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Breast cancer and progestins in menopausal hormone therapy: a literature review

Abstract

Menopausal signs and symptoms challenge the patient's quality of life. Fortunately, menopausal hormone therapy (MHT) has been proved to be the most effective strategy, with oestrogen as the gold standard treatment. Addition of progesterone is mandatory in women with an intact uterus to protect the endometrium from hyperplasia that predisposes to uterine cancer. Newly synthetic progestins used in MHT differ in some pharmacological properties, and fewer data analyze profoundly its potential risks, which can influence decision-making process in menopause consultations. This literature review explores the differences between the preclinical and clinical profiles of progestins, particularly investigating its association with breast cancer risk. We focused on analyzing the most common prescriptions such as; Medroxyprogesterone acetate, Nomegestrol Acetate, Norethisterone, Drospirenone, Norgestimate, Levonorgestrel, and Desogestrel. Evidence suggests there is a greater breast cancer risk for synthetic progestins than natural progesterone, with differences among each type as well. Larger, long-term studies are needed to strengthen this outcome and provide evidenced-based clinical guidance.

Keywords: menopause, menopause hormone therapy, progesterone, progestins, breast cancer risk

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Background

Menopause is the time of life when menstrual cycles ceases for over an year, and is caused by reduced secretion of the ovarian hormones oestrogen and progesterone.[1] As longevity expands, women are spending a third of their existence in menopause and beyond. The average age of menopause is 51.5 years.[2] Although menopause is a normal event for women, individual experiences vary, and the vast majority suffer from symptoms that negatively impact their quality of life, so it is described that twenty percent of women have essentially no symptoms, and 20% of women have severe symptoms.[3]

The menopausal transition is usually characterized by irregularity of the menstrual cycle and by hot flashes and night sweats. Of all the symptoms, only vasomotor symptoms and vaginal dryness are consistently associated with menopause in epidemiological studies.[4] Hot flashes are reported in up to 85% of menopausal women, and the average duration is of approximately 5 years.[5–7] Both hormone therapy and non hormonal regimens can be useful in relieving vasomotor symptoms. Genitourinary symptoms include vulvovaginal atrophy and dryness, urinary frequency, urgency, and nocturia.[8] Urogenital tissues are exquisitely sensitive to estrogen, and a sustained low estrogen levels after menopause can render these tissues fragile and cause distressing symptoms.[5,9] Systemic or vaginal estrogen are highly effective, and local estrogen is recommended. Currently, data is insufficient to define the minimum effective dose, but vaginal rings, creams, and tablets have all been tested and demonstrated to reduce vaginal symptoms.[10]

Treatment approach is essential in climacteric gynecological consultations. It must be personalized, balancing the risk and benefits in each woman, with the aim of improving the patient's quality of life and reducing the long-term adverse effects of a hypoestrogenic state. The three treatment strategies include menopausal hormone therapy, bioidentical menopausal hormone therapy, and non-hormonal therapies.

Firstly, menopausal hormone therapy (MHT) is considered the most effective medical intervention for the relief of menopause symptoms. Most international guidelines recommend it to be started as soon as these ones appear.[3] Exogenous oestrogen, progestins, combinations of both, selective oestrogen receptor modulators such as raloxifene, and tibolone synthetic hormones are the essential alternatives.[11] Oestrogen, the 'gold standard', is the most effective component for reducing symptomatology.[12] As it is a proliferative agent in certain tissues, an unopposed exposure in the endometrium derives to hyperplasia and increased risk of cancer. This is why progesterone is indispensable for women who preserve the uterus,[13] and the MHT is administered as a combination of both hormones. The scheme consists of daily oestrogen administration with addition of progestogen for 10-14 days every month,[14] or a continuous administration of both hormones, with a lower progesterone dose in order to minimize the breast cancer risk (BC-risk) and to avoid inconvenient bleeding.

Secondly, Bioidentical menopausal hormone therapy (BMHT) involves hormones that are molecularly identical to the hormones produced by the organism. Its main difference with Conventional Hormone Therapy (CHT) is that BMTH does not contain extra structural fragments which may alter hormone receptor binding and function in the human body.[15] They are used to produce compounded preparations, which are perceived to be more effective, better tolerated, with fewer health risks than its conventional MHT counterpart.[16] There is evidence to suggest that dydrogesterone and micronized progesterone have better risk profiles than medroxyprogesterone acetate (MPA)[17] and are associated with a lower risk of breast cancer compared with other progestins.[18] Anyhow, there is still limited conclusive evidence, and compounded preparations are not approved nor regulated by the FDA.[19]

Last, non hormonal therapies are also available for patients who prefer to avoid systemic hormone therapies. There is limited evidence for the efficacy of natural products such as isoflavones in menopause

management, and safety data is inadequate.[20] Also, results indicate that mind and body practices may be of benefit in reducing stress. In particular, hypnosis is a mind-body intervention that has consistently shown to have a clinically significant effect on reducing hot flashes.[21]

Increased breast cancer risk has been pinpointed for decades as the major adverse effect that hormone therapy has. Breast cancers are classified depending on the presence or absence of hormonal estrogen receptor (ER), progesterone receptor (PR) and overexpression of human epidermal growth factor receptor 2 (HER2/neu) . This is very important, as it defines sensitivity to targeted therapy and prognosis.[22] The known mitotic activity of estrogen and progesterone on breast cells, and the presence of hormone receptors unleashed a series of biologically plausible concerns in terms of MHT and breast cancer risk. The MISSION trial, a prospective cohort study involving 4949 women, did not find a significant difference for breast cancer risk when comparing MHT users with non-users (non-adjusted RR 0.91; 95% CI 0.45–1.86), and the risk did not differ between therapy type and duration of use.[23] Nonetheless, in 1997, The Lancet released a collaborative reanalysis of data from 51 epidemiological studies of 161 116 women.[24] It was found that breast cancer risk increases in women using MHT and rises with increasing duration of use, yet the excess risk is reduced after cessation of use and has largely, if not completely, disappeared after approximately 5 years.

On the other hand, the Women's Health Initiative (WHI), the only large double-blind placebo-controlled study testing the risk of breast cancer (BC) using MHT, found an association between MHT and increased BC-risk.[25] Anyhow, the WHI tested the use of a gestagen in particular, Medroxyprogesterone Acetate (MPA). Since this controversial study, many have questioned the cancer risk associated with gestagens, even though the apparent risk was not significant when adjusted by confounding variables, and subsequent studies evidenced that the risk-to-benefit ratio endorses its administration.[26,27] The trend of thought nowadays is that the breast cancer risk in combined therapy is associated with duration of treatment, but still being essentially low (<1 case per 1000 women-years among MHT users).[28] This is less than other risk factors such as obesity, sedentarism and alcohol consumption.[13] It may have a significant effect on promoting already existing tumors, however it is still considered a safe option for treating symptomatic menopausal women.[29]

In this purpose, the main objective of this review is to evaluate and summarize research on the use of progestin and breast cancer risk in menopausal patients. Taking into account the relevance of breast cancer nowadays, possible factors that may modulate this cancer risk need to be identified.

Progesterone vs progestins: general considerations

Progesterone is a natural progestogen used primarily for endometrial protection during hormonal therapy with oestrogens. It has a low bioavailability (<5%) after an extensive hepatic first pass and due to the binding to corticosteroid binding globulin.[30] Even though the estradiol's mitogenic effect on breast cells has been established, the effect of progesterone is still uncertain.[31] In an updated report on the E3N cohort evaluating 80,377 postmenopausal women 40–65 years of age at enrollment and followed for up to 12 years, use of estrogen alone was associated with a 29% increased breast cancer risk (95% CI: 1.02–1.65).[32] In vitro studies evidenced that progesterone counteracts oestrogen-induced breast cancer cell's proliferation and actually decreases breast epithelial cell's mitotic activity.[33,34] However, this differs from the in vivo appreciations, and from extensive evidence that supports that oestrogen and progesterone are both needed for cellular proliferation.[30,35,36] Progesterone is not sufficient to stimulate cellular proliferation in the absence of estrogen, as demonstrated by PR expression in mammary epithelium being dependent on interactions of estrogen with ERα to induce PR transcription.[37] A systematic review analyzing the combination of estrogen and micronized progesterone on the mammary gland showed that mammographic density may increase or either remain unchanged, proliferation induction was less pronounced and breast cancer risk was not affected after 5 years of treatment.[14]

On the other hand, progestins used in MHT are structurally related to either progesterone (C-21 progestins) or testosterone (C-19 progestins).[38] Although they are PR ligands, some bind to the androgen receptor (AR), glucocorticoid receptor (GR), mineralocorticoid receptor (MR) and ER-α,[39] all of which have been implicated in breast cancer biology.[32,40,41] Once in the cell, they may be metabolised by steroidogenic enzymes, and the progestin and/or its metabolites would exert transcriptional activities by binding to steroid receptors. Other hypotheses for progestin action in the breast include probable pro-tumorigenic effects by off-target interactions that favour cell viability, proliferation, receptor expression and decreased cellular apoptosis. This has been evidenced in vitro studies particularly for the progestin Norethisterone Acetate and overexpression of progesterone receptor membrane component 1 (PGRMC1), a membrane protein binding PR that is over expressed in breast cancer tissue and associated with a poor prognosis.[42]

Multiple studies have been carried out to attain the differences between natural progesterone and progestins in MHT for BC-risk. The increased risk of BC-risk is primarily associated with the addition of a synthetic progestin to oestrogen therapy and is related to duration of use.[35] A systematic review and meta-analysis evidenced there was a lower breast cancer risk in the use of progesterone compared to synthetic progestins (when both are combined with oestrogen).[43] The association of estrogen-progestogen combinations with BC-risk varied significantly according to the type of progestogen. The RR was 1.00 (95% CI: 0.83–1.22) for estrogen-progesterone, 1.16 (95% CI: 0.94–1.43) for estrogen-dydrogesterone, and 1.69 (95% CI: 1.50–1.91) for estrogen combined with other progestins, which included medrogestone, chlormadinone acetate, promegestone, nomegestrol acetate, norethindrone acetate, and MPA.[44]

E3N is a prospective cohort study initiated in France from 1990 to 2002 and which included 98,995 women aged 40-65 years. In the first report of the study, there was a significant increase of BC-risk for any combined MHT use, and was not altered by duration of use. When differentiating progestogen type, oral estrogens plus micronized progesterone (MP) were not associated with an increased risk (RR 0.9; 95% CI 0.7–1.2), while when combined with synthetic progestins the RR was of 1.4 (95% CI 1.2–1.7).[45] The second report expressed these same results, however this time there was a significant time trend observed in women with combined therapy involving MP (p for trend = 0.04).[46] The third report from 2014 found that there was an increased BC-risk for women using combined MHT with MP after 6.1 years (RR 1.22; 95% CI 1.11–1.35). The use of MHT with synthetic progestins had an ever greater risk (RR 1.98; 95% CI 1.73–2.26). The risk was dissolved when interrupting MHT with MP, but was still elevated 5–10 years after stopping MHT containing synthetic progestins.[47]

Notwithstanding the fact that the gynecologist's positions about MHT in menopausal women are diverse, some consensus was drawn based upon literature reviews and available information. An international expert panel declares that the combination of oestrogen

and MP do not increase breast cancer risk (up to 5 years of treatment, and there is little evidence beyond this duration). They also suggest that women should be counselled upon breast cancer's risk factors, but MHT should not be accounted for.[48–50]

To facilitate the comprehension we subcategorized the review and described the differences between the preclinical and clinical profiles of each progestin used in menopausal hormone therapy, focusing on breast cancer risk. Below you will find; 1.1) Medroxyprogesterone acetate, 1.2) Nomegestrol Acetate, 1.3) Norethisterone, 1.4) Drospirenone, 1.5) Norgestimate, 1.6) Levonorgestrel, and 1.7) Desogestrel.

Medroxyprogesterone acetate

Medroxyprogesterone acetate (MPA) is structurally related to progesterone, does not bind to CBG or SHBG, and has high bioavailability (>90%). Common daily doses for endometrial protection are 2.5 and 5 mg. It is indicated in MHT, but also for contraception during pregnancy, secondary amenorrhea, abnormal uterine bleeding, endometrial carcinoma, and endometriosis.[51]

MPA is probably the most controversial progestin, mainly because it was the one involved in the Women's Health Initiative (WHI). As mentioned above, this was a study conducted in 2002 involving 16608 menopausal women between the ages of 50 and 79 years recruited by 40 US clinical centers in 1993-1998 with an intact uterus at baseline.[25] Participants received conjugated equine estrogens (0,625 mg/d) plus medroxyprogesterone acetate (2,5mg/d), in 1 tablet (n=8506) or placebo (n=8102). The primary adverse outcome was invasive breast cancer. In 2002, after a mean of 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial because the test's statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect, supporting that risks exceeded benefits. There were 290 cases of breast cancer, with estimated hazard ratios (HRs) (nominal 95% confidence intervals [CIs]) of, 1.26 (1.00-1.59).

It's important to mention that the WHI has been the only large double-blind placebo-controlled study testing the risk of breast cancer (BC) using MHT. In about 20 observational studies using mostly MPA or estradiol-norethisterone acetate (NETA), an increased BC-risk was observed comparable with the WHI.[42] Only for natural progestogen, progesterone and for dydrogesterone (retro-isomer of progesterone) was no increased risk seen for up to 5–8 years, when compared directly with other progestins, but for longer treatment an increased risk cannot be excluded.[42]

The evidence exposed in this study created a great dispute within the medical community. The posterior analysis of the WHI's methodology and further studies demystified the BC-risk associated with progestins. Firstly, it was argued that the results were not statistically significant because the confidence interval included one. Criticism also proposed that actually, the time needed for breast cancer cells to multiply and fully develop in order to become clinically relevant are at least ten years, so the duration of 2.5-3 years of intervention cannot give biologically plausible results.[52,53] The main argument however is that the results were not properly adjusted by confounders. The previous use of MHT was not taken into account. For women who were MHT naive before the intervention the BC-risk was not affected by the use of CEE + MPA. Consequently, the hazard ratio was not due to an increased risk in the group randomized to CEE + MPA, but rather due to the decreased risk of the group randomized to placebo which used MHT previously.[27] When considering age, race, body mass index, smoking history, physical activity, parity, oral contraceptive use, alcohol use, family history and mammography use, the statistic became non-significant (HR, 1.20; 95% CI, 0.94–1.53).[52]

Debatable evidence unleashed further investigations in order to clarify information. A study compared the use of oral conjugated equine estrogens (o-CEE) + MPA, with transdermal estrogen (t-E2) combined with oral micronized progesterone (o-MP).[54,55] Core needle biopsies were performed at baseline and at the end of the intervention (after 2 months), to study by immunohistochemistry the endpoints of breast cell proliferation (Ki-67/MIB1), apoptosis (bcl-2) and gene expression. Breast cell proliferation was significantly increased with o-CEE + MPA in comparison with t-E2 + o-MP, while apoptosis had no difference or was decreased with t-E2+o-MP. With regards to altered gene expression, 255 genes involved in mammary tumor development were identified, 198 attributable to 0-CEE + MPA and 34 to t-E2 + o-MP. It should be noted that the estrogen levels were also different in both groups, as transdermal absorption is not the same as oral administration.

Several studies use breast density to assess the impact of different MHT schemes on the mammary gland, as it is considered an independent risk factor for breast cancer. Combination therapy with progestins has a strong association with an increase in breast density in comparison to estrogen alone, and this is greater in continuous therapy.[56] Greendale et al. carried out a study using enrollment and results from the PEPI trial, a 3-year multicenter, double-bling and randomized placebo-controlled trial. Measurements after 1 year of treatment were done, with results of percentage increase of 0% (95% CI, 0.0% to 4.6%) in the placebo group, 3.5% (CI, 1.0% to 12.0%) in the o-CEE group, 23.5% (CI, 11.9% to 35.1%) in the o-CEE + cyclic MPA group, 19.4% (CI, 9.9% to 28.9%) in the o-CEE + daily MPA group, and 16.4% (CI, 6.6% to 26.2%) in the o-CEE + cyclic micronized progesterone group.[57] Another study of 158 women in Sweden found a greater increase in mammographic density (40%) in users of continuous o-CEE + MPA treatment (0.625 mg and 5mg respectively), than in those using low-dose oral estrogen (6%) and transdermal estrogen (2%) treatment.[58] Last, a retrospective study performed in Turkey evidenced a 23.5% increase in mammographic density in combined MHT with MPA, and a still greater increase (34.1%) in women taking Norethisterone Acetate (NETA).[59] However, the number of participants involved in this case was significantly low (17 women using o-CEE + MPA and 44 using o-CEE + NETA).

To conclude, there is evidence that suggests MPA carries an increased BC-risk. However, the clinical relevance is related primarily to long-term use, and in this case there are limited studies which assess this kind of implication. Decades away from the WHI, there are diverse perspectives about MPA use and MHT in general, however another important consequence is that professionals had to develop a critical eye upon the reading and understanding of the available literature in order to develop an adequate risk-benefit analysis.

Nomegestrol acetate (NoMAC)

Nomegestrol acetate (NOMAc) is a synthetic progesterone analog and classified as a fourth-generation progestin medication that is used in birth control pills, menopausal hormone therapy, and for the treatment of gynecological disorders.[60] It is structurally similar to 19-norprogesterone and characterized as a full agonist of the progesterone receptor, with no or minimal binding to other steroid receptors. It is metabolized by the hepatic cytochrome P450 (CYP) system enzymes into inactive metabolites.[61]

NOMAC is structurally similar to the physiological hormone progesterone and lacks estrogenic and androgenic activity, a potential

advantage in terms of breast cell response.[62] Unlike androgenic progestins which may act indirectly on the breast by inducing modifications of sex hormone binding globulin (SHBG) and insulin-like growth factor-I (IGF-I), NOMAC is devoid of any androgenic activity. With MHT combining estrogen and NOMAC, clinical trial results showed low incidence of mastodynia while under treatment.[63] NOMAC/E2 was found to cause less breast cell proliferation when compared to E2 alone[64] and has some anti-proliferative effect on human breast cancer cells.[65] Although NOMAC has no growth-stimulating activity on breast cancer cells in the absence of E2, some evidence suggests that it may also help attenuate the proliferative effects of endogenous E2 by preventing E2 formation from estrone sulfate (E1S) and by enhancing the conversion of E2 to less potent metabolites. NOMAC was able to inhibit estrone sulfatase and 17β-hydroxysteroid dehydrogenase activity, 2 enzymes responsible for the conversion of E1S to E2.[66] In vitro studies have shown that NOMAC blocks the conversion of estrone sulfate to estradiol in MCF-7 and T47-D hormone-dependent breast cancer cell lines.[67]

According to the global proliferative measurements, NOMAC had a similar or better antiproliferative effect than LNG and DRSP. The intermittent regimen stimulated the breast less than the continuous one and it was associated with reduced estrogen receptor a expression. Estrogens enhance the antiapoptotic protein bcl-2,[68] which is strongly reduced by progestins and, among them, NOMAC seem to be one of the most effective molecules in promoting breast cell apoptosis and in reducing cell proliferation.[69] Also, recent data on MHT have demonstrated no increased risk of breast cancer[70] with lower estrogen content and non-androgenic progestins being responsible for this effect.[71]

In conclusion, NOMAC is an anti-sulfatase agent, not only in isolated breast cancer cells, but also in the intact tissue. Seems to be a good combination with E2 regarding the oncological perspective, but it also has further advantages such as a neutral effect on glucose metabolism, which is related to breast cancer risk, and on the lipid profile.[72] The data can open attractive perspectives for unborn clinical trials with this progestin on menopausal patients.

Norethisterone

Norethisterone acetate (NET-A), also known as norethindrone, a "first-generation" progestin, is structurally related to testosterone. It binds with relatively high affinity to progesterone receptors (PRs), and has also some androgenic activity. Its bioavailability is 64% and half-life is 8 hours. It is part of combined MHT, commonly indicated for treating menopausal symptoms and osteoporosis prevention, particularly in European countries.

Numerous investigations are advocated to in vitro studies of the effects of progestins on the mammary glands. Even though they are far from in vivo scenarios, they provide a solid base of information about molecular mechanisms and biological plausibility for the effects that different components may have. NET-A has been particularly studied due to its involvement with the PGRMC1 receptor mentioned previously. This protein is an oncogene which, when overexpressed in breast cancer cells (BC-cells), is related to advanced tumour grade, poor outcomes, risk of metastasis and reduced survival rate.[73] Studies revealed that breast cancer cellular lines (MCF-7) were highly sensitive to the proliferative effects of NET-A[74] but this was confined to already existing tumours, and hence does not assess the potential breast cancer risk. Anyhow, further investigation evidenced its effect on normal breast cellular lines, MCF10A. In this scenario, NET-A exhibited pro-tumorigenic effects due to increased cell proliferation, migration, and colony formation. It also caused overexpression of the Epidermal Growth Factor Receptor (EGFR), which is upregulated in certain tumours leading to proliferation, angiogenesis and decreased apoptosis.[75]

A systematic review[77] evaluated the association between estradiol-progesterone therapy and risk of breast cancer. The data was stratified into subgroups by types of progestogen. The results proved that estradiol combined with MPA, NET-A and LNG was related to an increased risk of breast cancer. A study using the Norwegian Prescription Database and the Cancer Registry of Norway was performed from 2004 to 2009 in order to investigate the effects of different MHT schemes. Including a total of 686,614 women and 7,920 invasive breast cancer diagnosis, it was evidenced that users of combined estradiol-NETA preparations had a 4-to - 5 fold elevated risk of breast tumours grade I, 3- to-4 fold risk of ER+/PR+ tumors, and a 2 to 3 fold risk of grade II tumors with lymph involvement.[76] Other studies even suggested that the higher BC-risk registered in Europe in comparison to the United States may be explained because NETA is commonly prescribed in European countries while MPA is more common in the Americas.[77]

When compared to other progestins, in an interventional study 120 postmoenpausal women were randomized to receive 0.5mg of NET-A or 2mg of Drospirenone (DRSP), both in continuous combination with 1 mg of oral estrogen (E2). At baseline and after six months they underwent a mammography and a fine-needle aspiration biopsy. A significant increase in mammographic breast density was found in both groups, slightly higher for the DRSP (5.5% for E2/DRSP and 2.3% for E2/NETA). In the biopsies, proliferation of breast epithelial cells was also present, and significantly higher for the E2/DRSP2 group (2.5% versus 0.7% in E2/NET-A, $p < 0.05$).[78] Different results were evidenced when being compared to other progestins. Two case-control studies involving 98,611 women aged 50-79 who had breast cancer diagnosis, and 456,498 female controls were carried out. In comparison to never-users, the use of oestrogen only and combined therapy was associated with an increased BC-risk. In combinations with progestins, the highest risk was found for NET-A users (1.88, 1.79 to 1.99), while the lowest of Dydrogesterone (1.24, 1.03 to 1.48) at a long term use (≥5 years), when compared to MPA and LNG as well, but not to DRSP. Anyway, the odds ratio for MPA was not far from it, being 1.87 at ≥5 years of use.[79]

In another study, the distinctions between different administration routes of NET-A and BC-risk was analysed. 202 postmenopausal women were randomized to receive transdermal MHT (50 mg estradiol (E2)/140 mg norethisterone acetate (NETA) daily; n = 297) or oral MHT (2 mg E2/1 mg NETA daily; n = 99). The mean breast density of mammographies obtained after 1 year of treatment were significantly higher for the group receiving oral therapy in comparison to transdermal (46.9%, standard error 1.5 and 38.4%, standard error 0.9 respectively).[80]

To conclude, there is in vitro evidence that reveals a potential pathological mechanism that can explain the association between NET-A and increased BC-risk. Studies performed in women show that the increased risk becomes more significant with the long term use of this component. Even though it has been portrayed as one of the progestins with greater risk, differences among them are still subtle and need a major insight and larger studies.

Drospirenone

Drospirenone (DRSP) is a relatively new progestogen.[81] It is structurally related to spironolactone, and does not bind to SHBG or CBG. It has a bioavailability of 66%, half-life of 32 hours, and

exhibits both anti-androgenic and anti-mineralocorticoid properties. These characteristics of DRSP contrast those of older progestins.

A trial[82] was conducted with the goal of investigating the effects of 17β-estradiol 1 mg plus drospirenone 2 mg (E2/DRSP) treatment on mammographic breast density in perimenopausal women. In this prospective study, 80 healthy perimenopausal women aged 41–49 years were enrolled and assigned to either E2/DRSP (n = 40) or a control group (n = 40). Mammograms were performed at baseline and after 12 months of treatment. The results demonstrated an increase in mammographic breast density in 37% (95% CI (confidence interval): 18.8–55.3%) of women treated with E2/DRSP after 12 months. The percentage of women with increased density was 0% (95% CI: 0.0–0.0%) in the control group. The difference in breast density between the E2/DRSP group and the control group was statistically very significant ($p < 0.001$). Anyhow, the number of patients enrolled is very low, so larger trials are needed in order to draw solid conclusions.

Another study[83] evaluated the genotoxicity induced by drospirenone and ethinylestradiol in human breast cells (MCF-7) in vitro and in bone marrow cells of female mice in vivo. It was proved that both of the drugs produced DNA damage in human breast cells at exposure concentrations which are about 100-fold and above than normally found in human blood after their lowest recommended doses. Thus it is concluded that drospirenone and ethinylestradiol cause DNA damage in mammary epithelial cells and in female bone marrow cells. The co-exposure with drospirenone and ethinylestradiol results in potentiation of genotoxicity which may pose a threat of cancer development in women taking these drugs for long periods.

In closing, DSRP is a new generation of progestins that has distinctive properties that differentiate it considerably from other drugs used in MHT However, studies analyzing its efficacy and risk in comparison with traditionally used drugs are currently lacking. More research is needed to expose the a priori benefits of anti-androgenic and anti-mineralocorticoid properties in menopausal women.

Norgestimate

Norgestimate (NGM) is a newer, more selective progestin, structurally similar to 19-nortestosterone. Being a prodrug, after an extensive first-pass metabolization in the liver and gastrointestinal tract, its metabolite 17-deacetyl norgestimate (norelgestromin) has an approximate half life of 37 hours.[84] The active metabolite has the most favorable binding to progesterone/androgen receptors of all the progestins. This provides progestational activity with minimal androgenic effects.[85] This characteristic is also due to the fact that NGM inhibits the 5α-reductase activity and increases the SHBG when combined with estrogen. It has a safer cardiovascular profile than other progestins as it has a lower impact on lipid and carbohydrate metabolism.[86,87] What makes this prostagen a really interesting option is that it is also a very good modulator of the effects of ethinyl-estradiol on thromboembolic risk, being pinpointed as one of the prostagens with lower venous thromboembolic risk. Other studies focused primarily on the tolerability of NGM in MHT, but did not precisely investigate the BC-risk. It was found it is effective in eliminating menopausal symptoms.[88–90] Evidence shows lower incidence of breast discomfort, abdominal pain, edema, dysmenorrhea and a better metabolic profile than NET-A.[90,91]

It was described a mild estrogenic activity, as it was evidenced it agonizes the ER-α receptor. This subtype has a prominent role in the breast. In many breast cancers, its activation by estrogens is considered an important proliferation trigger. Anyhow, this is just something to acknowledge when thinking about the potential risks regarding its pharmacodynamic profile, but it has not been associated with BC-risk.[92,93]

Two multicenter, double-blind parallel group studies, which included a total of 1252 women compared the use of estradiol alone, intermittent estradiol + norgestimate and continuous estradiol + norgestimate. Only 3 cases of malignant breast neoplasms were diagnosed after 1 year, all of them in the subgroups receiving intermittent estradiol and norgestimate in different doses. It was not considered significant, however the small total number of women enrolled should be taken into account when assessing the validity of this conclusion.[94,95]

Studies have shown that progestins not only inhibit the synthesis of estrogen receptors in the endometrium, but also the synthesis of its own receptors. Regular intermittent use of norgestimate eliminates this inhibition. When norgestin is stopped, unused estrogen increases the number of estrogen and progestin receptors. As a result, target cells are re-sensitized to these two hormones, allowing for a lower total dose distribution of norgestimate.[96] Anyhow, it is not evidenced that a lower dose can effectively reduce any risk. BC-risk has rather been associated with duration of treatment.

In conclusion, there are currently no studies evaluating the risk of breast cancer following norgestimate administration. The available evidence suggests cardiovascular benefits; both in terms of better impact on the cholesterol lipoprotein profile and lower thromboembolic risk. An additional property of this hormone is its clinical profile, which is almost devoid of androgenic effects. Prospective trials are urgently needed to estimate the breast cancer risk in patients treated with this drug.

Levonorgestrel

Structurally related to testosterone , it has very limited liver metabolism. It binds to SHBG, has a bioavailability of 89-99% and half-life of 10-13 hours. It binds with high affinity to the PRs and AR, and has substantial androgenic activity. Levonorgestrel is used in combination with an estrogen in menopausal hormone therapy, and there is also another form that involves a gradual-release intrauterine device, called IUS.

The levonorgestrel (LNG) releasing intrauterine system (IUS) has been suggested as an alternative to oral progestins for postmenopausal hormonal treatment and protection of the endometrium. The use of the levonorgestrel-releasing IUS as the progestogen agent results in circulating plasma levels of levonorgestrel that are much lower than the levels achieved with oral or transdermal hormone therapy regimens.[97] Backman et al.[98] investigated the association between the use of a levonorgestrel-releasing IUS and the development of breast cancer in 17,360 Finnish women. They noted that there was no difference in breast cancer incidence among the general population of the same age as the study patients. In other recent but small study, Lundstrom et al.[99] showed that breast density remained unchanged from baseline in postmenopausal women treated with levonorgestrel-releasing IUS in addition to 2 mg of oral estradiol valerate.

On the other hand, considering that epidemiological studies have repeatedly shown increased mammographic breast density to be a strong and independent risk factor,[100] a pilot study was performed on the effects of IUS on the breast.[99] A group of 20 postmenopausal women were investigated during combined treatment with 2 mg of oral E2V daily and the 20 g/24 hours LNG–IUS. The effects on mammographic breast density, breast cell proliferation, and hormonal levels were followed for 18 months. No clinical or mammographic breast

abnormalities were recorded during the study period. The individual density increase in just one patient, in all of the other women density was unchanged compared to baseline. In terms of digitized Density Assessment; the baseline mean value for the percentage area of dense breast (35.4%) showed a slight increase (38.6%) after 6 months (P.01). After 18 months no further significant increase was recorded. Clearly the population sample was much too small to allow any conclusive comparisons. Nevertheless, in vitro studies using MCF-7 or T47D breast cell lines reported that levonorgestrel derivatives, promoted proliferation.[101,102]

A meta-analysis including nine observational studies evaluated the association between LNG and BC-risk.[103] Data were categorized by progesterone type, including MPA, NETA, LNG, dydrogesterone, progesterone, and mixed progesterone. Subgroup analysis showed a statistically significant increase in breast cancer risk in the LNG subgroup (pooled OR ¼ 1.47, 95% CI (1.17, 1.85). Also, the BC-risk rises progressively by prolonged use, furthermore, compared to sequential therapy, continuous therapy carries a higher risk.

Last, the MARIE study was carried out from August 2002 to September 2005 in 2 study regions in Germany.[104] Analyses of progestagenic content by regimen revealed a significantly higher risk for continuously administered norethisterone or levonorgestrel-derived progestagens than for continuously administered progesterone-derived progestagens (OR, 2.27, 95% CI, 1.98–2.62 vs. 1.47, 95% CI, 1.12–1.93, respectively, p = 0.003), which may be explained by dose rather than type of progestagen. Furthermore, risks for all invasive cancers associated with current use were of similar magnitude for preparations containing norethisterone-derived progestagens and for those containing levonorgestrel-derived progestagens, when considered separately by type of regimen (ORs 2.27, 2.43, for continuous and ORs 1.55, 1.38, for cyclical, respectively), however consistently higher for continuous than for cyclical EP therapy (pdifference = 0.05, both for norethisterone and for levonorgestrel derivatives). There was less difference in risk by regimen associated with current use of estrogen combined with progesterone-derived progestogens (p difference = 0.29).

So in conclusion, the results suggest that the use of the levonorgestrel-releasing intrauterine system is not associated with an increased risk of breast cancer. It is safe to say that levonorgestrel-releasing IUS is a promising therapeutic tool for localized, rather than systemic, progesterone administration for women who have already entered menopause, and should therefore be investigated further.

Desogestrel

A third-generation progestin derived from levonorgestrel, structurally related to testosterone. It is a prodrug converted to etonogestrel in the first hepatic pass. This metabolite binds to SHBG and has a bioavailability of approximately 70% and a half life between 12 and 24 hours. What characterizes the new third generation is that they have a higher affinity for progesterone receptor (PRs), and a lower affinity for androgenic receptor (AR) (40% affinity for AR in Desogestrel (DSG) while 70% in LNG.[105,106] An advantage of this progestin is that it has a neutral metabolic profile.[107]

The Million Women Study, which had great repercussions, already expressed the concerns regarding the increase in BC-risk associated in particular with the 19-nortestosterone derivatives such as DSG.[108] DSG was studied in a prospective population based cohort in Norway. It included 96,362 women recruited between 1991 ans 1997. In never users, a low dose of DSG (<0.1) had RR of 0.63 RR and a high dose (≥0.1) had an RR 1.48. This latter, in comparison with the high doses of LNG and NET-A, the RR was greater. Anyway, 25% of the users of third generation progestins were ever users, hence it was difficult to draw a solid conclusion. This is because what was specially evidenced is that there is a positive trend for total duration of use, meaning that long-term users had a higher BC-risk.[71] Another investigation also studied the testosterone-related progestins in rodents. It was found that they induce the PR signaling and consequently induce cell proliferation, while other non-androgenic progestins did not. In the same study, women xenografts were also analysed and evidenced that androgenic progestins (including DSG, gestodene and LNG) promoted proliferation in breast epithelial cells.[109]

Another hypothesis involves the Insulin Growth Factor 1 (IGF-1), which promotes cell proliferation in the breast, and this is associated with the increased BC-risk related to high glucose levels in hyperinsulinemia and insulin resistance.[110] One of the effects that estrogen has on the liver is to increase IGF-binding protein, hence reducing the circulating IGF-1 levels. It was evidenced that progestins have different effects on this mechanism depending on their level of androgenicity. Heald et al.[111] conducted a randomized triple-crossover study which evidenced that conjugated estrogen reduced IGF-1 levels, and this effect was reversed by progestins MPA, DSG and norethindrone.

Another study was conducted in breast cancer cell lines, HCCC15000. It was found that DSG led to a reduction in the rate of apoptosis to proliferation, therefore potentiating the proliferative effects of the growth factors used in the cell culture. It was also evidenced that the other progestins studied (NETA, LNG and DNG) inhibited the stimulatory effect of estrogen on these cells, but not DSG.[112] Anyway, this in vitro study was tested in already existing tumors. Although many women may have cancerous cells not manifested clinically when initiating MHT, this is not an issue considered when prescribing hormonal therapy, and this study does not assess the BC-risk.

Conclusion

We reviewed all the available evidence on the preclinical and clinical characteristics of the different progestins that are currently marketed in conjunction with estrogen in menopausal menopausal hormone therapy. We have found and described the advantages and weaknesses of each in order to facilitate the decision-making process in climacteric consultations. Evidence suggests in a generic way that natural progesterone (micronized progesterone and dydrogesterone) have a lower BC-risk than progestins. Furthermore, it has been proved that the BC-risk is mostly related to duration of MHT. Firstly, we found that Medroxyprogesterone acetate studies revealed an increased risk, even though the WHI has been revised and criticized multiple times. Likewise, Norethisterone and Desogestrel, both related to testosterone, also exhibited an increased risk in the trials included in this revision. Their androgenic activity (even though much lower for DSG) should be further investigated as a risk factor. Anyway, most of these studies were developed in vitro and when attempted in vivo, mostly in rodents, the results did not match. Even though molecular mechanisms, such as the implication of the PGRMC1 receptor and IGF-1 levels related to both of these progestins, are a great source of information, larger studies performed in women are needed to assess the clinical relevance of these findings. Additionally, there are mostly in vitro and little studies for both Drospirenone and Norgestimate progestins. The ones exposed involve small populations that makes it impossible to obtain significant conclusions. On the other hand, Nomegestrol Acetate appears as an attractive alternative, as it does not bind to steroid receptors and has the ability to inhibit

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the estrone sulfatase, possibly antagonizing estrogenic proliferation. Levonorgestrel also is a good candidate for risk reduction in MHT, as it has the possibility of being administered as an IUS. In this way, the progestogen can act antagonizing endometrial proliferation and have minimal systemic absorption. Needless to say that these results should be considered in the context of the benefits and other risks associated with the use of MHT; as BMI, duration of treatment, and the hormonal changes inherent in the menopausal state. Last, it should be noted that most of the available evidence consists of studies performed as far as two decades ago, with no long-term studies. Newer and larger trials are needed in order to clarify the association between each progestin and BC-risk, so as to have consistent and evidenced-based clinical guidance.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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