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Review

Progestogen use in women approaching the menopause and breast cancer risk

Carlo Campagnoli*, Simona Ambroggio, Maria Rosa Lotano, Clementina Peris

S.C. Ginecologia Endocrinologica Ospedale Ostetrico Ginecologico, ASO OIRM-S.Anna, Torino, Corso Spezia 60, Italy

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ABSTRACT

Objective: Progestogens, particularly synthetic progestins, are widely used to contrast the clinical consequences of the relative hyperestrogenism that characterizes the years preceding the menopause. As a large body of data on postmenopausal hormone therapy (HT) demonstrates that the addition of synthetic progestins to estrogen increases the breast cancer risk compared to estrogen alone, it is important to evaluate if the use of progestogens in premenopausal years is associated with the risk of breast cancer.
Methods: Main literature data on the association with breast cancer risk of progestogens, either used alone in premenopausal years or added to estrogen in postmenopausal HT, were reviewed.
Results: Available data suggest that long-term current use of progestogens in premenopausal women after the age of 40 years can increase the risk of breast cancer. Consistently with the data on postmenopausal HT, the risk increase is higher for lobular cancer than for ductal cancer.
Conclusions: The most important and widely accepted indications to the use of progestogens in the years preceding the menopause are anovulatory menstrual disorders, for which a limited period of treatment is generally sufficient. Awaiting for further data, when using progestogens for longer periods to treat other problems (endometriosis, cyclical mastalgia, etc.), the possibility of increased breast cancer risk and clinical benefits have to be weighed. Anyway, as micronized progesterone and dydrogesterone, at least when they were used in postmenopausal HT, seem to have, according to a large observational study, a safer risk profile on the breast, the preferential use of these preparations could be suggested.

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1. Introduction

Progesterone has a role in mammary gland development. In mice, it contributes to the growth and differentiation of the Terminal Ductal Lobular Units (TDLU), promoting lobulo-alveolar development, whereas estradiol stimulates ductal elongation. In humans, the role of progesterone is less clear: it is assumed that progesterone has a similar role and stimulates TDLU formation and expansion during puberty and pregnancy. It is noteworthy that this unit is the site from which many epithelial hyperplasia and carcinoma arise [1].

However, whether progesterone and/or synthetic progestins have a role in promoting breast cancer is a highly controversial topic. Natural progesterone can act on breast tissue in various ways: by interacting with two nuclear receptors (PR-A and PR-B) that can have different influence on the proliferative responses of breast tissue [2,3]; by influencing autocrine/paracrine factors (e.g. growth factors) [4]; by acting through metabolites that bind to specific membrane receptors and that could have opposite effects on cell proliferation and adhesion [5]; and by influencing the activity of the enzymes involved in the formation and transformation of estrogens in breast tissue [6]. This complexity of effects

* Corresponding author at: Sant'Anna Gynecological Hospital, Endocrinological Gynecology, Corso Spezia 60, 10126 Turin, Italy. Tel.: +39 0113134605; fax: +39 0113134798.
E-mail address: carlo.campagnoli@alice.it (C. Campagnoli).

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contributes to explain the fact that, while the proliferative activity of estrogens is well established, the *in vitro* studies on progesterone activity give contrasting results, even if an antiproliferative effect seems to prevail, due to the antiestrogenic action, favoured, for instance, by the inhibition of estrogen receptor activation [7]. Overall *in vivo* data suggest that natural progesterone does not have detrimental effects on breast tissue (as reviewed; [8]), consistently with epidemiological findings showing that high levels of endogenous progesterone do not increase [9] or may even reduce [10,11] breast cancer risk in premenopausal women. Moreover, the risk of breast cancer does not appear increased when natural micronized progesterone is added to estrogen in hormone therapy (HT) for postmenopausal women [12,13]. By contrast, most of the studies showed that the addition of synthetic progestins to estrogen in HT significantly increases breast cancer risk compared to estrogen alone [8,12,14]. The increase of the risk refers to both ductal and lobular cancer, but it is particularly elevated for the latter, *id est*, the histological subtype originating from the functional unit whose development is stimulated by progesterone [13–17].

Progestogens, particularly synthetic progestins, are widely used to contrast the relative hyperestrogenism that characterizes the years preceding the menopause, the so called "menopausal transition" [18,19]. An accepted indication to the cyclical use of progestogens are menstrual irregularities, particularly anovulatory metrorrhagia [20–22] and meno-metrorrhagia associated with miomas [23]. Progestins are also used in the treatment of endometriosis-related complaints [23] or for contraception, particularly as injectable depot medroxyprogesterone acetate (DMPA) or levonorgestrel-releasing intrauterine system (LNG-IUS) [24]. Further indications could be fibrocystic mastopathy, that occurs mainly between the ages of 35 and 50 years [25], and cyclical mastalgia [26,27]. Progestogens to contrast breast problems in premenopausal women are widely prescribed in France [28–30]. This practice was supported by the results of a cohort study of premenopausal women with benign breast disease, in which the long-term use of 19-nortestosterone derivatives was found to be significantly associated with a lower risk of breast cancer [31]. However, a recent large cohort study from France showed an increased breast cancer risk with long-term use of progestogens in premenopausal years [32].

2. Progestogen-only medications in women approaching the menopause and breast cancer risk: epidemiological findings

A comprehensive review on the breast cancer risk associated with the use of progestin-only contraceptives has been recently published by a joint Committee of two Canadian Societies [33]. Some of the "summary statements" were that in general population: (1) use of DMPA does not increase the risk of breast cancer; (2) although not as well-studied as the combined contraceptive pill, progestin-only pills do not appear to increase the risk of breast cancer; (3) the limited data available suggest that LNG-IUS does not seem to increase the risk [33].

The main findings on the breast cancer risk associated with the cyclical use of progestogens to contrast the consequences of the relative hyperestrogenism come from France. This is not surprising, as cyclical progestogens were used in a high percentage of French women, 36%, according to a recent study on 2254 pre- or perimenopausal women aged 45 years or older [30]. Another French study showed that the main indications of progestogen use were functional disorders of perimenopause (57%) and breast problems (47%) [29].

The association of premenopausal progestogen use with breast cancer risk was first studied in a cohort of 1150 French women, 80% aged >35 years at first visit, with benign breast disease, who were followed-up for 10 years [31]. In this cohort the overall progestogen use and the duration of use were not found to be associated with breast cancer risk. When progestogens were classified in two categories (19-nortestosterone derivatives *vs.* other progestogens), 19-nortestosterone derivatives at high doses were found to be significantly associated with a lower breast cancer risk (relative risk (RR): 0.48; 95% confidence interval (CI): 0.25–0.90). These results did not seem to support the hypothesis that progestogens increase breast cancer risk. They suggested instead that high doses of progestogens endowed with strong antigonadotropic activity might have a beneficial effect on the risk of breast cancer in premenopausal women, possibly because they cause a decrease in estradiol levels [34]. In the same cohort study of women with benign breast disease, no association between breast cancer risk and the use of percutaneous progesterone (topically applied on the breast) was observed [35]. The main problem of this cohort study of 1150 women is the limited number of breast cancer ($n = 44$) observed during the 10 years follow-up period.

Different findings were obtained by another study from France, based on the E3N cohort, which includes approximately 100,000 teachers followed up with periodic questionnaires. The association between progestogen-only intake prior to menopause and after the age of 40 years and breast cancer risk was recently studied in approximately 70,000 women of this large cohort [32]. Overall, ever use of progestogens before menopause was not significantly associated with risk. However, a significant increase in risk associated with the duration of use was found. Among current users of progestogens, use longer than 4.5 years was significantly associated with risk (RR: 1.44; 95% CI: 1.03–2.00), but not use shorter than 4.5 years. After discontinuation, and whatever the duration, the risk were close to unity [32]. The data of E3N cohort were furtherly evaluated to assess the risk of breast cancers defined by their histology [F. Clavel-Chapelon, personal communication; 36]. An increased risk of lobular carcinoma associated with premenopausal use of progestogens among both current and past users (Hazard Ratio (HR): 1.51; 95% CI: 1.02–2.24 and HR: 1.38; 95% CI: 1.08–1.75, respectively) was found. Regarding ductal carcinoma, only current use of progestogens for more than 4.5 years was significantly associated with increased risk (HR: 1.49; 95% CI: 1.00–2.22), while current use for less than 4.5 years and past use were not associated with increased risk [36]. Patterns of risk did not show marked differences with the use of different synthetic progestins, either antigonadotropic (chlormadinone acetate, cyproterone acetate, ethynodiol, lynestrenol, medroxyprogesterone acetate (MPA), nomegestrol acetate, norethisterone acetate, promegestone) or not (demegestone, dydrogesterone, medrogestone), and also of micronized progesterone [32]. This latter finding diverges from the result of the study of postmenopausal women of the same cohort suggesting that, contrarily to most of the synthetic progestin, the use of micronized progesterone in the menopausal HT is not associated with an increase in breast cancer risk [12,13].

3. Discussion

The most relevant data on the association of breast cancer risk with progestogens come from studies on the use of these preparations as a part of menopausal HT. According to a comprehensive review published in 2005 [14], evidence from either randomized controlled trials (RCTs) or observational studies indicated that breast cancer risk was increased with estrogen plus progestin more than with estrogen alone. The risk was lower in RCTs than in observational studies (Table 1). As suggested by two recent reports based on the Women's Health Initiative (WHI) trials and the large WHI