REVIEW ARTICLE

In Defense of Progesterone: A Review of the Literature

Allan Lieberman, MD, FAAEM; Luke Curtis, MD, MS

ABSTRACT

Context • The medical literature on the use of progesterone in postmenopausal women is often confusing and contradictory. Some physicians implicate natural progesterone in an increase in the risk of breast cancer. The chemical structure of natural progesterone (P4) is quite different from chemically altered, synthetic chemicals called progestins, which results in different actions at the cell level.

Objective • The research team intended to review the literature to examine the benefits and safety of natural progesterone and determine whether it can cause an increase or decrease in breast cancer risk.

Design • A review of the medical literature to examine the benefits and safety of natural progesterone as compared with synthetic progestins.

Intervention • Studies examined compared controls not receiving hormone therapy with women receiving estrogen alone and in combination with natural progesterone and with various synthetic progestins, such as medroxyprogesterone acetate—the most commonly used synthetic progestin.

Outcome Measures • Outcome measures included factors such as progression and survival of breast and other cancers and other epidemiological and laboratory data.

Results • A meta-analysis of 3 studies involving 86 881 postmenopausal women reported that the use of natural progesterone was associated with a significantly lower risk of breast cancer compared with synthetic progestins. Anovulation and low levels of serum progesterone have been associated with a significantly higher risk of breast cancer in premenopausal women. Use of progesterone has been linked to lower rates of uterine and colon cancers and may also be useful in treating other cancers such as ovarian, melanoma, mesothelioma, and prostate. Progesterone may also be helpful in preventing cardiovascular disease and preventing and treating neurodegenerative conditions such a stroke and traumatic brain injury.

Conclusions • Physicians should have no hesitation prescribing natural progesterone. The evidence is clear that progesterone does not cause breast cancer. Indeed, progesterone is protective and preventative of breast cancer. (*Altern Ther Health Med.* 2017;23(6):24-32)

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The literature is extensive on the effects of estrogen and progesterone and their relationships to breast and other cancers and other health-related effects. Much of the medical literature on progesterone or progesterone-like compounds is contradictory,[1-5] with progesterone sometimes implicated as a cause of breast cancer. These contradictory results are the result of researchers confusing the effects of synthetic progestins with those of natural progesterone.

The chemical structure of natural progesterone (P4) is quite different from chemically altered, synthetic chemicals called progestins. The difference in chemical structure is profound and results in different actions at the cell level. This difference is important for clinicians prescribing progesterone for various clinical uses. The evidence strongly suggests that natural progesterone is protective and preventive of breast cancer.

Figure 1. Structure of Progesterone

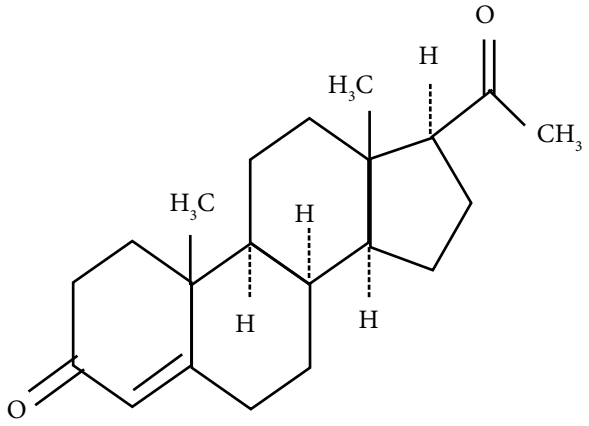


Figure 2. Structure of Dydrogesterone

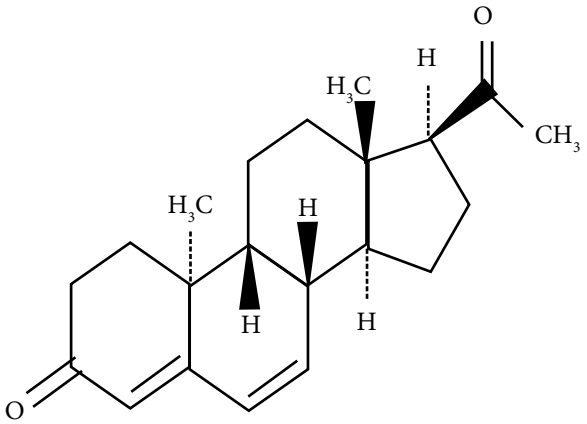
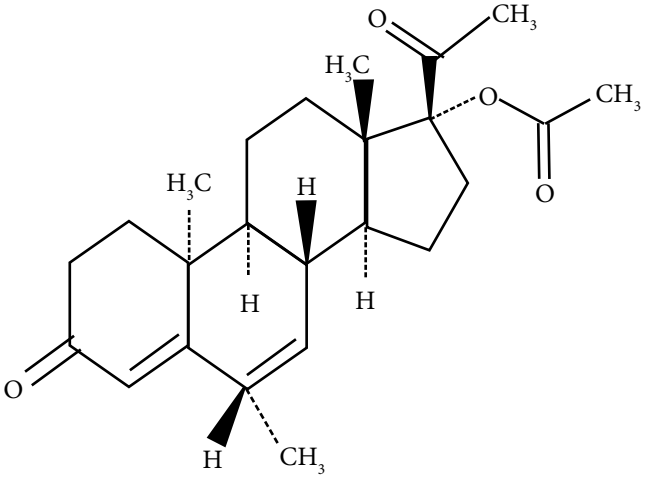


Figure 3. Structure of Medroxyprogesterone Acetate



In the interests of defending progesterone, the authors reviewed the literature examining the benefits and safety of natural progesterone and determined that progesterone does not increase breast cancer risk. Indeed, natural progesterone is protective and preventive of breast cancer.

Misuse of Terminology

The misuse of terminology, which confuses *progesterone* with *synthetic progestins*, was astutely discussed by Carroll et al[1]:

> Correct terminology is critical. Misuse of the terms *progesterone*, *progestogen*, and *progestin* is common in the medical, scientific, and public literature, which contributes to misconceptions about these compounds and their relative clinical benefits and risks. Any substance, natural or synthetic, that exerts progesterone-like activity via the activation of the progesterone receptor (PR) is called a *progestogen*. The name reflects its function in promoting and sustaining pregnancy (ie, progestation). Indeed, the main test to qualify a compound as a progestogen is its ability to induce a secretory uterine epithelium following estrogen priming. Progesterone (P4) is the only naturally occurring progestogen and is predominantly produced by the ovaries during the cycles of premenopausal women. Clinically available forms of P4 include oral micronized progesterone (OMP), which is identical to P4, and dydrogesterone, a structural isomer of progesterone. … The synthetic progestogens are specifically referred to as *progestins* and include compounds such as medroxyprogesterone acetate (MPA), levonorgestrel, and norethindrone acetate (NETA) and are prescribed worldwide. Progestins are structurally diverse but most are synthesized from molecules similar to progesterone or testosterone. To avoid confusion surrounding the long-term health benefits and consequences of using progestogenic drugs, we recommend that the term *progesterone* be used only for the naturally occurring progestogen, P4, whereas the term *progestin* be used for any of the synthetic versions. The interchangeable use of these terms in scientific, medical, and lay articles confounds the interpretation of data from these different classes of progesterone receptor (PR) ligands and their implications for human health.

Although that type of error is rampant in the medical literature, one illustrative example can be found in an article by Andrea Eisen, which refers to the Women's Health Initiative Study (WHI) as using estrogen and progesterone.[6] That statement is incorrect, because the WHI used a combination of equine estrogen and medroxyprogesterone acetate (MPA), which is a progestin.

Chemical Structures

The structures of natural progesterone, dydrogesterone, and MPA—the most commonly used synthetic progestin—are presented in Figures 1, 2, and 3.

Physiologic Effects

Progesterone. Progesterone prepares the uterus for implantation of the fertilized ovum and causes the glandular elements of the mammary gland to grow and develop into the secretory epithelium, with the ultimate effect of acting in

concert with other hormones, particularly prolactin, to facilitate milk production.[6] As stated aptly by Clarke and Sutherland[6]:

> … Progesterone might be seen as the *differentiating* female sex steroid, which inhibits the *proliferative* effects of estrogen and directs the tissue toward its normal differentiated function. Biological regulation, of course, is never so simple, and progesterone is known to have a number of other normal physiological functions, including the regulation of ovulation at both neural and ovarian loci, and major behavioral effects, including the control of sexual receptivity. Furthermore, progesterone is not always antiproliferative, and in some tissues, induces proliferative responses of its own. The induction of stromal proliferation in the uterus represents a corollary of its primary function in facilitating implantation and stimulation of lobuloalveolar proliferation in the mammary gland and is a requirement for the development of lactation.

Progestins. The most commonly used synthetic progestin in the United States, Australia, and Europe, excluding France, is MPA, also known as Provera.[1,7] A number of randomized clinical trials and epidemiological studies have reported that a combined treatment with estrogen and synthetic progesterone—progestin—is associated with significantly higher rates of breast cancer in postmenopausal women.[8] The WHI's randomized trial of 44 449 postmenopausal women reported that the women using equine estrogen—Premarin—plus progestin—MPA—showed a significantly increased risk of breast cancer compared with nonusers, a 0.60% versus a 0.42% annualized rate, respectively (hazard ratio [HR], 1.55; 95% confidence interval [CI], 1.41 to 1.70; $P < .001$).[9,10]

METHODS

Participants

Most of the studies involved pre- and postmenopausal women, although some of the studies also involved men, laboratory animals, and cell cultures.

Search Strategy. The research team searched the following data sources: PubMed, Google Scholar, and Clinical Trials.Gov. Various keywords were used for search included *progesterone*, *progestin*, *estrogen*, *MPA*, *breast cancer*, and *other cancers*.

Interventions

The studies compared controls not receiving hormone therapy with women receiving estrogen alone and in combination with natural progesterone and with various synthetic progestins, such as MPA—the most commonly used synthetic progestin.

Outcome Measures. Various outcomes were described included cancer progression and survival and other health measures.

RESULTS

Benefits of Natural Progesterone

Most studies on menopausal hormone therapy (MHT) have used synthetic progestins such as MPA, which can increase the risk for breast cancer. Alternatively, natural progesterone has been shown to be breast cancer preventive.[11-15] Asi et al[16] analysis of 3 studies involving 86 881 postmenopausal women—with a mean age 59 years and a follow-up range of 3 to 20 years—examined the relationship between the use of bioidentical progesterone versus synthetic progesterone—progestins—and breast cancer risk. The meta-analysis of those 3 studies reported that natural or bioidentical progesterone was associated with a significantly lower breast cancer risk compared to synthetic progestins when each was given in combination with estrogen (relative risk [RR], 0.67; 95% CI, 0.55 to 0.81).[16] A description of 5 studies examining the effects of MHT with either natural progesterone or dydrogesterone is presented in Table 1.[17-21]

A meta-analysis by Shah et al[22] of 8 observational studies involving more than 1 million women reported that their use of estrogen and synthetic progestin was associated with a significantly higher breast cancer risk as compared with women receiving no hormone therapy, with an odds ratio (OR) of 1.39 and a 95% CI of 1.12 to 1.72. A meta-analysis by Greiser et al[8] of 5 randomized controlled studies from 1992 to 2000 with 1 140 892 postmenopausal women reported that use of estrogen and synthetic progestin was associated with a significantly higher risk of breast cancer as compared to no use of hormone therapy (RR, 1.70; 95% CI, 1.62 to 1.78). The increased breast cancer rates reported in studies using synthetic progestins have led to a decline in worldwide hormone use for the menopause.[23]

Almost all of the reported studies showed natural progesterone to be breast cancer preventive, and it usually reduced the breast cancer risk, or at least did not increase the risk, compared with both women using synthetic progestins and women not using hormones.

In a model of breast cancer carcinogenesis induced by 7,12-dimethylbenz(a)anthracene (DMBA) in mice, Jabara and Anderson[11] found that progesterone inhibited carcinogenesis. In mice, pretreatment with progesterone markedly inhibited the DMBA induction of breast cancer. The researchers concluded, "Progesterone acts directly on the mammary gland to inhibit carcinogenesis."[11]

In vitro studies by Formby et al[12] on 2 breast cancer cell lines showed that progesterone "exhibited a strong antiproliferative effect" and induced apoptosis in the cancer cell line expressing the progesterone receptor. Ferretti et al[13] and Jerry[14] suggest a protective role for progesterone, citing the work of Rajkumar,[15] who showed a protective effect for combined estrogen and progesterone in animal models of breast cancer.

Progesterone Deficiency

Progesterone deficiency has been linked to higher rates of breast cancer. Cowan et al[24] studied 1083 Caucasian women

Table 1. Studies Examining Breast-cancer Risk of Women Given Menopausal Hormone Therapy (MHT) Containing Estrogen Plus Either Natural Progesterone (P4) or Dydrogesterone Compared With Those Receiving Synthetic Progestins

Study	Population Demographics	Follow-up	Treatment	Results Breast-cancer Risks	Interpretation
Fournier et al[17] (2008)	• 80 377 postmenopausal French women • Total of 2354 cases of breast cancer • Mean age of 53.1 y at start of follow-up	Average of 8.1 y	• No MHT • Estrogen alone • Estrogen with OMP • Estrogen and dydrogesterone • Estrogen and other progestogens, including retroprogesterone, pregnane, MPA, chlormadinone acetate, medrogestone, nomegestrol acetate, or promegestone	• No MHT—1.00 • Estrogen alone—RR, 1.29; 95% CI, 1.02 to 1.65 • Estrogen and OMP—RR, 1.00; 95% CI, 0.82 to 1.22 • Estrogen and dydrogesterone—RR, 1.16; 95% CI, 0.94 to 1.43 • Estrogen and other synthetic progestogens—RR, 1.69; 95% CI, 1.50 to 1.91	Estrogen and natural progesterone were not associated with increase in breast cancer risk. Estrogen and synthetic progestogens other than dydrogosterone were associated with a significantly higher rate of breast cancer.
Espie et al[18] (2007)	• 4949 French women • Mean age of 64.2 y in women exposed to MHT; 60.6 y in women not exposed to hormones	Approximately 2.5 y	• No MHT • Estradiol only • Estradiol plus natural progesterone • Estradiol plus synthetic progestogens	Annual breast cancer risk rates • No MHT—0.70% • Estradiol only—0.28% • Estradiol plus natural progesterone—0.40% • Estradiol plus synthetic progestins—0.94%	• Estradiol plus natural progesterone was associated with a lower breast cancer risk than estradiol plus synthetic progestins. • Differences not statistically significant.
Cordina-Duverger et al[19] (2013)	• 1555 postmenopausal French women • 739 intervention group, 816 controls • Age range intervention group—35 to 54 y, 16.5%; 55 to 64 y, 47.0%; ≥65 y, 36.5%; controls—35 to 54 y, 17.6%; 55 to 64 y, 43.6%; ≥65 y, 38.7%		• No MHT • Estrogen only • Estrogen plus natural progesterone • Estrogen plus synthetic progestins	• No MHT—1.0 • Estrogen only—OR, 1.19; 95% CI, 0.69 to 2.04 • Estrogen plus natural progesterone—OR, 0.80; 95% CI, 0.44 to 1.43 • Estrogen plus synthetic progestins-estrogen derivatives—OR, 1.57; 95% CI, 0.99 to 2.49 • Estrogen plus synthetic progestins-testosterone derivatives—OR, 3.35; 95% CI, 1.07 to 10.4	Estrogen plus natural progesterone was associated with a nonsignificant decrease in breast cancer risk, whereas estrogen plus synthetic progestin was associated with a significantly higher risk of breast cancer.
de Lignieres et al[20] (2002)	• 3175 French postmenopausal women	• Mean of 8.9 y	• No hormones • Estrogen and progestogens, with 58% of participants receiving natural progesterone, 10% dydrogesterone, and 32% other synthetic progestins	• Relative to no MHT—RR, 1.10; 95% CI, 0.73 to 1.66 for women in all groups	Breast cancer risk slightly increased group of women treated with estrogen and either natural progesterone or treated with synthetic progestogens.
Schneider et al[21] (2009)	• Case control study of 1261 British females with breast cancer and 7566 controls • Mean age at start of 51.3 y	• Mean of 6.0 y for MHT users, 5.7 y for nonusers of MHT	• No MHT • Estradiol/dydrogesterone • CEE/norgestrel • Estradiol/norethisterone • CEE/MPA	• No MHT—OR, 1.0 • Estradiol/dydrogesterone—OR, 0.68; 95% CI, 0.38 to 1.20 • CEE/norgestrel—OR, 0.73; 95% CI, 0.52 to 1.03 • Estradiol/norethisterone—OR, 0.61; 95% CI, 0.42 to 0.89 • CEE/MPA—OR, 0.78; 95 CI%, 0.50 to 1.20	Use of estradiol/dydrogesterone was associated with a somewhat lower risk of breast cancer, as were the 3 other hormone combinations.

Abbreviations: CEE, conjugated equine estrogens; CI, confidence interval; MHT, menopausal hormone therapy; MPA, medroxyprogesterone acetate; OMP, oral micronized progesterone; OR, odds ratio; RR, relative risk.

prospectively, who had been treated for infertility between 1945 and 1965, with a follow-up period of about 16 months. Progesterone deficiency, based on endometrial biopsies, cervical mucous, and basal temperature charts, was associated with a significantly higher risk of premenopausal breast cancer (HR, 5.4; 95% CI, 1.1 to 49). The risk of overall mortality was also significantly higher in the progesterone-deficient women as compared with women with normal progesterone levels (HR, 3.3; 95% CI, 1.3 to 9.1).[24]

A case-control study of 285 premenopausal women who later developed breast cancer and 555 matched controls reported that baseline levels of serum progesterone were lower in the women with breast cancer than in controls (OR for the highest versus lowest tertile, 0.61; 95% CI, 0.38 to 0.98; $P = .01$).[25]

In a prospective study of 5963 premenopausal women who gave a blood sample on day 20 to day 24 of their menstrual cycles, women in the highest tertile of blood progesterone had lower rates of breast cancer than women in the lowest tertile (RR, 0.40; 95% CI, 0.15 to 1.08; $P = .077$).[26] Two other studies reported little difference in premenstrual progesterone levels in breast cancer patients and controls.[27,28]

Li[29] et al showed that women with menstrual cycles of normal length but with subclinical anovulatory disturbances (ie, anovulation or short luteal phases) have lower progesterone-to-estrogen levels. Prior et al[30] reported that approximately one-third of all normal menstrual cycles are anovulatory, resulting in unchecked proliferation in the absence of progesterone. Anovulation is also associated with reduced bone formation and osteoporosis[29,30] and has also been associated with other health problems, such as breast cancer,[31] ovarian cancer,[32] and heart disease.[33] Some evidence indicates that exposure to endocrine-disrupting chemicals, such as polychlorinated biphenyls (PCBs) may increase the risk of anovulation.[34] A number of other studies have linked exposures to endocrine-disrupting chemicals—such as PCBs, pesticides, parabens, and bisphenol A—to breast cancer and other cancers.[35-37] **These observations of health problems associated with anovulation emphasize the importance of progesterone in reducing cancer, heart disease, and osteoporosis**.[29,30]

Prior et al[38] also stressed the positive effects of P4 progesterone in preventing sudden death/long QT syndrome, venous thromboembolism, and decreases in breast cell proliferation as well as improving breast cancer prognosis through P4 receptor alteration of estrogen-receptor. Thus, breast cancer does not increase when P4 natural progesterone is given together with estradiol. Anovulation and short luteal cycles, estimated to occur in approximately 37% of normal menstruating women, can be a critical factor in the increasing incidence of breast cancer as well as other diseases and disorders, such as osteoporosis and heart disease.[30]

Low Serum Progesterone

Low serum progesterone may also be associated with poorer survival from breast cancer. A study of 289 premenopausal women with breast cancer reported that overall survival was significantly better among women with progesterone levels exceeding 4 ng/mL.[39] Fifteen-year survival was approximately 80% in women with progesterone levels exceeding 4 ng/mL and approximately 60% in women with progesterone levels lower than 4 ng/mL.[39]

Because progesterone levels are significantly higher during the luteal phase in premenopausal women, some researchers believe that the timing of premenopausal breast cancer surgery may affect breast cancer prognosis.[40,41] A 2000 meta-analysis reported that premenopausal breast cancer survivorship was improved by an estimated 15% if the surgery was performed during the luteal phase with relatively high serum progesterone.[42] A recent review of 58 studies—10 in the United States and 48 internationally—reported that premenopausal breast cancer survivorship improved significantly in 20 studies when surgery was performed during the luteal phase and was significantly better in 8 studies when it was performed in the follicular phase, but no significant difference in survivorship existed between the 2 phases in 30 studies.[41]

But as discussed previously, if approximately one-third of premenopausal women undergoing surgery in the luteal phase are anovulatory and progesterone deficient, the 58 studies cited previously would be inaccurate and add another dimension to breast cancer initiation and survival.

Breast Cell Proliferation

Studies with humans and monkeys suggest that natural progesterone may reduce breast tissue proliferation, whereas synthetic progestins, such as MPA, may increase it.[43,44] One study treated 40 premenopausal women who had breast cancer with a topical gel containing either estrogen, natural progesterone, a combination of estrogen and progesterone, or a placebo, for 10 to 13 days preceding breast cancer surgery.[43] Analysis of breast tissue reported that mean mitosis per 1000 cells was significantly higher in women treated with estrogen alone and was significantly lower in women treated with progesterone as compared with women treated with a placebo. The mean mitosis per 1000 cells was 0.51 for the placebo-treated patients, 0.17 for the patients receiving progesterone, 0.83 for the patients receiving estrogen, and 0.52 for the patients receiving a combination of estrogen and progesterone.[43]

In Foidart et al[45] study of 40 postmenopausal women treated with topical breast gels, the mitotic index was significantly increased in women given estradiol gels—0.60 per 1000 cells—as compared with those treated with a placebo gel—0.15 per 1000 cells, whereas the mitotic index was not significantly increased in women treated with gels containing estradiol and natural progesterone or natural progesterone alone—0.20 and 0.19 per 1000 cells, respectively.

In a randomized cross-over study, 26 female, adult, cynomolgus monkeys (*Macaca fascicularis*) were treated with the following 4 oral treatments: (1) placebo, (2) estradiol, (3) estradiol plus natural micronized progesterone, and

(4) estradiol plus MPA. Relative to the monkeys given the placebo, breast cell proliferation was significantly increased in both the breast lobule and the duct cells of the monkeys given estrogen and MPA but not in the monkeys given estrogen and natural progesterone.[44] These studies suggest that use of supplemental natural progesterone may be useful before breast cancer surgery.

Mammographic Density

Mammographic breast density is a significant independent risk factor for breast cancer susceptibility that is believed to be largely genetically determined.[46,47] Several studies have reported a higher probability of developing high mammographic breast density when treated with estrogens and MPA as compared with estrogens and micronized progesterone.[48,49]

Endometrial Uterine and Ovarian Cancer

A 1995 meta-analysis of 30 studies reported that use of estrogen alone was associated with a 2.3-fold increased risk of endometrial cancer as compared with no hormone use.[50] Among estrogen and progestin users, a decreased risk of endometrial cancer was reported.[50] The Million Women Study reported that the number of endometrial cancers per 1000 women in 5 years was 3.0 without MHT, 4.9 with unopposed estrogen, and 2.0 with combined estrogen and MPA progestin therapy.[51,52] In terms of an RR of 1.0 in women never using hormones, the risk for endometrial cancer for estrogen-only users was 1.45 (95 CI, 1.02 to 2.06; $P = .04$) and the risk for users receiving combined estrogen and MPA was 0.71 (95% CI, 0.56 to 0.090; $P = .005$).[51] The use of synthetic progestins does paradoxically appear to reduce the risk of endometrial cancer, as opposed to breast cancer.

But why use synthetic progestins when at the same time they may increase breast cancer risk? A clinical trial reported that the 3-year survival of stage III ovarian cancer was significantly better in patients treated with depot progesterone acetate and platinum-based chemotherapy agents as compared with women treated with platinum-based chemotherapy alone.[53] But again, why use a progestin when natural progesterone can do the same thing more safely?

Other Cancers

Progesterone may also be useful in preventing and treating cancers that are not typically associated with hormones (ie, breast, endometrial/uterine, ovarian and prostate cancer). Ishibashi et al[54] reported that the progesterone receptor was positive in 106 of 228 individuals with non-small-cell lung cancer (46%). Proliferation was inhibited by progesterone in the cells, both in cell cultures and when injected into nude mice.[54]

The WHI study reported that use of HRT containing estrogens and progestin significantly reduced the risk of colon cancer, by 28% (RR, 72%; 95% CI, 0.38 to 0.81).[55,56] Estrogen and progesterone receptors appear to be rare on colon cancer cells. Biopsies from 156 female colon cancer patients reported that none of the colon cancer cells were estrogen-receptor positive and only 1 sample was progesterone-receptor positive.[57] Therefore, it is unlikely that progestogens exert their anti-colon-cancer effects through the progesterone receptor but rather do it through an independent mechanism.

Fang et al reported that progesterone inhibits the growth of progesterone-negative, malignant melanoma cells.[58] This finding again suggests that progesterone is effective in downregulating proliferation and increasing apoptosis in a manner independent of a progesterone receptor. A review of 22 published studies involving 31 407 patients with malignant melanoma reported that 17 studies showed a significant survival advantage for females, suggesting that progesterone may be useful in controlling malignant melanoma.[59] Huang et al[60] reported that survival in mesothelioma was significantly better in 24 females, with 15 younger than 51 years old, than in 28 males, which suggests that progesterone may be protective. Progesterone was found to induce apoptosis in malignant mesothelioma cells.[61]

Progesterone also shows promise in treating prostate cancer.[62] No matter how you interpret this data, progesterone unequivocally does not cause malignancy or decrease survival. These studies reinforce the antiproliferative effect of progesterone, independent of a progesterone receptor, and also suggest that progesterone treatment may be more effective if the progesterone receptor is positive.

Cardiovascular Risks

Natural progesterone may have safer cardiovascular effects than synthetic progestins. Use of estradiol with natural progesterone has been associated with significantly higher levels of high-density lipoprotein (HDL) cholesterol as compared with use of estradiol with MPA.[63]

Synthetic progestogens may increase the risk of venous thrombus embolism (VTE), whereas natural progesterone does not increase the risk. Renoux et al found a higher risk for individuals using oral estrogen and progestin (RR, 1.54; 95% CI 1.44 to 1.65), but not those using transdermal estrogen plus progestin (RR, 0.96; 95% CI, 0.77 to 1.20).[64]

A large prospective study reported that compared to women who did not use hormones, women who used estrogen only (RR, 1.42; 95% CI 1.21 to 1.66), estrogen and MPA (RR, 2.67; 95% CI, 2.35 to 3.17), and estrogen and norethisterone or norgestrel (RR, 1.91; 95% CI, 1.69 to 2.17) all showed significantly higher rates of VTE.[65] On the other hand, use of bioidentical micronized progesterone did not increase VTE risk in either the ESTHER Study (OR, 0.7; 95% CI, 0.3 to 4.9)[66] or the E3N Study (OR, 0.9; 95% CI, 0.6 to 1.15).[67]

Some studies have examined the relationships between MHT and heart disease. One double-blind study reported that coronary heart disease (RR, 1.23; 95% CI, 0.99 to 1.53) and stroke (RR, 1.31; 95% CI, 1.03 to 1.68) were somewhat more common in 8606 women treated with conjugated equine estrogens (CEEs) and MPA versus placebo.[68]

Neuroprotection

Progesterone has multiple nervous system functions, including stimulation of neurogenesis, myelin-sheath production, and reduction of infarct size after a stroke, and may have significant protective functions in traumatic brain injury and neurodegenerative diseases.[52,62,69-71] Other clinical trials have suggested that progesterone treatment may be useful in limiting disability and improving outcomes following traumatic brain injury.[72,73]

Rat studies have shown that the neuroprotective effects seen with natural progesterone are not seen with synthetic progestins.[74] Natural progesterone was shown to stimulate rat neural-cell proliferation, whereas MPA inhibited proliferation.[75] Other research has reported that natural progesterone can stimulate myelin regeneration in rat cells, whereas MPA has no effect.[76] These findings again emphasize the difference between natural progesterone and synthetic progestins.

Sherwin et al[77] reported other neurological and neuropsychiatric benefits of using natural progesterone in MHT as compared with synthetic progestins. Postmenopausal women treated with CEEs and oral micronized progesterone (OMP) performed significantly better on tests of working memory than women treated with either CEE and placebo or CEE and MPA. A cross-sectional study of 176 postmenopausal women *formerly* treated with estrogen plus MPA reported significant improvements in depression, anxiety, vasomotor symptoms, and somatic symptoms after they were switched to estrogen plus natural OMP for a period of 1 to 6 months.[78]

DISCUSSION

In defense of progesterone, the weight of the evidence, as presented previously, clearly shows that natural progesterone is unequivocally safe and effective in the treatment of hormone-related and hormone-independent disorders. As of 2016, research has indicated that natural progesterone has various health effects.

Natural progesterone, or P4, is not associated with an increased risk of breast cancer and is actually breast cancer preventive,[11-15] whereas synthetic progestins, such as MPA, increase breast cancer risk. Progesterone deficiency may be linked to increased breast cancer risk and/or poorer prognosis in premenopausal women. Synthetic progestins increase breast cell proliferation, whereas progesterone does not.

Progesterone prevents endometrial hyperplasia and may be combined with estrogen therapy for prevention of endometrial cancer.[79] Progesterone therapy may be useful for treating other cancers including colon, non-small-cell lung, melanoma, mesothelioma, and prostate cancers. As natural progesterone or P4 is able to reduce proliferation in melanoma cells that are progesterone receptor negative, progesterone must have hormonal effects independent of its receptors.

Natural progesterone therapy also offers significant benefits compared with the use of synthetic progestins, including a better cardiovascular profile—higher HDL cholesterol and less risk of venous thromboembolism—and neuroprotection—reduced damage from strokes and traumatic brain injury and stimulation of regeneration of nerve cells and myelin.

Interest seems to be growing in the use of bioidentical or natural progesterone and other hormones for MHT and other conditions.[80,81] The recently underway REPLENISH phase III trial is currently treating postmenopausal women with a combination of 17β-estradiol and natural progesterone contained in a single oral capsule.[82] A 2013 survey of 801 US women aged 45 to 60 years reported that 28% to 68% of prescriptions for MHT were for bioidentical compounded hormone therapy.[80]

CONCLUSIONS

Because of confusion in the medical literature, synthetic progestins have been mistakenly described as natural progesterone. Flawed studies have attributed adverse risk factors to progesterone, when in fact synthetic progestins were used. Natural progesterone (P4) is chemically very different from synthetic progestins. Although synthetic progestins can cause cancer and heart disease, natural progesterone does not. Natural progesterone is safe and effective for clinical use.

The authors emphasize the importance of progesterone deficiency, manifested premenstrually with anovulation occurring in approximately one-third of normally menstruating women. This deficiency results in unopposed estrogen proliferation in the presence of decreased levels of progesterone, which may be related to the ever-increasing incidence of hormone-related and non-hormone-related cancers. This occurrence of anovulation is believed to be related to chemical pollution by xenoestrogens in our air, food, and water. The data also suggest that supplemental use of progesterone prior to breast cancer surgery may be beneficial, and its continuing use after surgery may be helpful in improving prognosis.

The authors wish to emphasize that natural progesterone is preventive of breast and endometrial cancer, and physicians should have no hesitation prescribing it.

ACKNOWLEDGEMENTS

This study received no outside funding. We thank of the researchers and the participants in the epidemiological and clinical studies.

AUTHOR DISCLOSURE STATEMENT

This review received no outside funding. Neither author has any financial interest in natural progesterone or other pharmaceutical products.

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