

Life Extension Magazine November 2013

## AS WE SEE IT

### Surprise Findings in Estrogen Debate

By William Faloon

A dispute has raged for 70 years as to whether or not maturing **women** should replace their **sex hormones**. The **age-reversal** impact of **hormone replacement** is quite noticeable. As a result, many women want to stay on their hormones for life.

By year **2002**, doctors were liberally prescribing **estrogens** and synthetic **progestin** to females with **menopausal** symptoms.

When the **Women's Health Initiative** study showed these drugs increased risk of **breast cancer** and **vascular disease**, a stampede to halt their use ensued.<sup>1</sup>

For the past decade, mainstream medicine struggled to accurately interpret and understand the results of the **Women's Health Initiative** data. They also largely ignored the potential benefits of individualized dosing using natural human **estrogens** and **progesterone**.

**Life Extension**® long ago analyzed the underlying data. We built a strong case **against** the use of synthetic **progestin** in favor of natural **progesterone**.<sup>2-9</sup> We also argued that if aging women did not maintain **youthful** hormone balance, tragic impacts on **quality of life** and **longevity** would result.<sup>10</sup>

In **2013**, a published analysis emanating from **Yale School of Medicine** provided further evidence that synthetic **progestin** was the villain that caused female sex hormones to be abandoned beginning between **2002-2004**.<sup>11</sup>

Even more compelling, these researchers estimated that over the past decade, anywhere from **18,600** to **91,600** postmenopausal women ages 50-59 years who had undergone a hysterectomy may have **died** prematurely because they did not take **estrogen** drugs.<sup>11</sup>

The **2013** Yale report is not an aberration. A combined analysis from **27** published studies reveals a **28%** reduction in **mortality** in menopausal women under age 60 who replace their sex hormones.<sup>12</sup> The studies also show profound **quality of life** improvements in **hormone-replenished** women.<sup>12</sup>

These findings do not mean that women should rush out and seek conventional treatment. Even though some doctors today prescribe natural human hormones, most don't optimally adjust individual dosing, and almost all fail to recommend protocols designed to protect women against carcinogenic and vascular risks.

This article updates women on the benefits of **restoring** natural sex hormone balance based on the latest **scientific evidence**.



William Faloon



Estrogen is required for youthful cellular function. A **deficiency of** estrogen is associated with the onset of **age-related** disease.<sup>13,14</sup>

As women enter their perimenopausal years, their bodies' production of estradiol (an important estrogen) and progesterone declines.<sup>13</sup> Yet these hormones are needed to maintain youthful vitality.

While symptoms of **menopause** vary depending upon individual hormone balance, most women suffer because their bodies no longer produce enough **estrogen** and **progesterone**. Depression, irritability, and short-term memory lapses are common **menopausal** complaints, along with hot flashes, night sweats, sleep difficulties, and weight gain.<sup>15</sup>

In the absence of rational hormone replacement, health issues encountered during menopause may adversely impact a woman for the rest of her lifetime.

Starting between the years **2002-2004**, women were told by their doctors to **limit prolonged** use of hormone drugs. Doctors were so concerned that they prescribed hormones only long enough to obtain relief from menopausal symptoms and then no more.

In depriving women of their sex hormones, doctors failed to recognize that **estrogen** and **progesterone** are involved in critical life processes. Disorders relating to **estrogen deficit** include glaucoma, dementia, osteoporosis, heart failure, fragility, genital atrophy, loss of muscle mass and strength, and thinning of the skin.<sup>16-33</sup>



**Estrogen deficiency** may thus be characterized as a state of **accelerated** aging.<sup>14</sup> Today's women are suffering because the mainstream did not bother to embrace alternatives to synthetic **progestin** and **inappropriate estrogen** prescribing.

### WHAT DRUG WAS CAUSING THE PROBLEMS?

In their panic to "do no harm," conventional doctors minimized all sex hormone prescribing. Yet the two drugs specifically linked to increase cancer and vascular risks in the Women's Health Initiative trial data were **PremPro<sup>®</sup>** and **Premarin<sup>®</sup>**.<sup>1,34</sup>

**Premarin<sup>®</sup>** is a horse urine-derived drug that contains some estrogens that are unnatural to the human body.<sup>34</sup> It is avoided by enlightened women and some doctors today, but is still the most frequently prescribed oral estrogen drug.<sup>34</sup>

**PremPro<sup>®</sup>** is a combination of **Premarin<sup>®</sup>** and a synthetic **progestin**.<sup>1</sup> This **progestin**, called **medroxyprogesterone**, is not the same compound as the natural **progesterone** it was supposed to function as.<sup>35,36</sup>

A review of the published literature reveals that **progestin** is a major culprit behind the higher rates of vascular disease and cancer that caused doctors to abandon all female hormone drugs beginning in **2002-2004**.<sup>11</sup>

### PRESCRIBING ERRORS

**Premarin<sup>®</sup>** (*horse urine-derived estrogens*), **Provera<sup>®</sup>** (*progestin*), and **Prempro<sup>®</sup>** (*horse urine-derived estrogens and progestin*) were heavily marketed to doctors as simple solutions for menopausal complaints.

Doctors often prescribed the same oral dose of these drugs to all their menopausal patients, which might explain why a **2004** analysis showed higher incidences of **stroke** in Premarin<sup>®</sup>-prescribed females.<sup>34</sup>

What was overlooked was the adverse impact on **arterial blood clotting** based on the **route** of estrogen administration. This is important because increased blood clotting mechanisms are observed more often after **oral** rather than transdermal estrogen.<sup>47,48</sup> This emphasizes the importance of women using natural estrogen (and progesterone) as a **topical cream** and not taking oral estrogen drug pills.

One of estrogen's benefits in vascular health is to protect against **endothelial dysfunction** by increasing endothelial **nitric**

**oxide.**<sup>24</sup> Data shows that the effect of equine (horse urine-derived) estrogens markedly **decreased** gene transcription of a crucial enzyme (nitric oxide synthase) involved in the production of **nitric oxide** in endothelial cells. Compared to natural **human** estrogens, gene transcription of endothelial **nitric oxide synthase** was **30 to 50%** lower in response to **equine** estrogens.<sup>49</sup>

Several studies have shown that the cardio-protective effects of estrogen are largely negated following the addition of synthetic **progestin** as was used in the **Women's Health Initiative** trials. For example, estradiol has been associated with beneficial effects on **endothelial function**, as assessed by brachial artery flow-mediated vasodilation, but the effect was **negated** by the addition of **progestin**.<sup>50</sup>

Other study data shows that progestin, but not natural progesterone, increases the risk of coronary vasospasm.<sup>51</sup>

If physicians carefully monitored their patients' symptoms as well as checked their menopausal patients' blood levels in response to hormone restoration with natural **estrogen** and **progesterone** creams (not pills), they could have individualized the dose to potentially maximize benefit and ideally minimize risk.

Fortunately, women today have access to **low-cost** natural **estrogens** and **progesterone**. They don't have to rely on antiquated drugs (Premarin<sup>®</sup>/Prempro<sup>®</sup>/Provera<sup>®</sup>) that Big Pharma continues to promote to hurried physicians.

## WHAT ARE "NATURAL" HORMONES?

When you see the term "natural" before a hormone, such as "**natural estrogen**" that does not mean it was derived from natural sources.

What it means is that the estrogen is made in a laboratory to be natural to the human body.

Health-conscious people sometimes erroneously believe that a "natural" source of something is safer. An example of why this may not be the case is the drug **Premarin<sup>®</sup>**, which is derived from "**natural horse urine**." It contains hormones natural to **humans** (e.g. estrone) and hormones natural to **horses** (e.g. equilin, equilenin).<sup>37</sup>

**Natural bioidentical estrogen** drugs, on the other hand, contain **only** natural-to-the-human-body estrogens. In order to obtain these **100%** natural human estrogens, **bioidentical** to those produced in the human body, they have to be synthesized in a laboratory setting.

A phytoestrogen (plant estrogen) called **diosgenin** found in wild yams can be converted in a laboratory into **progesterone**.<sup>38</sup> Diosgenin cannot be converted by the human body into progesterone. Wild yam does not contain progesterone.<sup>38</sup> So to obtain **natural progesterone**, it also has to be made in a laboratory to ensure it is **100%** natural-to-the- human-body progesterone.

**Progestins** are patented, synthetic drugs that protect against estrogen-induced endometrial cancer.<sup>36</sup> **Progestins** are not "**natural-to-the-human-body**" as is natural **progesterone**.

**Progestins** are meant to function like **natural progesterone**, but a huge body of data indicates potential for adverse side effects. For example, some data suggests **natural progesterone** may confer a protective effect against **breast cancer**,<sup>39-42</sup> whereas **progestins** have been linked with increased risk.<sup>41-45</sup>

So while both **progestin** and **progesterone** are made in a laboratory, **progestin** is a foreign compound that is never naturally produced inside a woman's body.

**Progesterone** is the **bioidentical** natural-to-the-human-body hormone that provides many health benefits.

As it relates to "bioidentical" terminology, here is where the various hormone drugs stand:

### **Bioidentical**

Natural estrogen

### **Non-Bioidentical** 1,34,35,37

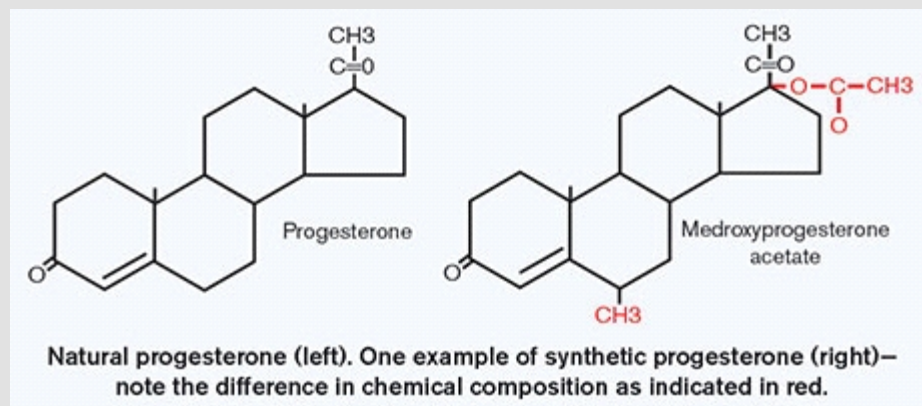
Premarin<sup>®</sup> (horse urine derived)

Natural Progesterone

Provera<sup>®</sup> (progesterin)

Prempro<sup>®</sup> (Premarin<sup>®</sup> + progesterin)

**Life Extension** recommends **bioidentical** natural **estrogen** and **progesterone** to be used in topically applied creams to avoid degradation in the liver.<sup>46</sup>



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### YALE STUDY SHOWS THAT PREMARIN<sup>®</sup> IS BETTER THAN NO ESTROGEN



In **2013**, a new analysis from the **Women's Health Initiative** was published on women aged 50-59 who had undergone a hysterectomy. These women had significantly reduced levels of estrogen (in particular estradiol) production occurring in their bodies.

This study analysis, emanating from the **Yale School of Medicine**, estimated that between 2002 and 2011 a minimum of about **18,000** and as many as about **91,000** excess deaths occurred among hysterectomized women aged 50 to 59 years who did not take Premarin<sup>®</sup>.<sup>11</sup>

For women in this age group taking oral Premarin<sup>®</sup> (without progesterone), the reduction in deaths from coronary heart disease and colon cancer appear to outweigh the increase in deaths from breast cancer, stroke, and pulmonary embolism.

What makes this finding so compelling is that these women were taking oral Premarin<sup>®</sup>...

- n without **individualized dosing** (to optimize tolerability);
- n without **natural progesterone** (to protect against unopposed estrogen on hormone-responsive tissues like the breast, potentially reducing breast cancer risk);<sup>39-42</sup>

- n without **topical** preparations (to avoid the first-pass effect of oral estrogen in the liver linked to inflammation and arterial blood clotting);<sup>46-48</sup>
- n without estrogen modifiers like **indole-3-carbinol** (to inhibit formation of estrogenic metabolites linked to increased risk of breast cancer);<sup>52,53</sup>
- n without enough **vitamin D** (to regulate breast cell proliferation);<sup>54-56</sup> and
- n without being on a comprehensive program that involves ingesting **healthy foods** and reducing intake of dangerous ones.

The size of this analysis by Yale researchers makes a compelling argument that it may be better for **estrogen-deficient** women age 50-59 years to blindly take what many believe to be the worst estrogen drug (oral Premarin<sup>®</sup>) than to do without **any estrogen at all**.

In addition to the mortality benefit for women ages 50-59 years, hormone therapy in this analysis provided an improvement in **quality-of-life** measures during the first several years of treatment.

Women over 59 did not see these benefits with **Premarin<sup>®</sup>-only** therapy, nor would we expect them to. Aging humans have to be far more careful as to how they implement a hormone balancing program.

What few have yet to understand is that as women move through **menopause**, their estrogen blood levels can plummet to the range of hysterectomized females. We now know these low estrogen levels can cause significantly higher **death rates**, along with **menopausal miseries**.

The good news is this does not have to happen to women just because they are growing older. There are protocols using only natural bioidentical forms of **estrogen** and **progesterone** absorbed **topically** that, when combined with healthy lifestyle/supplement choices, can more safely induce a rejuvenating effect!

## FINDINGS FROM 27 ADDITIONAL STUDIES ON HORMONE REPLACEMENT

No matter how prestigious the institution, or the size or quality of the study, one should always seek out confirmatory data when making a decision as substantive as restoring **sex hormones** back to youthful ranges.

From a mechanistic standpoint, when one understands how essential **estrogen** and **progesterone** are to a woman's life processes, it would be logical to seek to maintain these hormones at youthful levels for life. But there is always concern about side effects.

To evaluate the worst case scenario, **Life Extension** researchers evaluated data derived from 27 published studies that looked at the long-term effects of many different forms of conventional estrogen and progestin drugs on menopausal women.<sup>12</sup> Eight of these studies were observational, while 19 were randomized controlled trials involving 16,000 women followed for 83,000 patient-years. Some of the trials used hormone drugs we consider hazardous or suboptimal.

None of these trials follow the comprehensive natural hormone protocols to include nutrient support that **Life Extension** recommended decades ago.

We reviewed data from all these studies to ascertain the **mortality risk** in women taking conventional hormone replacement compared to those who did not. The pooled analysis from these twenty-seven independent studies showed that women under age 60 who replaced their **sex hormones** were **28%** less likely to die!<sup>12</sup>

In the process of not dying, the **quality-of-life** measures showed clear benefit to women who restored their sex hormones.<sup>12</sup>

So what does this tell us? Since **2002-2004**, warnings have emanated from the FDA, mainstream medical groups, and practicing physicians that replacing hormones in maturing women is dangerous. Yet the **2013** Yale study of hysterectomized postmenopausal women, **plus** an analysis of **27** hormone therapy trials using **suboptimal** hormone preparations in women age 60 years and younger, shows a mortality reduction in women who replace their sex hormones.

There is no question that improperly prescribed hormone replacement is going to increase cancer and vascular risks. But women no longer have to be subjected to outmoded prescribing practices. There is solid data to enable women of all ages to regain a more youthful hormone profile, using natural forms of estrogen and progesterone that have intriguing studies indicating reductions in cancer and vascular risks.

## NATURAL PROGESTERONE PROTECTS AGAINST BREAST CANCER

Compared to **synthetic progestin** that stimulates breast cell proliferation, **natural progesterone** has demonstrated a protective effect.

There are at least **17** studies showing that **progestins** significantly **increase** breast cell replication and growth largely due to stimulation of the estrogen receptor by progestins.<sup>42,45,57-71</sup> In stark contrast, at least **11** studies have shown that natural **progesterone** does not induce estrogen-stimulated breast cell proliferation.<sup>68-78</sup>



Numerous studies have demonstrated an **increased** risk of breast cancer with the use of synthetic **progestins**.<sup>1,45,79-81</sup> However, the use of natural (bioidentical) **progesterone** has not been associated with an increased risk of breast cancer.<sup>39-42,80,82</sup>

Quite to the contrary, research has revealed that natural progesterone **decreases** the risk of **breast cancer**. In a study published in the journal *Breast Cancer Research and Treatment*, 80,000 postmenopausal women using various forms of hormone replacement therapy (HRT) were followed for more than 8 years. Women who used estrogen in combination with synthetic **progestin** had a **69% increased** risk of breast cancer, compared to women who had never used HRT. However, for women who used natural **progesterone** in combination with estrogen, the increased risk of breast cancer was **completely eliminated** with a significant **reduction** in breast cancer risk compared with synthetic progestin use.<sup>82</sup>

In another investigation, these same researchers found a **40% increased** risk of breast cancer for women who used estrogen with synthetic progestin.<sup>80</sup> Interestingly, in women who used estrogen combined with natural progesterone, there was a promising trend toward a **reduced** risk of breast cancer, compared to women who had never used HRT.<sup>80</sup> In essence, natural progesterone appeared to **protect** women against the development of breast cancer. These findings confirm work done six years earlier that found a trend toward a reduced risk of breast cancer in 1,150 women using natural **progesterone**, compared to non-users of progesterone.<sup>83</sup>

Compelling research offers further insight into natural progesterone's ability to defend against breast cancer. In a fascinating study, scientists administered estrogen alone, natural progesterone alone, estrogen plus natural progesterone, or placebo to 40 women prior to surgery to remove a breast lump. The hormones were applied topically to the breast for about 12 days before surgery. As expected, when given alone, estrogen caused a **62% increase** in breast cell proliferation rates compared to placebo. Conversely, the addition of natural progesterone to estrogen resulted in a significant **decrease** in the estrogen-induced increase in breast cell proliferation rates. Even more impressive was the finding that the group receiving natural progesterone alone had a nearly **76% lower** breast cell proliferation rate compared to the placebo group.<sup>72</sup>

### BREAST CANCER IS NOT THE ONLY CAUSE OF PREMATURE DEATH

With all the media attention and fundraising by support groups, you might be lulled into thinking the **only** disease women prematurely die from is **breast cancer**.

Each year, over **40,000** women in the United States do die of metastatic breast cancer.<sup>89</sup> But there are a total of about **1,250,000** female deaths each year in this country.<sup>90</sup> That means for every one breast cancer death, there are approximately 31 women who die from something else.

Many of those "**something else**" diseases relate to hormone deficiencies. That does not mean women should ignore breast cancer risk and blindly take hormone drugs. It does, however, bring into context the health issues maturing women really face. These "**something else**" deaths provide a rationale for the **natural hormone restoration** approaches long advocated by progressive physicians and the Life Extension Foundation®.

As you'll read in an article in this month's issue of *Life Extension*, there are prudent ways women can reduce breast cancer risk.

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#### HIGHER PROGESTERONE = LOWER BREAST CANCER INCIDENCE



A growing body of literature has documented a strong connection between a woman's progesterone levels and her subsequent risk for breast cancer. A trial reported in the *International Journal of Cancer* measured blood levels of progesterone in 5,963 premenopausal women. Incredibly, the analysis of the data revealed that those women with the *highest* blood levels of **progesterone** who had regular menses experienced an **88% decreased** risk of breast cancer.<sup>84</sup>

These findings corroborate another study in which 1,083 women treated for infertility were followed for upwards of **33 years** to determine their subsequent breast cancer risk. Compared to women with normal progesterone levels, progesterone *deficient* women had a **5.4 times increased** risk of premenopausal breast cancer and were **10 times** as likely to die from any cancer.<sup>85</sup>

Similarly, researchers at the University of North Carolina School of Public Health measured progesterone levels in pregnant women, who were then followed for upwards of **32 years**. The researchers discovered that those women with the *highest* blood levels of progesterone during pregnancy had a promising trend toward a lower risk of breast cancer, compared to women with the lowest levels of progesterone during pregnancy. When the researchers analyzed the risk of breast cancer in women under age 51, those with the *highest progesterone* levels had a staggering **70% decreased** risk compared to the group with the lowest progesterone levels.<sup>86</sup>

Findings from two other investigations revealed that survival rates for breast cancer are strongly correlated with the patient's **progesterone** levels at the time of surgery.<sup>87,88</sup> One study noted that in cases where cancer had spread to local lymph nodes, **65%** of women with a progesterone level of **4.0 ng/mL** or more on the day of their surgical treatment of **breast cancer** were alive **18 years** later, while only **35%** of women with low progesterone levels on the day of surgery were still living after 18 years.<sup>88</sup> The scientists noted that progesterone lowers the expression of *vascular endothelial growth factor*, which promotes the increase in new blood vessels (angiogenesis) that is essential for tumor growth. These scientists concluded: **"This study has confirmed that a raised level of progesterone at the time of tumor excision is associated with an improvement in prognosis for women with operable breast cancer."**<sup>88</sup>



#### NATURAL PROGESTERONE AND CARDIOVASCULAR HEALTH

The *Women's Health Initiative*, a large randomized clinical trial, demonstrated that the addition of synthetic progestins to estrogen therapy resulted in a substantial increase in the risk of heart attack and stroke.<sup>1</sup>

Numerous studies, on the other hand, document that *natural* progesterone has *beneficial* effects on cardiovascular health.

In one trial published in the *Journal of the American College of Cardiology*, researchers studied postmenopausal women with a history of heart attack or coronary artery disease. The women were given estrogen in combination with either natural

progesterone or synthetic progestin. After 10 days of treatment the women underwent exercise treadmill tests. Compared to the synthetic progestin group, the amount of time it took to produce myocardial ischemia (reduced blood flow to the heart) on the exercise treadmill was substantially *improved* in the natural progesterone group.<sup>91</sup>

The risk of a blood clot is a serious concern with the use of **estrogen** replacement therapy, especially by the oral route. This risk doesn't occur when natural **progesterone** is added to the mix.<sup>92</sup> One investigation compared the risk of blood clots in postmenopausal women taking natural progesterone to the risk in women taking synthetic progestin. The group of women who used synthetic progestin in combination with estrogen had a startling **290% greater risk of blood clots**, compared to the group who never used HRT. The group receiving natural **progesterone** in combination with estrogen, on the other hand, had a **30% decreased risk of blood clots**, compared to women who never used HRT.<sup>92</sup>

## NATURAL PROGESTERONE PROTECTS AGAINST ATHEROSCLEROSIS

Atherosclerosis (hardening of the arteries) is a leading cause of heart disease. Several studies have determined that synthetic **progestin** promotes the formation of atherosclerosis.<sup>93-95</sup>

The story is quite different for natural **progesterone**, where multiple animal studies have shown that natural progesterone *inhibits* the process of atherosclerosis.<sup>95-97</sup>

To illustrate, scientists fed monkeys with surgically induced menopause a diet known to cause atherosclerosis for a total of 34 months. The scientists then divided the monkeys into groups that received estrogen alone, estrogen plus synthetic progestin, or a control group that did not receive hormones. The control group developed substantial atherosclerotic plaque. The administration of **estrogen** resulted in a **72% decrease** in atherosclerotic plaque, compared to the control group.<sup>95</sup>

Treatment with synthetic progestin yielded disturbing results. The group of postmenopausal monkeys that received **estrogen** combined with synthetic **progestin** had a similar amount of atherosclerotic plaque as the control group. This showed that synthetic progestin completely *reversed* estrogen's inhibitory effects on the formation of atherosclerosis.<sup>95</sup>

In contrast, when the same investigators administered natural **progesterone** along with estrogen, no such inhibition of estrogen's cardiovascular benefit was seen.<sup>98</sup>

## NATURAL PROGESTERONE INCREASES HDL



**High-density lipoprotein (HDL)** functions to *remove* cholesterol from the arterial wall and thus helps protect against the development of atherosclerosis.<sup>99</sup> Low HDL is a proven risk factor that contributes to heart disease.<sup>99</sup>

Synthetic progestin is known to cause reductions in HDL levels.<sup>100-102</sup> One mechanism by which natural progesterone enhances cardiovascular health is its ability to maintain or even increase **HDL** levels in women receiving estrogen replacement therapy.<sup>103-105</sup>

In one study published in the *Journal of the American Medical Association*, 875 postmenopausal women were randomized to receive estrogen alone, estrogen combined with synthetic (non-natural) progestin, estrogen combined with natural progesterone, or placebo. The results demonstrated that the group receiving natural progesterone demonstrated much higher **HDL** levels than the group receiving progestin.<sup>106</sup>

These results confirm earlier preliminary data provided by researchers who administered estrogen combined with either **progestin** or natural **progesterone** to postmenopausal women. The use of progestin resulted in an undesirable **15% decrease** in **HDL** levels, compared to only minor changes to HDL levels in those patients prescribed natural progesterone.<sup>100</sup>

## WHAT HAPPENS DURING MENOPAUSE?



The average age of menopause in the United States is only **51**.<sup>107</sup>

**Perimenopause** is the time period leading up to menopause, a time when a woman's hormones may fluctuate quite wildly, producing a variety of uncomfortable effects.<sup>108</sup> Although **estradiol**, a critical estrogen in the body, is significantly reduced in menopause, **estrone**, another important estrogen found naturally in a woman's body, does not drop as precipitously, and in some cases, levels of **estrone** may increase in the perimenopausal period.<sup>109</sup>



**Estrogen dominance** is a term that is relatively unrecognized in conventional medicine, yet alternative medical practitioners estimate that this syndrome may affect nearly half the women over age 35 in the United States.<sup>110</sup> Caused by an imbalance between estrogen and progesterone, this syndrome may cause many undesirable and dysfunctional issues.<sup>110</sup>

When the adrenal glands are stressed, they secrete excess cortisol. Cortisol is made from progesterone in the body. Progesterone is depleted as cortisol levels increase because more progesterone is being used to make cortisol.<sup>111</sup>

As more progesterone is shunted or sequestered to make cortisol, less is available to balance estrogen. Another common reason for low progesterone levels is an anovulatory cycle (a menstrual cycle in which there is no ovulation), often observed in perimenopause.<sup>111,112</sup> Without ovulation there is no corpus luteum to make additional progesterone for the cycle. The reduced progesterone level leads to excessive estrogen and relative deficiency of progesterone.

So for a period of time, perimenopausal women in particular may have relatively high **estrogen** in relation to **progesterone**. Yet progesterone is **required** to protect against the adverse effects of a relative increase in estrogen.<sup>110</sup> Is it any wonder why incidences of cancer and thrombosis (arterial blood clotting) begin to increase in the perimenopausal time period? Progesterone is needed to balance the normal effects of estrogen, which is especially important when estrogen replacement is initiated.

A **blood test** can reveal a woman's own, individualized hormonal needs to include **progesterone** replacement, as well as estrogen, like **estradiol**. Tragically, conventional doctors today are blindly prescribing estrogen drugs without testing their female patients to ascertain their individual needs.

The consequences of untreated menopause from a **longevity** and **quality-of-life** standpoint are severe. Simply defined, menopause is a deviation from youthful **estrogen/progesterone** balance. Proven methods exist to rationally restore hormone status, but most maturing women never learn about it. That's all about to change.

### A VINDICATION FOR SUZANNE SOMERS



For the past decade, actress and best-selling author **Suzanne Somers** has passionately advocated natural hormone replacement for maturing women. She endured blistering criticism from mainstream doctors who warned of catastrophic problems if women dared to restore their **estrogen/progesterone** to youthful ranges.

Suzanne's fervent position was that individualized dosing of natural **estrogens** and **progesterone** markedly improves life quality and extends healthy life span.

Mainstream doctors based their dire warnings on the huge **Women's Health Initiative** study whose initial results were released in the **2002-2004** period. This study looked at women taking oral **Premarin**<sup>®</sup> or **PremPro**<sup>®</sup> and linked these drugs to increased disease risk.<sup>1</sup> Subsequent studies and analysis reveal these deadly effects were caused by **synthetic progestin** and probably the **orally** administered **Premarin**<sup>®</sup>. Suzanne figured this out before mainstream medicine.

**Premarin**<sup>®</sup> by itself was linked to increased **stroke** risk, which is probably related to:

1. It being prescribed **orally** (instead of transdermal),
2. The **horse estrogens** counteracting estrogen's endothelial benefits, plus
3. Doctors failing to prescribe **natural progesterone** to balance out the effects of **estrogen**.<sup>34</sup>

As of **2012** the maker of **PremPro®** has paid out **\$896 million** to resolve lawsuits alleging that the drug caused cancer in women. Another **\$330 million** has been reserved to pay future claims.<sup>113</sup>

The **FDA** has not removed **Prempro®** from the market. If you type "**PremPro**" into **Google**, the drug maker has an attractive website ([www.prempro.com](http://www.prempro.com)) to induce menopausal women to take it.<sup>114</sup>

So the question begs, who is going to alert the American public to avoid these lethal hormone drugs?

### SUZANNE'S COMMITMENT

Suzanne Somers is **66** years old. A lot of people retire before this age or are forced to quit working because of health impairments.

Instead, Suzanne is dedicating herself to educating the world about the lethal effects of **synthetic progestin** and the advantages of natural **estrogens** and **progesterone**. She has been a personal beneficiary of natural hormone replacement. Don't be surprised to see her on major television shows airing this year and next.

A dilemma Suzanne recognized long ago was the difficulty women had in locating physicians knowledgeable about prescribing **natural sex hormones** to maturing women. She has spent the last decade interacting with doctors to find out where women could go to have their hormones restored to a youthful range based on individual need.

In her new book, Suzanne describes the profound anti-aging effects that occur in response to natural hormone replacement and reveals a new network of physicians ([www.ForeverHealth.com](http://www.ForeverHealth.com)) committed to properly prescribing them.

### BIG PHARMA'S CATASTROPHIC IMPACT ON LONGEVITY

In **1994**, I wrote *Life Extension's* first article warning against synthetic **progestins** and horse urine-derived **estrogens**.

An incredible amount of evidence from nearly **20 years ago** showed that **natural progesterone** was safer and more effective than **synthetic progestin** found in **PremPro®** and **Provera®**. Yet the public was kept largely in the dark. The number of female lives that could have been spared had the **FDA** acted humanely (by removing **progestin** drugs) is difficult to calculate. Instead, the FDA issued proclamations that made it more challenging for American women to access **natural progesterone** creams.



**Premarin®** (horse urine-derived estrogen) was first introduced in **1942**.<sup>115</sup> It may have had a place in medical history when properly used. Why women today would choose this **71-year old drug**, when **natural estrogen** creams are widely available indicates how progress is impeded when medicine is dominated by FDA **regulation** in lieu of free market **innovation**.

This editorial revealed startling new findings showing that **estrogen** protects against premature death in women who are deficient in it.<sup>11</sup> This is confirmed by 27 prior studies showing a **28%** reduction in mortality reduction in maturing women who replace their hormones.<sup>12</sup>

What makes these reductions in premature death so compelling is that most of the women in these studies were not using the natural forms of **estrogen** and **progesterone** that have shown superior benefits. The clear message is that restoring youthful hormone balance may be one of the most effective ways to **feel better today** and live much longer in the future.

In this issue of *Life Extension*, we feature an exclusive interview with **Suzanne Somers** and describe ways maturing women can reduce their cancer risks.

It costs **\$75 a year** to belong to the **Life Extension Foundation®**. If the only benefit a woman received was learning about the lethal effects of **synthetic progestin** nearly **20 years ago**, then membership may have resulted in one of life's grand bargains.

For longer life,



William Faloon

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## Surprise Findings in Estrogen Debate

By William Faloon

### REFERENCES

1. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002 July 17;288(3):321-33.
2. Available at: <http://www.lef.org/magazine/mag96/96jan1b.htm?source=search&key=synthetic%20progestin>. Accessed August 5, 2013.
3. Available at: [http://www.lef.org/magazine/mag98/jun98\\_cover.htm?source=search&key=synthetic%20progestin](http://www.lef.org/magazine/mag98/jun98_cover.htm?source=search&key=synthetic%20progestin). Accessed August 5, 2013.
4. Available at: [http://www.lef.org/magazine/mag98/jun98\\_cover2.html?source=search&key=synthetic%20progestin](http://www.lef.org/magazine/mag98/jun98_cover2.html?source=search&key=synthetic%20progestin). Accessed August 5, 2013.
5. Available at: <http://www.lef.org/magazine/mag99/june99-report1.html?source=search&key=synthetic%20progestin>. Accessed August 5, 2013.
6. Available at: [http://www.lef.org/magazine/mag2002/dec2002\\_report\\_hormone\\_01.html](http://www.lef.org/magazine/mag2002/dec2002_report_hormone_01.html). Accessed August 5, 2013.
7. Available at: [http://www.lef.org/magazine/mag2002/dec2002\\_cover\\_premarin\\_01.htm?source=search&key=synthetic%20progestin](http://www.lef.org/magazine/mag2002/dec2002_cover_premarin_01.htm?source=search&key=synthetic%20progestin). Accessed August 5, 2013.
8. Available at: [http://www.lef.org/magazine/mag2003/jun2003\\_report\\_female\\_01.htm?source=search&key=synthetic%20progestin](http://www.lef.org/magazine/mag2003/jun2003_report_female_01.htm?source=search&key=synthetic%20progestin). Accessed August 5, 2013.
9. Available at: [http://www.lef.org/magazine/mag2006/apr2006\\_report\\_progesterone\\_01.htm?source=search&key=synthetic%20progestin](http://www.lef.org/magazine/mag2006/apr2006_report_progesterone_01.htm?source=search&key=synthetic%20progestin). Accessed August 5, 2013.
10. Available at: [http://www.lef.org/magazine/mag2009/oct2009\\_Bioidentical-Hormones\\_06.htm](http://www.lef.org/magazine/mag2009/oct2009_Bioidentical-Hormones_06.htm). Accessed August 12, 2013.
11. Sarrel PM, Njike VY, Vinante V, Katz DL. The mortality toll of estrogen avoidance: An analysis of excess deaths among hysterectomized women aged 50 to 59 years. *Am J Public Health*. 2013 Jul 18.
12. Salpeter SR, Cheng J, Thabane L, Buckley NS, Salpeter EE. Bayesian meta-analysis of hormone therapy and mortality in younger postmenopausal women. *Am J Med*. 2009 Nov;122(11):1016-22.
13. Horstman AM, Dillon EL, Urban RJ, Sheffield-Moore M. The role of androgens and estrogens on healthy aging and longevity. *J Gerontol A Biol Sci Med Sci*. 2012 Nov;67(11):1140-52.
14. Birge SJ. The use of estrogen in older women. *Clin Geriatr Med*. 2003 Aug;19(3):617-27, viii.
15. Available at: <http://www.medicinenet.com/menopause/article.htm>. Accessed August 5, 2013.
16. Vajaranant TS, Pasquale LR. Estrogen deficiency accelerates aging of the optic nerve. *Menopause*. 2012 Aug;19(8):942-7.
17. Pasquale LR, Rosner BA, Hankinson SE, Kang JH. Attributes of female reproductive aging and their relation to primary open-angle glaucoma: a prospective study. *J Glaucoma*. 2007 Oct-Nov;16(7):598-605.
18. Altintas O, Caglar Y, Yüksel N, Demirci A, Karabas L. The effects of menopause and hormone replacement therapy on quality and quantity of tear, intraocular pressure and ocular blood flow. *Ophthalmologica*. 2004 Mar-Apr;218(2):120-9.
19. Rocca WA, Grossardt BR, Shuster LT, Stewart EA. Hysterectomy, oophorectomy, estrogen, and the risk of dementia. *Neurodegener Dis*. 2012 10(1-4):175-8.

20. Paganini-Hill A, Henderson VW. Estrogen deficiency and risk of Alzheimer's disease in women. *Am J Epidemiol*. 1994 Aug 1;140(3):256-61.
21. Nappi RE, Sinforiani E, Mauri M, Bono G, Polatti F, Nappi G. Memory functioning at menopause: impact of age in ovariectomized women. *Gynecol Obstet Invest*. 1999 47(1):29-36.
22. Aydin A, Kenar H, Atmaca H, et al. The short- and long- term effects of estrogen deficiency on apoptosis in musculoskeletal tissues: an experimental animal model study. *Arch Iran Med*. 2013 May;16(5):271-6.
23. Syed FA, Mödder UI, Roforth M, et al. Effects of chronic estrogen treatment on modulating age-related bone loss in female mice. *J Bone Miner Res*. 2010 Nov;25(11):2438-46.
24. Novella S, Dantas AP, Segarra G, Medina P, Hermenegildo C. Vascular aging in women: Is estrogen the fountain of youth? *Front Physiol*. 2012;3:165.
25. Bairey Merz CN, Johnson BD, Sharaf BL, et al. Hypoestrogenemia of hypothalamic origin and coronary artery disease in premenopausal women: a report from the NHLBI-sponsored WISE study. *J Am Coll Cardiol*. 2003 Feb 5;41(3):413-9.
26. Seeman E. Estrogen, androgen, and the pathogenesis of bone fragility in women and men. *Curr Osteoporos Rep*. 2004 Sep;2(3):90-6.
27. Lynch C. Vaginal estrogen therapy for the treatment of atrophic vaginitis. *J Womens Health (Larchmt)*. 2009 Oct;18(10):1595-606.
28. Available at: [http://www.obgmanagement.com/index.php?id=20667&tx\\_ttnews\[tt\\_news\]=175742](http://www.obgmanagement.com/index.php?id=20667&tx_ttnews[tt_news]=175742). Accessed August 6, 2013.
29. Available at: <http://www.clinicaladvisor.com/tissue-changes-associated-with-vaginal-atrophy/article/177880/#>. Accessed August 6, 2013.
30. Maltais ML, Desroches J, Dionne IJ. Changes in muscle mass and strength after menopause. *J Musculoskelet Neuronal Interact*. 2009 Oct-Dec;9(4):186-97.
31. Lowe DA, Baltgalvis KA, Greising SM. Mechanisms behind estrogen's beneficial effect on muscle strength in females. *Exerc Sport Sci Rev*. 2010 Apr;38(2):61-7.
32. Shu YY, Maibach HI. Estrogen and skin: therapeutic options. *Am J Clin Dermatol*. 2011 Oct 1;12(5):297-311.
33. Hall G, Phillips TJ. Estrogen and skin: the effects of estrogen, menopause, and hormone replacement therapy on the skin. *J Am Acad Dermatol*. 2005 Oct;53(4):555-68.
34. Anderson GL, Limacher M, Assaf AR, et al. Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004 Apr 14;291(14):1701-12.
35. Goletiani NV, Keith DR, Gorsky SJ. Progesterone: review of safety for clinical studies. *Exp Clin Psychopharmacol*. 2007 Oct;15(5):427-44.
36. Otto C, Fuchs I, Vonk R, Fritzemeier KH. Comparative analysis of the uterine and mammary gland effects of progesterone and medroxyprogesterone acetate. *Maturitas*. 2010 Apr;65(4):386-91.
37. Bhavnani BR. Pharmacokinetics and pharmacodynamics of conjugated equine estrogens: chemistry and metabolism. *Proc Soc Exp Biol Med*. 1998 Jan;217(1):6-16.
38. Available at: <http://umm.edu/health/medical/altmed/herb/wild-yam>. Accessed August 7, 2013.
39. Formby B, Wiley TS. Progesterone inhibits growth and induces apoptosis in breast cancer cells: inverse effects on Bcl-2 and p53. *Ann Clin Lab Sci*. 1998 Nov-Dec;28(6):360-9.
40. Campagnoli C, Clavel-Chapelon F, Kaaks R, Peris C, Berrino F. Progestins and progesterone in hormone replacement therapy and the risk of breast cancer. *J Steroid Biochem Mol Biol*. 2005 Jul;96(2):95-108.
41. Holtorf K. The bioidentical hormone debate: are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy? *Postgrad Med*. 2009 Jan;121(1):73-85.
42. Wood CE, Register TC, Lees CJ, Chen H, Kimrey S, Cline JM. Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys. *Breast Cancer Res Treat*. 2007 Jan;101(2):125-34.
43. Zhou J, Yu Q, Chen R, et al. Medroxyprogesterone acetate-driven increase in breast cancer risk might be mediated via cross-talk with growth factors in the presence of progesterone receptor membrane component-1. *Maturitas*. 2013 Jul 12.
44. Chlebowski RT, Manson JE, Anderson GL, et al. Estrogen plus progestin and breast cancer incidence and mortality in the Women's Health Initiative Observational Study. *J Natl Cancer Inst*. 2013 Apr 17;105(8):526-35.
45. Liang Y, Benakanakere I, Besch-Williford C, Hyder RS, Eilersieck MR, Hyder SM. Synthetic progestins induce growth and metastasis of BT-474 human breast cancer xenografts in nude mice. *Menopause*. 2010 Sep-Oct;17(5):1040-7.
46. Baker VL. Alternatives to oral estrogen replacement. Transdermal patches, percutaneous gels, vaginal creams and rings, implants, other methods of delivery. *Obstet Gynecol Clin North Am*. 1994 Jun;21(2):271-97.
47. Vehkavaara S, Silveira A, Hakala-Ala-Pietilä T, et al. Effects of oral and transdermal estrogen replacement therapy on markers of coagulation, fibrinolysis, inflammation and serum lipids and lipoproteins in postmenopausal women. *Thromb Haemost*. 2001 Apr;85(4):619-25.
48. L'hermite M. HRT optimization, using transdermal estradiol plus micronized progesterone, a safer HRT. *Climacteric*. 2013 Aug;16 Suppl 1:44-53.
49. Novensa L, Selent J, Pastor M, Sandberg K, Heras M, Dantas AP. Equine estrogens impair nitric oxide production and endothelial nitric oxide synthase transcription in human endothelial cells compared with the natural 17{beta}-estradiol. *Hypertension*. 2010 Sep;56(3):405-11.

50. Wakatsuki A, Okatani Y, Ikenoue N, Fukaya T. Effect of medroxyprogesterone acetate on endothelium-dependent vasodilation in postmenopausal women receiving estrogen. *Circulation*. 2001 Oct 9;104(15):1773-8.
51. Miyagawa K, Rösch J, Stanczyk F, Hermsmeyer K. Medroxyprogesterone interferes with ovarian steroid protection against coronary vasospasm. *Nat Med*. 1997 Mar;3(3):324-7.
52. Fowke JH, Longcope C, Hebert JR. Brassica vegetable consumption shifts estrogen metabolism in healthy postmenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2000 Aug;9(8):773-9.
53. Michnovicz JJ, Adlercreutz H, Bradlow HL. Changes in levels of urinary estrogen metabolites after oral indole-3-carbinol treatment in humans. *J Natl Cancer Inst*. 1997 May 21;89(10):718-23.
54. Bortman P, Folgueira MA, Katayama ML, Snitcovsky IM, Brentani MM. Antiproliferative effects of 1,25-dihydroxyvitamin D3 on breast cells: a mini review. *Braz J Med Biol Res*. 2002 Jan;35(1):1-9.
55. Lowe L, Hansen CM, Senaratne S, Colston KW. Mechanisms implicated in the growth regulatory effects of vitamin D compounds in breast cancer cells. *Recent Results Cancer Res*. 2003;164:99-110.
56. Holick MF. Vitamin d, sunlight and cancer connection. *Anticancer Agents Med Chem*. 2013 Jan 1;13(1):70-82.
57. Ory K, Lebeau J, Levalois C, et al. Apoptosis inhibition mediated by medroxyprogesterone acetate treatment of breast cancer cell lines. *Breast Cancer Res Treat*. 2001 Aug;68(3):187-98.
58. Hofseth LJ, Raafat AM, Osuch JR, Pathak DR, Slomski CA, Haslam SZ. Hormone replacement therapy with estrogen or estrogen plus medroxyprogesterone acetate is associated with increased epithelial proliferation in the normal postmenopausal breast. *J Clin Endocrinol Metab*. 1999 Dec;84(12):4559-65.
59. Jeng MH, Parker CJ, Jordan VC. Estrogenic potential of progestins in oral contraceptives to stimulate human breast cancer cell proliferation. *Cancer Res*. 1992 Dec 1;52(23):6539-46.
60. Kalkhoven E, Kwakkenbos-Isbrücker L, de Laat SW, van der Saag PT, van der Burg B. Synthetic progestins induce proliferation of breast tumor cell lines via the progesterone or estrogen receptor. *Mol Cell Endocrinol*. 1994 Jun;102(1-2):45-52.
61. Papa V, Reese CC, Brunetti A, Vigneri R, Siiteri PK, Goldfine ID. Progestins increase insulin receptor content and insulin stimulation of growth in human breast carcinoma cells. *Cancer Res*. 1990 Dec 15;50(24):7858-62.
62. Jordan VC, Jeng MH, Catherino WH, Parker CJ. The estrogenic activity of synthetic progestins used in oral contraceptives. *Cancer*. 1993 Feb 15;71(4 Suppl):1501-5.
63. Catherino WH, Jeng MH, Jordan VC. Norgestrel and gestodene stimulate breast cancer cell growth through an oestrogen receptor mediated mechanism. *Br J Cancer*. 1993 May;67(5):945-52.
64. Cline JM, Soderqvist G, von Schoultz E, Skoog L, von Schoultz B. Effects of conjugated estrogens, medroxyprogesterone acetate, and tamoxifen on the mammary glands of macaques. *Breast Cancer Res Treat*. 1998 Apr;48(3):221-9.
65. Cline JM, Soderqvist G, von Schoultz E, Skoog L, von Schoultz B. Effects of hormone replacement therapy on the mammary gland of surgically postmenopausal cynomolgus macaques. *Am J Obstet Gynecol*. 1996 Jan;174(1 Pt 1):93-100.
66. Menendez JA, Oza BP, Colomer R, Lupu R. The estrogenic activity of synthetic progestins used in oral contraceptives enhances fatty acid synthase-dependent breast cancer cell proliferation and survival. *Int J Oncol*. 2005 Jun;26(6):1507-15.
67. Seeger H, Rakov V, Mueck AO. Dose-dependent changes of the ratio of apoptosis to proliferation by norethisterone and medroxyprogesterone acetate in human breast epithelial cells. *Horm Metab Res*. 2005 Aug;37(8):468-73.
68. Murkes D, Conner P, Leifland K, et al. Effects of percutaneous estradiol-oral progesterone versus oral conjugated equine estrogens-medroxyprogesterone acetate on breast cell proliferation and bcl-2 protein in healthy women. *Fertil Steril*. 2011 Mar 1;95(3):1188-91.
69. Wood CE, Register TC, Cline JM. Transcriptional profiles of progestogen effects in the postmenopausal breast. *Breast Cancer Res Treat*. 2009 Mar;114(2):233-42.
70. Neubauer H, Ruan X, Schneck H, et al. Overexpression of progesterone receptor membrane component 1: possible mechanism for increased breast cancer risk with norethisterone in hormone therapy. *Menopause*. 2013 May;20(5):504-10.
71. Murkes D, Lalitkumar PG, Leifland K, Lundström E, Söderqvist G. Percutaneous estradiol/oral micronized progesterone has less-adverse effects and different gene regulations than oral conjugated equine estrogens/medroxyprogesterone acetate in the breasts of healthy women in vivo. *Gynecol Endocrinol*. 2012 Oct;28 Suppl 2:12-5.
72. Chang KJ, Lee TT, Linares-Cruz G, Fournier S, de Lignières B. Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo. *Fertil Steril*. 1995 Apr;63(4):785-91.
73. Foidart JM, Colin C, Denoo X, et al. Estradiol and progesterone regulate the proliferation of human breast epithelial cells. *Fertil Steril*. 1998 May;69(5):963-9.
74. Mueck AO, Seeger H, Wallwiener D. Comparison of the proliferative effects of estradiol and conjugated equine estrogens on human breast cancer cells and impact of continuous combined progestogen addition. *Climacteric*. 2003 Sep;6(3):221-7.
75. Inoh A, Kamiya K, Fujii Y, Yokoro K. Protective effects of progesterone and tamoxifen in estrogen-induced mammary carcinogenesis in ovariectomized W/Fu rats. *Jpn J Cancer Res*. 1985 Aug;76(8):699-704.
76. Barrat J, de Lignières B, Marpeau L, et al. The in vivo effect of the local administration of progesterone on the mitotic activity of human ductal breast tissue. Results of a pilot study. *J Gynecol Obstet Biol Reprod (Paris)*. 1990;19(3):269-74.
77. Malet C, Spritzer P, Guillaumin D, Kuttann F. Progesterone effect on cell growth, ultrastructural aspect and estradiol receptors of normal human breast epithelial (HBE) cells in culture. *J Steroid Biochem Mol Biol*. 2000 Jun;73(3-4):171-81.
78. Laidlaw IJ, Clarke RB, Howell A, Owen AW, Potten CS, Anderson E. The proliferation of normal human breast tissue implanted into athymic nude mice is stimulated by estrogen but not progesterone. *Endocrinology*. 1995 Jan;136(1):164-

79. van Leeuwen FE. Epidemiologic aspects of exogenous progestagens in relation to their role in pathogenesis of human breast cancer. *Acta Endocrinol (Copenh)*. 1991;125 Suppl 1:13-26.
80. Fournier A, Berrino F, Riboli E, Avenel V, Clavel-Chapelon F. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. *Int J Cancer*. 2005 Apr 10;114(3):448-54.
81. Porch JV, Lee IM, Cook NR, Rexrode KM, Burin JE. Estrogen-progestin replacement therapy and breast cancer risk: the Women's Health Study (United States). *Cancer Causes Control*. 2002 Nov;13(9):847-54.
82. Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. *Breast Cancer Res Treat*. 2008 Jan;107(1):103-11.
83. Plu-Bureau G, Lê MG, Thalabard JC, Sitruk-Ware R, Mauvais-Jarvis P. Percutaneous progesterone use and risk of breast cancer: results from a French cohort study of premenopausal women with benign breast disease. *Cancer Detect Prev*. 1999;23(4):290-6.
84. Micheli A, Muti P, Secreto G, et al. Endogenous sex hormones and subsequent breast cancer in premenopausal women. *Int J Cancer*. 2004 Nov 1;112(2):312-8.
85. Cowan LD, Gordis L, Tonascia JA, Jones GS. Breast cancer incidence in women with a history of progesterone deficiency. *Am J Epidemiol*. 1981 Aug;114(2):209-17.
86. Peck JD, Hulka BS, Poole C, Savitz DA, Baird D, Richardson BE. Steroid hormone levels during pregnancy and incidence of maternal breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2002 Apr;11(4):361-8.
87. Badwe RA, Wang DY, Gregory WM, et al. Serum progesterone at the time of surgery and survival in women with premenopausal operable breast cancer. *Eur J Cancer*. 1994;30A(4):445-8.
88. Mohr PE, Wang DY, Gregory WM, Richards MA, Fentiman IS. Serum progesterone and prognosis in operable breast cancer. *Br J Cancer*. 1996 Jun;73(12):1552-5.
89. Irvin W Jr, Muss HB, Mayer DK. Symptom management in metastatic breast cancer. *Oncologist*. 2011;16(9):1203-14.
90. Available at: [http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61\\_06.pdf](http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_06.pdf). Accessed August 7, 2013.
91. Rosano GM, Webb CM, Chierchia S, et al. Natural progesterone, but not medroxyprogesterone acetate, enhances the beneficial effect of estrogen on exercise-induced myocardial ischemia in postmenopausal women. *J Am Coll Cardiol*. 2000 Dec;36(7):2154-9.
92. Canonico M, Oger E, Plu-Bureau G, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation*. 2007 Feb 20;115(7):840-5.
93. Register TC, Adams MR, Golden DL, Clarkson TB. Conjugated equine estrogens alone, but not in combination with medroxyprogesterone acetate, inhibit aortic connective tissue remodeling after plasma lipid lowering in female monkeys. *Arterioscler Thromb Vasc Biol*. 1998 Jul;18(7):1164-71.
94. Levine RL, Chen SJ, Durand J, Chen YF, Oparil S. Medroxyprogesterone attenuates estrogen-mediated inhibition of neointima formation after balloon injury of the rat carotid artery. *Circulation*. 1996 Nov 1;94(9):2221-7.
95. Adams MR, Register TC, Golden DL, Wagner JD, Williams JK. Medroxyprogesterone acetate antagonizes inhibitory effects of conjugated equine estrogens on coronary artery atherosclerosis. *Arterioscler Thromb Vasc Biol*. 1997 Jan;17(1):217-21.
96. Morey AK, Pedram A, Razandi M, et al. Estrogen and progesterone inhibit vascular smooth muscle proliferation. *Endocrinology*. 1997 Aug;138(8):3330-9.
97. Houser SL, Aretz HT, Quist WC, Chang Y, Schreiber AD. Serum lipids and arterial plaque load are altered independently with high-dose progesterone in hypercholesterolemic male rabbits. *Cardiovasc Pathol*. 2000 Nov-Dec;9(6):317-22.
98. Adams MR, Kaplan JR, Manuck SB, et al. Inhibition of coronary artery atherosclerosis by 17-beta estradiol in ovariectomized monkeys. Lack of an effect of added progesterone. *Arteriosclerosis*. 1990 Nov-Dec;10(6):1051-7.
99. Tall AR. Cholesterol efflux pathways and other potential mechanisms involved in the athero-protective effect of high density lipoproteins. *J Intern Med*. 2008 Mar;263(3):256-73.
100. Fåhræus L, Larsson-Cohn U, Wallentin L. L-norgestrel and progesterone have different influences on plasma lipoproteins. *Eur J Clin Invest*. 1983 Dec;13(6):447-53.
101. Larsson-Cohn U, Fåhræus L, Wallentin L, Zador G. Lipoprotein changes may be minimized by proper composition of a combined oral contraceptive. *Fertil Steril*. 1981 Feb;35(2):172-9.
102. Hirvonen E, Mälkönen M, Manninen V. Effects of different progestogens on lipoproteins during postmenopausal replacement therapy. *N Engl J Med*. 1981 Mar 5;304(10):560-3.
103. Ottosson UB. Oral progesterone and estrogen/progestogen therapy. Effects of natural and synthetic hormones on subfractions of HDL cholesterol and liver proteins. *Acta Obstet Gynecol Scand Suppl*. 1984;127:1-37.
104. Ottosson UB, Johansson BG, von Schoultz B. Subfractions of high-density lipoprotein cholesterol during estrogen replacement therapy: a comparison between progestogens and natural progesterone. *Am J Obstet Gynecol*. 1985 Mar 15;151(6):746-50.
105. Jensen J, Riis BJ, Strøm V, Nilas L, Christiansen C. Long-term effects of percutaneous estrogens and oral progesterone on serum lipoproteins in postmenopausal women. *Am J Obstet Gynecol*. 1987 Jan;156(1):66-71.
106. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. *JAMA*. 1995 Jan 18;273(3):199-208.
107. Available at: <http://www.nia.nih.gov/health/publication/menopause>. Accessed August 13, 2013.

108. Available at: <http://www.mayoclinic.com/health/perimenopause/DS00554>. Accessed August 13, 2013.
109. Available at: <http://www.altmedrev.com/publications/10/1/36.pdf>. Accessed August 13, 2013.
110. Available at: <http://www.liveto110.com/estrogen-dominance-syndrome/>. Accessed August 14, 2013.
111. Available at: <http://www.westonaprice.org/metabolic-disorders/low-metabolic-energy-therapies>. Accessed August 14, 2013.
112. Burger HG, Hale GE, Dennerstein L, Robertson DM. Cycle and hormone changes during perimenopause: the key role of ovarian function. *Menopause*. 2008 Jul-Aug;15(4 Pt 1):603-12.
113. Available at: <http://www.businessweek.com/news/2012-06-19/pfizer-paid-896-million-in-prempro-accords-filing-shows>. Accessed August 7, 2013.
114. Available at: <http://www.prempro.com/>. Accessed August 14, 2013.
115. Available at: <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm168838.htm>. Accessed August 14, 2013.

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