N., Barrellier, M. T., Wahl, D., Emmerich, J. & Scarabin, P. Y. (2007). Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation*, Vol. 115, No. 7, (Feb 2007), pp. 840-845.
- Canonico, M., Plu-Bureau, G., Lowe, G. D. & Scarabin, P. Y. (2008). Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ*, Vol. 336, No. 7655, (May 2008), pp. 1227-1231.
- Cauley, J. A., Robbins, J., Chen, Z., Cummings, S. R., Jackson, R. D., LaCroix, A. Z., LeBoff, M., Lewis, C. E., McGowan, J., Neuner, J., Pettinger, M., Stefanick, M. L., Wactawski-Wende, J. & Watts, N. B. (2003). Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA*, Vol. 290, No. 13, (Oct 2003), pp. 1729-1738.
- Cauley, J. A., Seeley, D. G., Ensrud, K., Ettinger, B., Black, D. & Cummings, S. R. (1995). Estrogen replacement therapy and fractures in older women. Study of Osteoporotic Fractures Research Group. *Ann Intern Med*, Vol. 122, No. 1, (Jan 1995), pp. 9-16.
- Chlebowski, R. T., Anderson, G. L., Manson, J. E., Schwartz, A. G., Wakelee, H., Gass, M., Rodabough, R. J., Johnson, K. C., Wactawski-Wende, J., Kotchen, J. M., Ockene, J. K., O'Sullivan, M. J., Hubbell, F. A., Chien, J. W., Chen, C. & Stefanick, M. L. (2010). Lung cancer among postmenopausal women treated with estrogen alone in the women's health initiative randomized trial. *J Natl Cancer Inst*, Vol. 102, No. 18, (Sep 2010), pp. 1413-1421.
- Chlebowski, R. T., Schwartz, A. G., Wakelee, H., Anderson, G. L., Stefanick, M. L., Manson, J. E., Rodabough, R. J., Chien, J. W., Wactawski-Wende, J., Gass, M., Kotchen, J. M., Johnson, K. C., O'Sullivan, M. J., Ockene, J. K., Chen, C. & Hubbell, F. A. (2009). Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. *Lancet*, Vol. 374, No. 9697, (Oct 2009), pp. 1243-1251.
- Chlebowski, R. T., Wactawski-Wende, J., Ritenbaugh, C., Hubbell, F. A., Ascensao, J., Rodabough, R. J., Rosenberg, C. A., Taylor, V. M., Harris, R., Chen, C., Adams-Campbell, L. L. & White, E. (2004). Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med*, Vol. 350, No. 10, (Mar 2004), pp. 991-1004.
- Clarkson, T. B. (2007). Estrogen effects on arteries vary with stage of reproductive life and extent of subclinical atherosclerosis progression. *Menopause*, Vol. 14, No. 3 Pt 1, (May-Jun 2007), pp. 373-384.

- Clendenen, T. V., Koenig, K. L., Shore, R. E., Levitz, M., Arslan, A. A. & Zeleniuch-Jacquotte, A. (2009). Postmenopausal levels of endogenous sex hormones and risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev*, Vol. 18, No. 1, (Jan 2009), pp. 275-281.
- Coldham, N. G., Dave, M., Sivapathasundaram, S., McDonnell, D. P., Connor, C. & Sauer, M. J. (1997). Evaluation of a recombinant yeast cell estrogen screening assay. *Environ Health Perspect*, Vol. 105, No. 7, (Jul 1997), pp. 734-742.
- Colditz, G. A. (1993). Epidemiology of breast cancer. Findings from the nurses' health study. *Cancer*, Vol. 71, No. 4 Suppl, (Feb 1993), pp. 1480-1489.
- Conneely, O. M., Kettelberger, D. M., Tsai, M. J., Schrader, W. T. & O'Malley, B. W. (1989). The chicken progesterone receptor A and B isoforms are products of an alternate translation initiation event. *J Biol Chem*, Vol. 264, No. 24, (Aug 1989), pp. 14062-14064.
- Corrigan, E. C., Nelson, L. M., Bakalov, V. K., Yanovski, J. A., Vanderhoof, V. H., Yanoff, L. B. & Bondy, C. A. (2006). Effects of ovarian failure and X-chromosome deletion on body composition and insulin sensitivity in young women. *Menopause*, Vol. 13, No. 6, (Nov-Dec 2006), pp. 911-916.
- Cowley, S. M., Hoare, S., Mosselman, S. & Parker, M. G. (1997). Estrogen receptors alpha and beta form heterodimers on DNA. *J Biol Chem*, Vol. 272, No. 32, (Aug 1997), pp. 19858-19862.
- Cushman, M., Kuller, L. H., Prentice, R., Rodabough, R. J., Psaty, B. M., Stafford, R. S., Sidney, S. & Rosendaal, F. R. (2004). Estrogen plus progestin and risk of venous thrombosis. *JAMA*, Vol. 292, No. 13, (Oct 2004), pp. 1573-1580.
- Davis, S. R., Moreau, M., Kroll, R., Bouchard, C., Panay, N., Gass, M., Braunstein, G. D., Hirschberg, A. L., Rodenberg, C., Pack, S., Koch, H., Moufarege, A. & Studd, J. (2008). Testosterone for low libido in postmenopausal women not taking estrogen. *N Engl J Med*, Vol. 359, No. 19, (Nov 2008), pp. 2005-2017.
- De Lignieres, B., Basdevant, A., Thomas, G., Thalabard, J. C., Mercier-Bodard, C., Conard, J., Guyene, T. T., Mairon, N., Corvol, P., Guy-Grand, B. & et al. (1986). Biological effects of estradiol-17 beta in postmenopausal women: oral versus percutaneous administration. *J Clin Endocrinol Metab*, Vol. 62, No. 3, (Mar 1986), pp. 536-541.
- Doren, M. (2000). Hormonal replacement regimens and bleeding. *Maturitas*, Vol. 34 Suppl 1, (Jan 2000), pp. S17-23.
- Dossus, L., Allen, N., Kaaks, R., Bakken, K., Lund, E., Tjonneland, A., Olsen, A., Overvad, K., Clavel-Chapelon, F., Fournier, A., Chabbert-Buffet, N., Boeing, H., Schutze, M., Trichopoulou, A., Trichopoulos, D., Lagiou, P., Palli, D., Krogh, V., Tumino, R., Vineis, P., Mattiello, A., Bueno-de-Mesquita, H. B., Onland-Moret, N. C., Peeters, P. H., Dumeaux, V., Redondo, M. L., Duell, E., Sanchez-Cantalejo, E., Arriola, L., Chirlaque, M. D., Ardanaz, E., Manjer, J., Borgquist, S., Lukanova, A., Lundin, E., Khaw, K. T., Wareham, N., Key, T., Chajes, V., Rinaldi, S., Slimani, N., Mouw, T., Gallo, V. & Riboli, E. (2010). Reproductive risk factors and endometrial cancer: the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer*, Vol. 127, No. 2, (Jul 2010), pp. 442-451.
- Edwards, D. P. (2005). Regulation of signal transduction pathways by estrogen and progesterone. *Annu Rev Physiol*, Vol. 67, pp. 335-376.

- Eshtiaghi, R., Esteghamati, A. & Nakhjavani, M. (2010). Menopause is an independent predictor of metabolic syndrome in Iranian women. *Maturitas*, Vol. 65, No. 3, (Mar 2010), pp. 262-266.
- Farquhar, C., Marjoribanks, J., Lethaby, A., Suckling, J. A. & Lamberts, Q. (2009). Long term hormone therapy for perimenopausal and postmenopausal women. *Cochrane Database Syst Rev*, No. 2, pp. CD004143.
- Fournier, A., Fabre, A., Mesrine, S., Boutron-Ruault, M. C., Berrino, F. & Clavel-Chapelon, F. (2008). Use of different postmenopausal hormone therapies and risk of histology- and hormone receptor-defined invasive breast cancer. *J Clin Oncol*, Vol. 26, No. 8, (Mar 2008), pp. 1260-1268.
- Gallagher, J. C. (2007). Effect of early menopause on bone mineral density and fractures. *Menopause*, Vol. 14, No. 3 Pt 2, (May-Jun 2007), pp. 567-571.
- Gallagher, J. C., Baylink, D. J., Freeman, R. & McClung, M. (2001). Prevention of bone loss with tibolone in postmenopausal women: results of two randomized, double-blind, placebo-controlled, dose-finding studies. *J Clin Endocrinol Metab*, Vol. 86, No. 10, (Oct 2001), pp. 4717-4726.
- Greiser, C. M., Greiser, E. M. & Doren, M. (2005). Menopausal hormone therapy and risk of breast cancer: a meta-analysis of epidemiological studies and randomized controlled trials. *Hum Reprod Update*, Vol. 11, No. 6, (Nov-Dec 2005), pp. 561-573.
- Grodstein, F., Clarkson, T. B. & Manson, J. E. (2003). Understanding the divergent data on postmenopausal hormone therapy. *N Engl J Med*, Vol. 348, No. 7, (Feb 2003), pp. 645-650.
- Grodstein, F., Newcomb, P. A. & Stampfer, M. J. (1999). Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. *Am J Med*, Vol. 106, No. 5, (May 1999), pp. 574-582.
- Grodstein, F., Stampfer, M. J., Colditz, G. A., Willett, W. C., Manson, J. E., Joffe, M., Rosner, B., Fuchs, C., Hankinson, S. E., Hunter, D. J., Hennekens, C. H. & Speizer, F. E. (1997). Postmenopausal hormone therapy and mortality. *N Engl J Med*, Vol. 336, No. 25, (Jun 1997), pp. 1769-1775.
- Grodstein, F., Stampfer, M. J., Falkeborn, M., Naessen, T. & Persson, I. (1999). Postmenopausal hormone therapy and risk of cardiovascular disease and hip fracture in a cohort of Swedish women. *Epidemiology*, Vol. 10, No. 5, (Sep 1999), pp. 476-480.
- Guiochon-Mantel, A., Loosfelt, H., Lescop, P., Sar, S., Atger, M., Perrot-Appianat, M. & Milgrom, E. (1989). Mechanisms of nuclear localization of the progesterone receptor: evidence for interaction between monomers. *Cell*, Vol. 57, No. 7, (Jun 1989), pp. 1147-1154.
- Guyton, A. C. & Hall, J. E. (c2006). *Textbook of medical physiology*, Elsevier Saunders, 0721602401, Philadelphia.
- Hammes, S. R. & Levin, E. R. (2007). Extranuclear steroid receptors: nature and actions. *Endocr Rev*, Vol. 28, No. 7, (Dec 2007), pp. 726-741.
- Harman, S. M., Brinton, E. A., Cedars, M., Lobo, R., Manson, J. E., Merriam, G. R., Miller, V. M., Naftolin, F. & Santoro, N. (2005). KEEPS: The Kronos Early Estrogen Prevention Study. *Climacteric*, Vol. 8, No. 1, (Mar 2005), pp. 3-12.
- Hemelaar, M., Rosing, J., Kenemans, P., Thomassen, M. C., Braat, D. D. & van der Mooren, M. J. (2006). Less effect of intranasal than oral hormone therapy on factors

- associated with venous thrombosis risk in healthy postmenopausal women. *Arterioscler Thromb Vasc Biol*, Vol. 26, No. 7, (Jul 2006), pp. 1660-1666.
- Hersh, A. L., Stefanick, M. L. & Stafford, R. S. (2004). National use of postmenopausal hormone therapy: annual trends and response to recent evidence. *JAMA*, Vol. 291, No. 1, (Jan 2004), pp. 47-53.
- Hildebrand, J. S., Gapstur, S. M., Feigelson, H. S., Teras, L. R., Thun, M. J. & Patel, A. V. (2010). Postmenopausal hormone use and incident ovarian cancer: Associations differ by regimen. *Int J Cancer*, Vol. 127, No. 12, (Dec 2010), pp. 2928-2935.
- Huckaby, C. S., Conneely, O. M., Beattie, W. G., Dobson, A. D., Tsai, M. J. & O'Malley, B. W. (1987). Structure of the chromosomal chicken progesterone receptor gene. *Proc Natl Acad Sci U S A*, Vol. 84, No. 23, (Dec 1987), pp. 8380-8384.
- Hulka, B. S. & Moorman, P. G. (2008). Breast cancer: hormones and other risk factors. *Maturitas*, Vol. 61, No. 1-2, (Sep-Oct 2008), pp. 203-213; discussion 213.
- Hulley, S., Grady, D., Bush, T., Furberg, C., Herrington, D., Riggs, B. & Vittinghoff, E. (1998). Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA*, Vol. 280, No. 7, (Aug 1998), pp. 605-613.
- Jaakkola, S., Lyytinen, H. K., Dyba, T., Ylikorkala, O. & Pukkala, E. (2011). Endometrial cancer associated with various forms of postmenopausal hormone therapy: a case control study. *Int J Cancer*, Vol. 128, No. 7, (Apr 2011), pp. 1644-1651.
- Jackson, R. D., Wactawski-Wende, J., LaCroix, A. Z., Pettinger, M., Yood, R. A., Watts, N. B., Robbins, J. A., Lewis, C. E., Beresford, S. A., Ko, M. G., Naughton, M. J., Satterfield, S. & Bassford, T. (2006). Effects of conjugated equine estrogen on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the women's health initiative randomized trial. *J Bone Miner Res*, Vol. 21, No. 6, (Jun 2006), pp. 817-828.
- Kalantaridou, S. N., Naka, K. K., Papanikolaou, E., Kazakos, N., Kravariti, M., Calis, K. A., Paraskevaïdis, E. A., Sideris, D. A., Tsatsoulis, A., Chrousos, G. P. & Michalis, L. K. (2004). Impaired endothelial function in young women with premature ovarian failure: normalization with hormone therapy. *J Clin Endocrinol Metab*, Vol. 89, No. 8, (Aug 2004), pp. 3907-3913.
- Karim, R., Dell, R. M., Greene, D. F., Mack, W. J., Gallagher, J. C. & Hodis, H. N. (2011). Hip fracture in postmenopausal women after cessation of hormone therapy: results from a prospective study in a large health management organization. *Menopause*, (Jul 2011).
- Kastner, P., Krust, A., Turcotte, B., Stropp, U., Tora, L., Gronemeyer, H. & Chambon, P. (1990). Two distinct estrogen-regulated promoters generate transcripts encoding the two functionally different human progesterone receptor forms A and B. *EMBO J*, Vol. 9, No. 5, (May 1990), pp. 1603-1614.
- Kelsey, J. L. & Bernstein, L. (1996). Epidemiology and prevention of breast cancer. *Annu Rev Public Health*, Vol. 17, pp. 47-67.
- Khan, J. A., Amazit, L., Bellance, C., Guiochon-Mantel, A., Lombes, M. & Loosfelt, H. (2011). p38 and p42/44 MAPKs Differentially Regulate Progesterone Receptor A and B Isoform Stabilization. *Mol Endocrinol*, (Aug 2011).doi:10.1210/me.2011-1042

- Kiel, D. P., Felson, D. T., Anderson, J. J., Wilson, P. W. & Moskowitz, M. A. (1987). Hip fracture and the use of estrogens in postmenopausal women. The Framingham Study. *N Engl J Med*, Vol. 317, No. 19, (Nov 1987), pp. 1169-1174.
- Knauff, E. A., Westerveld, H. E., Goverde, A. J., Eijkemans, M. J., Valkenburg, O., van Santbrink, E. J., Fauser, B. C. & van der Schouw, Y. T. (2008). Lipid profile of women with premature ovarian failure. *Menopause*, Vol. 15, No. 5, (Sep-Oct 2008), pp. 919-923.
- Kopper, N. W., Gudeman, J. & Thompson, D. J. (2009). Transdermal hormone therapy in postmenopausal women: a review of metabolic effects and drug delivery technologies. *Drug Des Devel Ther*, Vol. 2, pp. 193-202.
- Kuhl, H. (2005). Pharmacology of estrogens and progestogens: influence of different routes of administration. *Climacteric*, Vol. 8 Suppl 1, (Aug 2005), pp. 3-63.
- Kuiper, G. G., Enmark, E., Peltö-Huikko, M., Nilsson, S. & Gustafsson, J. A. (1996). Cloning of a novel receptor expressed in rat prostate and ovary. *Proc Natl Acad Sci U S A*, Vol. 93, No. 12, (Jun 1996), pp. 5925-5930.
- Lagro-Janssen, A., Knufing, M. W., Schreurs, L. & van Weel, C. (2010). Significant fall in hormone replacement therapy prescription in general practice. *Fam Pract*, Vol. 27, No. 4, (Aug 2010), pp. 424-429.
- Lazovic, G., Radivojevic, U. & Marinkovic, J. (2008). Tibolone: the way to beat many a postmenopausal ailments. *Expert Opin Pharmacother*, Vol. 9, No. 6, (Apr 2008), pp. 1039-1047.
- Leonhardt, S. A., Altmann, M. & Edwards, D. P. (1998). Agonist and antagonists induce homodimerization and mixed ligand heterodimerization of human progesterone receptors in vivo by a mammalian two-hybrid assay. *Mol Endocrinol*, Vol. 12, No. 12, (Dec 1998), pp. 1914-1930.
- Levin, E. R. (2011). Minireview: Extranuclear steroid receptors: roles in modulation of cell functions. *Mol Endocrinol*, Vol. 25, No. 3, (Mar 2011), pp. 377-384.
- Lindsay, R., Gallagher, J. C., Kleerekoper, M. & Pickar, J. H. (2005). Bone response to treatment with lower doses of conjugated estrogens with and without medroxyprogesterone acetate in early postmenopausal women. *Osteoporos Int*, Vol. 16, No. 4, (Apr 2005), pp. 372-379.
- Loosfelt, H., Atger, M., Misrahi, M., Guiochon-Mantel, A., Meriel, C., Logeat, F., Benarous, R. & Milgrom, E. (1986). Cloning and sequence analysis of rabbit progesterone-receptor complementary DNA. *Proc Natl Acad Sci U S A*, Vol. 83, No. 23, (Dec 1986), pp. 9045-9049.
- Losel, R. & Wehling, M. (2003). Nongenomic actions of steroid hormones. *Nat Rev Mol Cell Biol*, Vol. 4, No. 1, (Jan 2003), pp. 46-56.
- Maclaran, K., Horner, E. & Panay, N. (2010). Premature ovarian failure: long-term sequelae. *Menopause Int*, Vol. 16, No. 1, (Mar 2010), pp. 38-41.
- Maclaran, K. & Panay, N. (2011). Premature ovarian failure. *J Fam Plann Reprod Health Care*, Vol. 37, No. 1, (Jan 2011), pp. 35-42.
- MacLennan, A. H., Taylor, A. W. & Wilson, D. H. (2004). Hormone therapy use after the Women's Health Initiative. *Climacteric*, Vol. 7, No. 2, (Jun 2004), pp. 138-142.
- Madak-Erdogan, Z., Kieser, K. J., Kim, S. H., Komm, B., Katzenellenbogen, J. A. & Katzenellenbogen, B. S. (2008). Nuclear and extranuclear pathway inputs in the

- regulation of global gene expression by estrogen receptors. *Mol Endocrinol*, Vol. 22, No. 9, (Sep 2008), pp. 2116-2127.
- Marzec, J. M., Christie, J. D., Reddy, S. P., Jedlicka, A. E., Vuong, H., Lancken, P. N., Aplenc, R., Yamamoto, T., Yamamoto, M., Cho, H. Y. & Kleeberger, S. R. (2007). Functional polymorphisms in the transcription factor NRF2 in humans increase the risk of acute lung injury. *FASEB J*, Vol. 21, No. 9, (Jul 2007), pp. 2237-2246.
- McPherson, C. P., Sellers, T. A., Potter, J. D., Bostick, R. M. & Folsom, A. R. (1996). Reproductive factors and risk of endometrial cancer. The Iowa Women's Health Study. *Am J Epidemiol*, Vol. 143, No. 12, (Jun 1996), pp. 1195-1202.
- Morch, L. S., Lokkegaard, E., Andreasen, A. H., Kruger-Kjaer, S. & Lidegaard, O. (2009). Hormone therapy and ovarian cancer. *JAMA*, Vol. 302, No. 3, (Jul 2009), pp. 298-305.
- Nelson, L. M., Covington, S. N. & Rebar, R. W. (2005). An update: spontaneous premature ovarian failure is not an early menopause. *Fertil Steril*, Vol. 83, No. 5, (May 2005), pp. 1327-1332.
- North American Menopause Society. Estrogen and progestogen use in postmenopausal women: 2010 position statement of The North American Menopause Society. (2010). *Menopause*, Vol. 17, No. 2, (Mar 2010), pp. 242-255.
- O'Connell, M. B. (1995). Pharmacokinetic and pharmacologic variation between different estrogen products. *J Clin Pharmacol*, Vol. 35, No. 9 Suppl, (Sep 1995), pp. 18S-24S.
- Oger, E., Alhenc-Gelas, M., Lacut, K., Blouch, M. T., Roudaut, N., Kerlan, V., Collet, M., Abgrall, J. F., Aiach, M., Scarabin, P. Y. & Mottier, D. (2003). Differential effects of oral and transdermal estrogen/progesterone regimens on sensitivity to activated protein C among postmenopausal women: a randomized trial. *Arterioscler Thromb Vasc Biol*, Vol. 23, No. 9, (Sep 2003), pp. 1671-1676.
- Olie, V., Canonico, M. & Scarabin, P. Y. (2010). Risk of venous thrombosis with oral versus transdermal estrogen therapy among postmenopausal women. *Curr Opin Hematol*, Vol. 17, No. 5, (Sep 2010), pp. 457-463.
- Panay, N. & Fenton, A. (2008). Premature ovarian failure: a growing concern. *Climacteric*, Vol. 11, No. 1, (Feb 2008), pp. 1-3.
- Panay, N. & Kalu, E. (2009). Management of premature ovarian failure. *Best Pract Res Clin Obstet Gynaecol*, Vol. 23, No. 1, (Feb 2009), pp. 129-140.
- Picard, D., Kumar, V., Chambon, P. & Yamamoto, K. R. (1990). Signal transduction by steroid hormones: nuclear localization is differentially regulated in estrogen and glucocorticoid receptors. *Cell Regul*, Vol. 1, No. 3, (Feb 1990), pp. 291-299.
- Powers, M. S., Schenkel, L., Darley, P. E., Good, W. R., Balestra, J. C. & Place, V. A. (1985). Pharmacokinetics and pharmacodynamics of transdermal dosage forms of 17 beta-estradiol: comparison with conventional oral estrogens used for hormone replacement. *Am J Obstet Gynecol*, Vol. 152, No. 8, (Aug 1985), pp. 1099-1106.
- Pratt, W. B. & Toft, D. O. (1997). Steroid receptor interactions with heat shock protein and immunophilin chaperones. *Endocr Rev*, Vol. 18, No. 3, (Jun 1997), pp. 306-360.
- Prentice, R. L., Manson, J. E., Langer, R. D., Anderson, G. L., Pettinger, M., Jackson, R. D., Johnson, K. C., Kuller, L. H., Lane, D. S., Wactawski-Wende, J., Brzyski, R., Allison, M., Ockene, J., Sarto, G. & Rossouw, J. E. (2009). Benefits and risks of postmenopausal hormone therapy when it is initiated soon after menopause. *Am J Epidemiol*, Vol. 170, No. 1, (Jul 2009), pp. 12-23.

- Raftogianis, R., Creveling, C., Weinshilboum, R. & Weisz, J. (2000). Estrogen metabolism by conjugation. *J Natl Cancer Inst Monogr*, No. 27, pp. 113-124.
- Ritenbaugh, C., Stanford, J. L., Wu, L., Shikany, J. M., Schoen, R. E., Stefanick, M. L., Taylor, V., Garland, C., Frank, G., Lane, D., Mason, E., McNeeley, S. G., Ascensao, J. & Chlebowski, R. T. (2008). Conjugated equine estrogens and colorectal cancer incidence and survival: the Women's Health Initiative randomized clinical trial. *Cancer Epidemiol Biomarkers Prev*, Vol. 17, No. 10, (Oct 2008), pp. 2609-2618.
- Rocca, W. A., Bower, J. H., Maraganore, D. M., Ahlskog, J. E., Grossardt, B. R., de Andrade, M. & Melton, L. J., 3rd. (2007). Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. *Neurology*, Vol. 69, No. 11, (Sep 2007), pp. 1074-1083.
- Rocca, W. A., Bower, J. H., Maraganore, D. M., Ahlskog, J. E., Grossardt, B. R., de Andrade, M. & Melton, L. J., 3rd. (2008). Increased risk of parkinsonism in women who underwent oophorectomy before menopause. *Neurology*, Vol. 70, No. 3, (Jan 2008), pp. 200-209.
- Rodriguez, C., Spencer Feigelson, H., Deka, A., Patel, A. V., Jacobs, E. J., Thun, M. J. & Calle, E. E. (2008). Postmenopausal hormone therapy and lung cancer risk in the cancer prevention study II nutrition cohort. *Cancer Epidemiol Biomarkers Prev*, Vol. 17, No. 3, (Mar 2008), pp. 655-660.
- Rosenfeld, M. G. & Glass, C. K. (2001). Coregulator codes of transcriptional regulation by nuclear receptors. *J Biol Chem*, Vol. 276, No. 40, (Oct 2001), pp. 36865-36868.
- Rossouw, J. E., Anderson, G. L., Prentice, R. L., LaCroix, A. Z., Kooperberg, C., Stefanick, M. L., Jackson, R. D., Beresford, S. A., Howard, B. V., Johnson, K. C., Kotchen, J. M. & Ockene, J. (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA*, Vol. 288, No. 3, (Jul 2002), pp. 321-333.
- Rossouw, J. E., Prentice, R. L., Manson, J. E., Wu, L., Barad, D., Barnabei, V. M., Ko, M., LaCroix, A. Z., Margolis, K. L. & Stefanick, M. L. (2007). Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA*, Vol. 297, No. 13, (Apr 2007), pp. 1465-1477.
- Salpeter, S. R., Walsh, J. M., Greyber, E. & Salpeter, E. E. (2006). Brief report: Coronary heart disease events associated with hormone therapy in younger and older women. A meta-analysis. *J Gen Intern Med*, Vol. 21, No. 4, (Apr 2006), pp. 363-366.
- Santen, R. J., Allred, D. C., Ardoin, S. P., Archer, D. F., Boyd, N., Braunstein, G. D., Burger, H. G., Codditt, G. A., Davis, S. R., Gambacciani, M., Gower, B. A., Henderson, V. W., Jarjour, W. N., Karas, R. H., Kleerekoper, M., Lobo, R. A., Manson, J. E., Marsden, J., Martin, K. A., Martin, L., Pinkerton, J. V., Rubinow, D. R., Teede, H., Thiboutot, D. M. & Utian, W. H. (2010). Postmenopausal hormone therapy: an Endocrine Society scientific statement. *J Clin Endocrinol Metab*, Vol. 95, No. 7 Suppl 1, (Jul 2010), pp. s1-s66.
- Scarabin, P. Y., Alhenc-Gelas, M., Plu-Bureau, G., Taisne, P., Agher, R. & Aiach, M. (1997). Effects of oral and transdermal estrogen/progesterone regimens on blood coagulation and fibrinolysis in postmenopausal women. A randomized controlled trial. *Arterioscler Thromb Vasc Biol*, Vol. 17, No. 11, (Nov 1997), pp. 3071-3078.
- Scarabin, P. Y., Hemker, H. C., Clement, C., Soisson, V. & Alhenc-Gelas, M. (2011). Increased thrombin generation among postmenopausal women using hormone therapy:

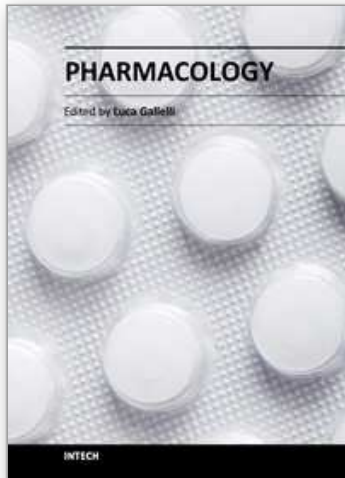
- importance of the route of estrogen administration and progestogens. *Menopause*, Vol. 18, No. 8, (Aug 2011), pp. 873-879.
- Scarabin, P. Y., Oger, E. & Plu-Bureau, G. (2003). Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet*, Vol. 362, No. 9382, (Aug 2003), pp. 428-432.
- Shuster, L. T., Rhodes, D. J., Gostout, B. S., Grossardt, B. R. & Rocca, W. A. (2010). Premature menopause or early menopause: long-term health consequences. *Maturitas*, Vol. 65, No. 2, (Feb 2010), pp. 161-166.
- Simon, T., Beau Yon de Jonage-Canonica, M., Oger, E., Wahl, D., Conard, J., Meyer, G., Emmerich, J., Barrellier, M. T., Guiraud, A. & Scarabin, P. Y. (2006). Indicators of lifetime endogenous estrogen exposure and risk of venous thromboembolism. *J Thromb Haemost*, Vol. 4, No. 1, (Jan 2006), pp. 71-76.
- Snowdon, D. A., Kane, R. L., Beeson, W. L., Burke, G. L., Sprafka, J. M., Potter, J., Iso, H., Jacobs, D. R., Jr. & Phillips, R. L. (1989). Is early natural menopause a biologic marker of health and aging? *Am J Public Health*, Vol. 79, No. 6, (Jun 1989), pp. 709-714.
- Sonnet, E., Lacut, K., Roudaut, N., Mottier, D., Kerlan, V. & Oger, E. (2007). Effects of the route of oestrogen administration on IGF-1 and IGFBP-3 in healthy postmenopausal women: results from a randomized placebo-controlled study. *Clin Endocrinol (Oxf)*, Vol. 66, No. 5, (May 2007), pp. 626-631.
- Stampfer, M. J., Colditz, G. A., Willett, W. C., Manson, J. E., Rosner, B., Speizer, F. E. & Hennekens, C. H. (1991). Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the nurses' health study. *N Engl J Med*, Vol. 325, No. 11, (Sep 1991), pp. 756-762.
- Steingold, K. A., Laufer, L., Chetkowski, R. J., DeFazio, J. D., Matt, D. W., Meldrum, D. R. & Judd, H. L. (1985). Treatment of hot flashes with transdermal estradiol administration. *J Clin Endocrinol Metab*, Vol. 61, No. 4, (Oct 1985), pp. 627-632.
- Straczek, C., Oger, E., Yon de Jonage-Canonica, M. B., Plu-Bureau, G., Conard, J., Meyer, G., Alhenc-Gelas, M., Levesque, H., Trillot, N., Barrellier, M. T., Wahl, D., Emmerich, J. & Scarabin, P. Y. (2005). Prothrombotic mutations, hormone therapy, and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration. *Circulation*, Vol. 112, No. 22, (Nov 2005), pp. 3495-3500.
- Sturdee, D. W., Pines, A., Archer, D. F., Baber, R. J., Barlow, D., Birkhauser, M. H., Brincat, M., Cardozo, L., de Villiers, T. J., Gambacciani, M., Gompel, A. A., Henderson, V. W., Kluff, C., Lobo, R. A., MacLennan, A. H., Marsden, J., Nappi, R. E., Panay, N., Pickar, J. H., Robinson, D., Simon, J., Sitruk-Ware, R. L. & Stevenson, J. C. (2011). Updated IMS recommendations on postmenopausal hormone therapy and preventive strategies for midlife health. *Climacteric*, Vol. 14, No. 3, (Jun 2011), pp. 302-320.
- Swanson, S. G., Drosman, S., Helmond, F. A. & Stathopoulos, V. M. (2006). Tibolone for the treatment of moderate to severe vasomotor symptoms and genital atrophy in postmenopausal women: a multicenter, randomized, double-blind, placebo-controlled study. *Menopause*, Vol. 13, No. 6, (Nov-Dec 2006), pp. 917-925.
- Taylor, H. S. & Manson, J. E. (2011). Update in hormone therapy use in menopause. *J Clin Endocrinol Metab*, Vol. 96, No. 2, (Feb 2011), pp. 255-264.

- Thimmulappa, R. K., Mai, K. H., Srisuma, S., Kensler, T. W., Yamamoto, M. & Biswal, S. (2002). Identification of Nrf2-regulated genes induced by the chemopreventive agent sulforaphane by oligonucleotide microarray. *Cancer Res*, Vol. 62, No. 18, (Sep 2002), pp. 5196-5203.
- Uygur, D., Sengul, O., Bayar, D., Erdinc, S., Batioglu, S. & Mollamahmutoglu, L. (2005). Bone loss in young women with premature ovarian failure. *Arch Gynecol Obstet*, Vol. 273, No. 1, (Nov 2005), pp. 17-19.
- Van den Belt, K., Berckmans, P., Vangenechten, C., Verheyen, R. & Witters, H. (2004). Comparative study on the in vitro/in vivo estrogenic potencies of 17beta-estradiol, estrone, 17alpha-ethynylestradiol and nonylphenol. *Aquat Toxicol*, Vol. 66, No. 2, (Feb 2004), pp. 183-195.
- van Der Voort, D. J., van Der Weijer, P. H. & Barentsen, R. (2003). Early menopause: increased fracture risk at older age. *Osteoporos Int*, Vol. 14, No. 6, (Jul 2003), pp. 525-530.
- Vehkavaara, S., Silveira, A., Hakala-Ala-Pietila, T., Virkamaki, A., Hovatta, O., Hamsten, A., Taskinen, M. R. & Yki-Jarvinen, H. (2001). Effects of oral and transdermal estrogen replacement therapy on markers of coagulation, fibrinolysis, inflammation and serum lipids and lipoproteins in postmenopausal women. *Thromb Haemost*, Vol. 85, No. 4, (Apr 2001), pp. 619-625.
- Vickers, M. R., MacLennan, A. H., Lawton, B., Ford, D., Martin, J., Meredith, S. K., DeStavola, B. L., Rose, S., Dowell, A., Wilkes, H. C., Darbyshire, J. H. & Meade, T. W. (2007). Main morbidities recorded in the women's international study of long duration oestrogen after menopause (WISDOM): a randomised controlled trial of hormone replacement therapy in postmenopausal women. *BMJ*, Vol. 335, No. 7613, (Aug 2007), pp. 239.
- Vujovic, S., Brincat, M., Erel, T., Gambacciani, M., Lambrinoudaki, I., Moen, M. H., Schenck-Gustafsson, K., Tremollieres, F., Rozenberg, S. & Rees, M. (2010). EMAS position statement: Managing women with premature ovarian failure. *Maturitas*, Vol. 67, No. 1, (Sep 2010), pp. 91-93.
- Walter, P., Green, S., Greene, G., Krust, A., Bornert, J. M., Jeltsch, J. M., Staub, A., Jensen, E., Scrace, G., Waterfield, M. & et al. (1985). Cloning of the human estrogen receptor cDNA. *Proc Natl Acad Sci U S A*, Vol. 82, No. 23, (Dec 1985), pp. 7889-7893.
- Welshons, W. V., Krummel, B. M. & Gorski, J. (1985). Nuclear localization of unoccupied receptors for glucocorticoids, estrogens, and progesterone in GH3 cells. *Endocrinology*, Vol. 117, No. 5, (Nov 1985), pp. 2140-2147.
- Wendler, A., Baldi, E., Harvey, B. J., Nadal, A., Norman, A. & Wehling, M. (2010). Position paper: Rapid responses to steroids: current status and future prospects. *Eur J Endocrinol*, Vol. 162, No. 5, (May 2010), pp. 825-830.
- WHO Report. Research on the menopause in the 1990s. Report of a WHO Scientific Group. (1996). *World Health Organ Tech Rep Ser*, Vol. 866, pp. 1-107.
- Wilson, R. A. ([1966]). *Feminine forever*, M. Evans; distributed in association with Lippincott, New York.
- Yaffe, K., Barnes, D., Lindquist, K., Cauley, J., Simonsick, E. M., Penninx, B., Satterfield, S., Harris, T. & Cummings, S. R. (2007). Endogenous sex hormone levels and risk of cognitive decline in an older biracial cohort. *Neurobiol Aging*, Vol. 28, No. 2, (Feb 2007), pp. 171-178.

- Ylikorkala, O. & Rozenberg, S. (2000). Efficacy and tolerability of fully transdermal hormone replacement in sequential or continuous therapy at two doses of progestogen in postmenopausal women. *Maturitas*, Vol. 37, No. 2, (Dec 2000), pp. 83-93.
- Zervoudakis, A., Strickler, H. D., Park, Y., Xue, X., Hollenbeck, A., Schatzkin, A. & Gunter, M. J. (2011). Reproductive history and risk of colorectal cancer in postmenopausal women. *J Natl Cancer Inst*, Vol. 103, No. 10, (May 2011), pp. 826-834.

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