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Review

Progestogens in postmenopausal hormone therapy and the risk of breast cancer

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ABSTRACT

Hormone therapy is the treatment of choice for the alleviation of menopausal symptoms and the treatment of urogenital atrophy. In women with an intact uterus a progestogen must be added to estrogen therapy to prevent endometrial hyperplasia and cancer. There is a wide variety of marketed progestogens which differ in their pharmacological properties according to their structure. Convincing evidence from both clinical trials and epidemiological studies indicates that combined estrogen–progestogen therapy confers a higher risk of breast cancer compared to estrogen monotherapy. Concerning the different types of progestogens, data from large observational studies suggest that natural progesterone and dydrogesterone are associated with a lower risk of breast cancer compared with the other progestins. Observational studies, furthermore, indicate that sequential estrogen–progestogen regimens may lead to a lower risk elevation compared to continuous regimens. The effect of tibolone on breast cancer is unclear. Concluding, both the type of the progestogen and the mode of HT administration may have an impact on breast cancer risk.

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1. Introduction

Hormone therapy (HT) is the treatment of choice for the management of bothersome menopausal symptoms and of urogenital atrophy [1]. Since the majority of menopausal complaints are attributed to estrogen deficiency, HT consisted originally of estrogen monotherapy. The increase, however, of endometrial hyperplasia and cancer has mandated the addition of a progestogen to the HT regimen for endometrial protection [2]. Beyond its effect on quality of life, HT increases bone mineral density, decreases the risk of both vertebral and hip fractures as well as the risk of colon cancer in postmenopausal women [3]. HT, furthermore, has a beneficial effect on the postmenopausal cardiometabolic risk by improving the lipid profile [4], by inhibiting abdominal fat accumulation [5] and by improving insulin sensitivity [6]. If administered

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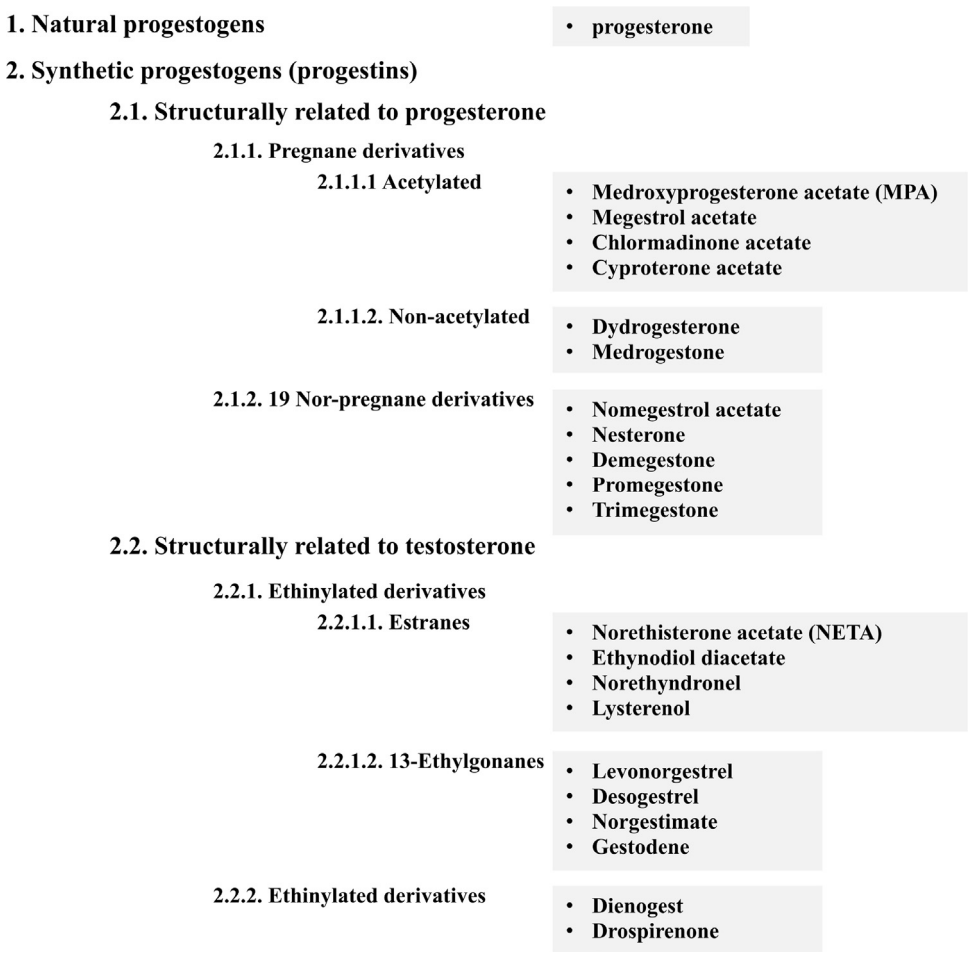

Fig. 1. Classification of progestogens. Adapted from reference [8].

early after menopause, HT may reduce the risk of ischemic heart disease [7].

During the past decades HT had been widely prescribed with the expectation of both osteoporosis and cardiovascular disease prevention. The results of the Women's Health Initiative (WHI) trial, however, indicated that long-term HT use is associated with a small but significant increase of cardiovascular events and breast cancer [3]. Whereas the increase in ischemic heart disease risk is probably confined in older women, in whom HT is not usually prescribed, breast cancer risk increase applies to younger women initiating HT soon after menopause [2].

Due to concerns about breast cancer, many clinicians are hesitant to prescribe HT, depriving thus their patients from multiple beneficial HT effects. On clinical grounds, however, this small risk may be modified by several factors dependent both on the patient profile and the characteristics of the HT regimen. The customization of treatment, therefore, according to the individual needs and risks ensures efficacy and safety of HT. In this review, the available evidence is summarized on how the progestogens used in HT may affect breast cancer risk.

2. Classification of progestogens (Fig. 1)

Progestogens are compounds with progestational activity, meaning the capacity to induce secretory endometrium and support gestation. Progestogens are divided into natural progesterone, which is produced by the human ovary and to synthetic progestogens which are also called progestins. Progestins are classified into those structurally related to progesterone and those structurally related to testosterone. Progestins related to progesterone are sub-classified into pregnane and 19-norpregnane derivatives, depending on the presence of a methylgroup at carbon 10. Pregnanes include the retroprogesterone dydrogesterone and the acetylated pregnanes like medroxyprogesterone acetate (MPA), megestrol acetate, chlormadinone acetate and cyproterone acetate. 19-norpregnanes include nomegestrol acetate, nesterone, demegestone, promegestone and trimegestone.

Fig. 1

Progestins structurally related to testosterone are subclassified into ethinylated compounds and non-ehinylated, like dienogest and drospirenone. Ethinylated compounds are subdivided into estranes (norethindrone or norethisterone acetate, ethynodiol diacetate, norethynodrel, lynestrenol) and 13-ethylgonanes (levonorgestrel, desogestrel, norgestimate, gestodene) [8]. Depending on their structure, progestogens differ with regard to potency and pharmacokinetic properties. Furthermore, the pharmacodynamics of each compound depend on binding to other steroid receptors, beyond the progesterone receptor, such as the androgen, the glucocorticoid and the mineralcorticoid receptor. For example, levonorgestrel has weak andogenic activity, cyproterone acetate has anti-androgenic activity and drospirenone has anti-mineralcorticoid activity [8,9]. Most progestogens are administered orally. Progesterone can also be delivered vaginally, norethisterone acetate transdermally and levonorgestrel directly to the endometrium through an intrauterine releasing system [10].