Progestins and Their Use in Menopause

PROGESTİNLER VE MENAPOZDA KULLANIMLARI

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Summary

Compliance is among the major concerns of hormone replacement therapy, likely to be effected by progesterone component. In this paper, the properties of currently applied progesterones in hormone replacement therapy regimens and the effects of progesterones on different body systems were reviewed.

Key Words: Hormone replacement therapy, Progesterone

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Özet

Hormon replasman tedavisi uygulanacak hastalarda tedavi uyumu, progesteron komponentinin de etki edebileceği önemli bir problem olarak karşımızda durmaktadır. Bu makalede, hormon replasman tedavi rejimlerinde uygulanan progesteronların özellikleri ve bu progesteronların farklı organ sistemleri üzerindeki etkileri gözden geçirilmiştir.

Anahtar Kelimeler: Hormon replasman tedavisi, Progesteron

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With increasing life expectancy, more women are estimated to enter menopause during the next years. Even though these women have been well informed and are more sensitive about the risks of this inevitable clinical consequence, they still constitute a major challenge to the health care system. Short term benefits such as alleviation of hot flushes were the major consideration to initiate hormone replacement therapy (HRT) in the past, but it is now well established that it has obvious beneficial effects on skeletal system, cardiovascular system and genital system.

Since estrogen and progestin receptors were identified in almost every organ of the body, it is wise to consider that HRT would reverse adverse effects associated with menopause. The major concern about adding progestins to estrogens in HRT regimens, is the suspicion of impairing beneficial effects provided by estrogens alone, especially of those related with cardiovascular system (1). Additionally compliance is a grave challenge with HRT use which was found to be around 50% after 1 year (2). Do progestins change compliance with HRT because of associating adverse effects?

In this paper recent literature was reviewed about the potential benefits and risks of progestins in HRT regimens.

Types of Progestins Used in HRT Regimens and Progestin Receptors

Since, oral absorption of natural progesterone is weak, synthetic compounds were developed. Basically progestins are divided into two groups (Table 1); those containing 21 carbon atoms are primarily used in HRT and for chemotherapy, whereas progestins containing 19 carbon atoms are used in oral contraception. Micronized progesterones are recently manufactured and has an increased rate of intestinal absorption mostly related with smaller particle diameter.

Primarily 3 types of progestins are used in HRT. Medroxyprogesterone acetate (MPA) has been the most widely used progestin that contains 21 carbon atoms. Oral micronized progestins are recently in use, but its absorption may be effected by food intake, diameter of the particle and by the type of the capsule (3). The most potent progestin is the norethisterone which contains 19 carbon atoms. 1mg of norethisterone is usually sufficient to induce secretory changes in the endometrium, but higher doses were frequently found to be associated with an increase in LDL cholesterol level. Norgestrel, desogestrel, gestoden and levenorgestrel are classified in the gonan group and are primarily used in the oral contraceptives.

Table 1. Classification of progestins

21 C	19 C
Progesterone	Norethisterone (norethindrone)
Medroxyprogesterone acetate	Norethynodrel
Megestrol acetate	Ethinylestrenol (lynestrenol)
Promegestone	Levo-norgestrel
Chlormadinone acetate	Desogestrel
Dydrogesterone	Norgestimate
Medrogestone	Gestodene
Cyproterone acetate	Norgestrel
	Ethynodiol acetate

Table 2. Tissue distribution of the progesterone receptors

Tissue type	Cell
Reproductive tissues	
Uterus	Myometrium, endometrial stroma and gland
Ovary	Granulosa, luteinized granulosa, corpus luteum
Mammary gland	Normal and neoplastic
Bone	Osteoclastic ve osteoblastic cells
Brain	Ventromedial nucleus, hypothalamus, preoptic area
Other	Pituitary gland, thymus, pancreatic islet cells, lungs, liver

Progestins may be used as orally, intramuscularly, intravaginally, transdermally or intranasally. If transdermal route is considered to be implemented, then potent progestins should be chosen.

Although progesterone receptors have been identified in almost every organ, since progesterone receptors are induced by estrogen, it seems to be complicated to isolate progesterone mediated events in the cell. In Table 2, the distribution of the progesterone receptors are presented.

The Effects of Progestins on Cardiovascular System

Coronary heart disease (CHD) is the leading cause of death in women after the age 50 and it comprises almost all of deaths in menopause (4). It was demonstrated in the clinical studies that hormone replacement therapy (HRT) may reduce the risk of coronary heart disease in postmenopausal women (5,6). Although progestins are generally included in the HRT regimens with an intent to reduce neoplastic changes in the endometrium, the beneficial cardiovascular effects of HRT are thought to be mediated predominantly by the estrogen component.

The major concern is the impairment of beneficial effects by adding progestins to the regimen, principally by impairing lipid profile. It goes without saying that, estrogens have positive effects on lipid profile by decreasing LDL-Cholesterol levels and increasing HDL-Cholesterol levels. In contrast to the classical opinion, there are contrary reports about effects of HRT on CHD. The Heart and Estrogen/Progestin Replacement Study (HERS) was the first randomised, double-blind, placebo-controlled study which evaluates the outcome of hormone replacement therapy (HRT) on subsequent cardiac events in postmenopausal women with established coronary heart disease (CHD) (7). The results were surprising which revealed that both groups had experienced similar rates of nonfatal myocardial infarction or death from CHD. This occurred despite a net 11% reduction in low density lipoprotein (LDL) and a net 10% increase in high density lipoprotein (HDL) after 1 year of follow-up. In a randomized large study, "Postmenopausal Estrogen/ Progestin Interventions (PEPI)", conjugated equine estrogens (CEE) with a daily dose of 0.625 mg in combination with cyclic or continue MPA or with cyclic micronized progesterone all will end up with a decrease in LDL-C levels and increase in HDL-C levels (8). In the MPA group, the increase in HDL-C levels was not as clear as of the other groups, but in spite of this HDL increase was more prominent than the placebo group. Interestingly, micronized progesterones did not alter cardioprotective effect of estrogens, in contrast to MPA. In a very recent study the effects of hormone replacement therapy on plasma lipids in type II diabetes mellitus was investigated and it was demonstrated that addition of MPA 5 mg daily abolished the increase in HDL-C level (9). Conversely Alwers and associates demonstrated that, positive effect of estrogens on was not seem to be adversely affected by progestins derived from pregnanes. Nortestosterone-derived progestins are more likely to reduce HDL-C levels than 21-C derived progesterones (10). In contrast, Tremolliers et al. reported that promegestone, a 19-derived progesterone with low androgenic activity did not impair lipid profile (11).

The effects of levonorgestrel coated IUD on lipid profile has also been investigated. The only significant harmful effect observed was a transient decrease in HDL-cholesterol in patients using levonorgestrel-IUD at 6 months (12).

As a result, evidence from recent studies suggests probability of existence of a negative effect on the lipid profile by adding MPA to estrogens and recommendation of micronized progesterones for those having known cardiovascular risk factors.

Cardioprotection afforded by HRT is not only results from a beneficial alteration in the lipid profile. There are complementary mechanisms exist. Plasminogen activator type I (PAI-1) is an inhibitor of fibrinolysis and may be used as a marker for cardiovascular risk. CEE alone or in

combination with MPA 2.5mg/day was demonstrated to effectively reduce circulating PAI-1 levels (13). Medroxyprogesterone acetate (MPA) was demonstrated to significantly inhibit platelet aggregation and ATP release which may contribute to the cardioprotective effect of HRT (14). Estrogens also directly effect smooth muscles of the arterial wall with a net effect of arterial vasodilatation and increased perfusion which was demonstrated not to be impaired by adding levanorgestrel (15). In respect to effect of HRT on blood pressure, estrogens with MPA 5 mg/day in comparison to estrogens alone lower blood pressure and basal vascular resistance in a similar rate (16). With an effort to bring the antioxidant activities of HRT to light, MPA was also shown to reduce peroxidase function in estrogen primed individuals to a further extent (17). Additionally estrogen and estrogen/progestin replacement therapy have been suggested to lower plasma homocysteine levels in postmenopausal women (18).

The Effects of Progestins on Bone

Osteoporosis is associated with changes in bone remodeling process that is characterized by an excessive bone resorption exceeding bone formation. The decrease in bone mineral density is about 3% per year in the first 5 years of the menopause. Osteoporosis is described when mineral density is below the 2.5 standard deviation of young adults. The fractures associated with osteoporosis include vertebra, humerus, distal forearm and hips and mortality rates in patients hospitalized for hip fractures reach up to 30%.

Evidence from clinical and animal studies suggest that progesterones might have direct effect on bone. Estrogen receptors were identified in rat osteoblasts and progesterone induction of nuclear binding of estrogens in osteoblasts was also reported (19). In bone culture systems, through mechanisms including mediation of local factors such as insulin like growth factor and skeletal growth factor, progesterone was demonstrated to stimulate cellular proliferation of osteoblasts in a dose dependent manner (20).

In early observational and cross sectional studies progesterones were described to act as a bone trophic hormone as decreasing bone resorption (21). The relative impact of progesterones on bone mineral density has been extensively studied. Norethisterone was demonstrated to prevent bone loss in cortical radius (22). In an another study, MPA was shown to effectively reduce the rate of bone loss in cortical areas, whereas it could not prevent bone loss in the spine that contains more trabecular bone (23). The same authors also observed that low dose combined estrogen/progestin therapy had the same effect on bone that of high dose estrogen alone, suggesting a synergistic effect afforded by progestin treatment. Miller and associates revealed that, sublingual micronized HRT favorably decreased serum and urine markers of bone metabolism, prevented bone loss, and resulted in a slight increase in spine and hip bone mineral density (24). Recker et al. put it into light that, continuous low-dose HRT with conjugated equine estrogen and oral medroxyprogesterone combined with adequate calcium and vitamin D provided a bone-sparing effect that is similar or superior to that of provided by higher-dose HRT regimens in elderly women. This combination is well tolerated by most patients (25). It is also suggested that norethindrone suffices to prevent bone loss in patients on GnRH-a therapy (26).

As a result it might be drawn from the clinical evidence that progesterones act synergistically with estrogens on bone tissue.

The Effects of Progestins on Breast Tissue

The most frequent cancer in women is breast cancer which is responsible for the second most leading cause of death among cancers after lung carcinoma. The mammary gland seems to be the only organ that is not fully developed at birth. Estrogens stimulate breast tissue via estrogen receptors.

The suspicion whether progestins increase the risk of breast carcinoma hinges on the evidence of increased mitotic activity in the breast tissue during the luteal phase of the menstrual cycle (27,28). Another hypothesis suggesting an increased risk with an early menarche, that is more ovulatory cycles, has been also considered in the etiology.

Studies conducted on human breast cancer cells revealed growth inhibition and differentiation induction actions of progesterones (29). The intense hormonal stimulation of pregnancy (both estrogen and progesterone) has no adverse impact on the course of breast cancer. Pregnancy, with its mammogenetic differentiation, results in the protection of this organ from carcinogenesis. Several studies suggest that short-term, continuous combined HRT does not increase breast cancer recurrence or mortality.

There are only two studies exist showing an enhanced risk with progesterone use, one of which have limited value because of the bias in treatment selection (30) and the other which is the only randomized prospective trial, obstructed by the limited number (31).

Since recent studies displayed an increased, decreased or constant risk, it is unlikely to make a decision to say that progesterones added to estrogens might increase or decrease breast cancer risk (4). To make a clear-cut conclusion regarding long term impacts of estrogen/progestin regimens, the results of "Women's Health Initiative Hormone Replacement Therapy Trial" should be awaited.

The Effects of Progestins On Emotional and Sexual Functions

Progestins are able to easily pass blood-brain barrier, causing potent influences on central nervous system and hypothalamus.

High doses of progesterones may trigger symptoms such as dizziness, sleeplessness and deep sleep. Progesterone-associated side effects other than central nervous system are mainly belong to MPA which includes a generalized bloating, constipation, breast pain, depression, fatigue, irritability and symptoms resembling of premenstrual syndrome. In a double-blind placebo controlled study, MPA with a dose of 10 mg/day during the last 14 days with transdermal estrogens did not have any adverse effect on physiological or psychological well being (32). Fitzpatrick et al. compared regimens containing oral micronized progesterone or medroxyprogesterone acetate on quality of life in postmenopausal women and, women using micronized progesterone-containing HRT experienced significant improvement in vasomotor symptoms, somatic complaints, and anxiety and depressive symptoms than those using MPA-containing regimen (33).

Progestins may also be effective in reducing vasomotor symptoms in patients with a contraindication to use estrogens for various reasons.

Libido is a comprehensive and yet elusive word that indicates basic human mental states, and their biological counterparts, involved in the beginning of sexual behavior. In general, there is not a real decrease in libido associated directly with menopause. It is more relevant with aging which causes impairment in the general body appearance or decreased vaginal lubrication and atrophy secondary to estrogen deprivation. Arousal disorders, dyspareunia, orgasmic difficulties, dissatisfaction, both physical and emotional, may contribute to a secondary loss of libido. Depression, anxiety and chronic stress, may interfere with central and peripheral pathways of the sexual response, reducing the quality of sexual function mostly in its motivational root. Since there are many confounding variables likely to be associated with decreases libido, it is fairly difficult to quantitate the relative impacts of estrogens or estrogen/progestin combinations on libido. Nevertheless, evidence is in view of a positive effect on self well being with HRT (34), with a subsequent improvement on libido.

The Effects of Progestins on Endometrium

It is well documented that, while estrogens promote endometrial cell growth, progestogens have protective effects and the risk of hyperplasia and endometrial carcinoma are reduced by progesterone administration (35). Any regimen should keep long-term endometrial safety.

Table 3. Potency of progestins to induce secretory changes in the endometrium

Progestin	Relative potency
Medroxyprogesterone acetate, 10 mg	1.0
Norethindrone, 5mg	>6.0
Micronor, 0.35 mg	0.5
Micronized progesterone, 100mg	0.5
Vaginal progesterone gel, 4%, 40mg	1.0

Several combinations of oral and transdermal estradiol or CEE, oral progestogens, transdermal norethisterone acetate and levonorgestrel and intrauterine levonorgestrel may achieve endometrial safety. This counter effect on endometrium achieved by progesterone includes; estrogen receptor down regulation (both on the cell surface and on the nucleus), induction of target enzymes causing ineffective estrogen metabolites and by suppression of oncogene transcription induced by estrogens.

In clinical studies it has been documented that progesterone use which is implemented at least during the last 10 days are usually recommended to attain endometrial safety (36). If it is not so, 2% of women taking HRT is likely to develop endometrial hyperplasia every year. In a large prospective randomized study, the PEPI trial, CEE use alone was found to be associated with a remarkably high incidence of endometrial hyperplasia than those of women using placebo or CEE in combination with cyclic MPA, 10 mg/day for 12 days, micronized oral progesterone, 200mg/day for 12 days, or continuous MPA, 2.5 mg/day (8). Micronized progesterone use, also with a continuous daily dose of 100 mg produces effective protection against endometrial hyperplasia (37).

There has been also concern existing on long term HRT use is whether associated with an increased risk of endometrial hyperplasia. In a study from Seattle an increased risk of endometrial carcinoma in patients receiving HRT for more than 5 years was demonstrated, especially in those with continuous combined regimens, besides with a progesterone administration of 21 days (38). But thereafter, it was perceived that this increased risk was attributed to patients who had received unopposed estrogens in any time before implementation of HRT. Patients who received unopposed estrogens might have an ongoing increased risk of endometrial carcinoma lasting up to 10 years, despite of combined regimen initiated thereafter.

Nevertheless, it con not be declared with reassurance that there is a uniform correlation between the timing of onset of bleeding produced by sequential regimen and a certain pattern of pathology. Regular endometrial shedding afforded by sequential regimen lies in the base of preven-

tion of endometrial cancer. But, since in every menstrual cycle only 1/3 upper part of functional endometrium sheds, it is unlikely to consider an absolute protection against endometrial cancer.

Postmenopausal "Progesterone Challenge Test"

A positive progesterone challenge test, on an endometrium which is found to be thicker than 4 mm in the ultrasonographic assessment, is usually associated with pathologies including endometrial hyperplasia, endometrial polyp or cancer.

Conclusion

Progestins have the potential of effecting every organ of the body since progesterone receptors are found in every organ. Progestins added to estrogens in hormone replacement therapy might effect compliance. The major concern about adding progestins to estrogens in HRT regimens, is the suspicion of impairing beneficial effects provided by estrogens alone, especially of those related with cardiovascular system. When a progestin is planned to be added in hormone replacement therapy these considerations should be taken account.

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