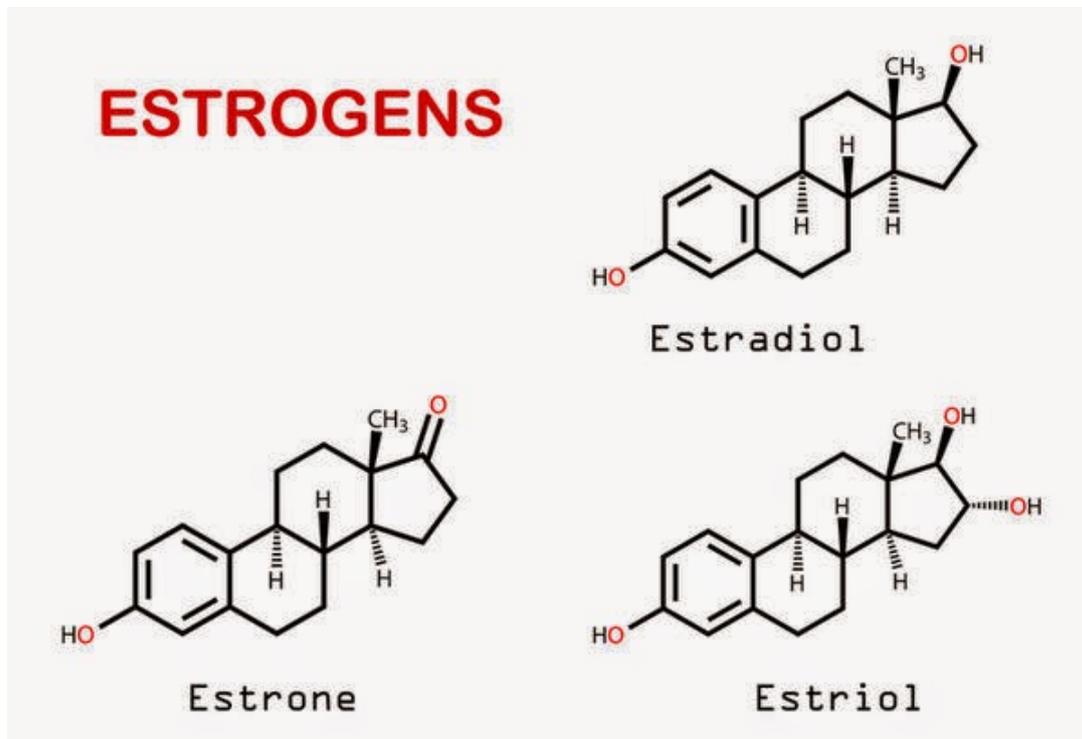


# NOT ALL ESTROGENS ARE CREATED EQUAL: What You Need to Know

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**Fig 1. The three main estrogens**

When discussing estrogen it is important to note that “estrogen” is an umbrella term for many different estrogens. The main three are estriol, estrone, and estradiol; all three of these estrogens are produced in the body and have physiological effects. Some of the benefits of estrogens are:

- control hot flashes
- maintain pelvic health
- improve cognitive function and memory
- improve mood
- restore sleep
- maintain thickness and fullness of skin and hair
- protect against colon cancer
- protect against macular degeneration
- prevent atherosclerosis, hypertension
- improve insulin sensitivity
- prevent osteoporosis

- prevent osteoarthritis

This list may surprise some people especially given how oestrogen has been demonised as “something to be feared”. It also gives glimpse into why tissues may function less well as estrogens decline at menopause, why certain symptoms occur and the likely gains from restoring levels of estrogen over and above the elimination of symptoms. The aim of this article is to clarify what we know about oestrogens and the way to optimise their safe use and also to lay to rest some of the misconceptions and misinformation that are prevalent in the public eye. The number of oocytes (eggs) decrease during ageing which causes a decreased production of estrogen and progesterone starting as early as age 30. Perimenopause is characterized by infrequent ovulation and low progesterone as the number of functional oocytes progressively declines. Ovarian failure leads to menopause.

It is important to note that Coronary heart disease, dementia, osteoporosis, hip fracture, stroke, Parkinsonism, cognitive impairment, depression, anxiety and breast cancer are associated with estrogen deficiency and all are rare before menopause. The first 3 diseases are clearly associated with estrogen deficiency and breast cancer – with progesterone deficiency. Early removal of the ovaries increases risk of heart disease, osteoporosis, and dementia. Estradiol (E2) and progesterone (P4) collaborate in bone re-modelling with resorption by estrogen and formation by progesterone. It is more likely that oestrogen together with progesterone are responsible for many of the above protective effects that are usually credited to estrogens alone (1-7).

Not all of the 3 main estrogens (see Fig 1) have the same potency. Estradiol (E2) is the predominant estrogen produced in pre-menopausal women while estrone (E1) is the primary estrogen produced after menopause. In the body, estradiol is reversibly oxidized to estrone and both estradiol and estrone can be converted to estriol. The potency of E2 is 12 times that of E1 and 80 times that of E3 (8).

In the literature, there is scant information regarding serum estriol values in non-pregnant, premenopausal women. In conventional medical practice, it is believed that estriol plays no significant role in non-pregnant women compared to other estrogens. Dr. Jonathan Wright’s study showed that serum estriol was always significantly higher than the sum of estrone and estradiol and less fluctuating (9). He concluded that estriol is probably a significant estrogen component. Reference values are available for serum estrone and estradiol, but serum estriol levels are listed in reference books only for pregnant women.

Research on estriol to date had been focused on concentrations in pregnant women. Prior to the 1970s, the technology was not sophisticated enough to accurately analyze estriol in non-pregnant patients and by the time estriol could be analyzed accurately, researchers had already conclusively demonstrated that estriol was a much weaker hormone than estradiol and estrone; therefore, it was believed to be of no known importance. Dr. Wright developed a solid-phase competitive-binding radio-immunoassay (RIA) procedure for estriol.

The data showed that the estriol in every case was at least three times as great as the concentration of estradiol and estrone combined. The average Estrogen quotient (EQ = Estriol level/ estradiol + estrone levels) for the population was 8.9. With estriol circulating at nearly 10 times the concentration of estrone and estradiol. It did appear from this data that there must be some unknown significant biological activity for this “weaker” hormone (9).

Furthermore, estriol has been used for decades without reported safety concerns and is a component of medications approved for use worldwide. The FDA has acknowledged that it is unaware of any adverse events associated with the use of compounded medications containing estriol (10).

Studies show that when estriol is given together with estradiol, the estradiol-specific stimulation to cells is decreased (11). Experimental studies also suggest that estriol has a protective effect against radiation-induced cancer of the breast (12).

### **ESTROGEN RECEPTORS**

Differences in effect of the 3 main estrogens are evident at the receptor level highlighting the likelihood that not all the estrogens will have the same effects at a cellular level. Estrogen effects are mediated through 2 different estrogen receptors: estrogen receptor-alpha (ER- $\alpha$ ) and estrogen receptor-beta (ER- $\beta$ ) (13-18). Estrogen receptor- $\alpha$  promotes breast cell proliferation, while ER- $\beta$  inhibits proliferation and prevents breast cancer development via G2 cell cycle Arrest (13, 19-24).

Because of its differing effects on ER alpha and ER beta, we would expect that estriol would be less likely to induce proliferative [potential cancerous growth] changes in breast tissue and to be associated with a reduced risk of breast cancer (10). Estradiol equally activates ER- $\alpha$  and ER- $\beta$ , while estrone selectively activates ER- $\alpha$  at a ratio of 5:1 (25,26). In contrast, estriol selectively binds ER- $\beta$  at a ratio of 3:1(25,26). This unique property of estriol, in contrast to the selective ER- $\alpha$  binding by other estrogens (14, 25-28) imparts to estriol a potential for breast cancer prevention (29-33) while other estrogens would be expected to promote breast cancer (13,19-22,34). The above is the reason why doctors who prescribe bio-identical estrogen will tend to combine estriol and estradiol (usually 80:20 ratio) and omit estrone.

It is worth noting that conjugated equine estrogens (CEE) are potent down-regulators of ER- $\beta$  receptors (35). Whether this activity is unique to CEE is unclear, but it could potentially increase carcinogenic properties. CEEs also contains at least one particularly potent carcinogenic estrogen, 4-hydroxy-equilenin, which promotes cancer by inducing DNA damage (36-40).

Acting alone, estriol is a weak estrogen, but when given with estradiol, it functions as an anti-estrogen (41). Estriol and/or tamoxifen, as opposed to other estrogens, prevented the development of breast cancer in rats after the administration of carcinogens (42,43).

In a large study of more than 30 000 women the use of estrogen-only HRT increased the risk of breast cancer compared with that in non-users; the addition of a synthetic progestin further increased breast cancer risk while the use of an estriol-containing preparation was not associated with the risk of breast cancer that was seen with other preparations (44).

The increased risk of uterine cancer in users of non-bio-identical estrogen is well-established in the scientific literature (45-47). In contrast, a case-controlled study reported that the use of topical lower-potency estriol is not associated with an increased risk of uterine cancer (48)

Estriol and progesterone levels dramatically increase during pregnancy (an approximate 15-fold increase in progesterone and a 1000-fold increase in estriol), and postpartum women continue to produce higher levels of estriol than nulliparous women (49). An increased exposure to progesterone and estriol during and after pregnancy confers a significant long-term reduction in the risk for breast cancer (50, 51-53, 49, 54-58). Urinary estriol levels in postmenopausal women show an inverse correlation with the risk for breast cancer in many studies (59, 60-65).

We conclude from all the evidence taken together, that not all estrogens are created equal and that estriol may play a greater role than is currently thought particularly as a more protective estrogen and as a regulator of its more potent sisters (estradiol and estrone). Furthermore, when combined with progesterone rather than with synthetic progestins, the risks associated with conventional HRT seem to be minimized or even negated. The role and actions of different progesterone and progestins are summarized in a companion article to this one **“Not All Progesterones are Created Equal”** ([https://thenaturaldoctor.org/wp-content/uploads/2019/07/PROGESTERONE-AND-BREAST-CANCER\\_compressed.pdf](https://thenaturaldoctor.org/wp-content/uploads/2019/07/PROGESTERONE-AND-BREAST-CANCER_compressed.pdf)).

As stated earlier the FDA has not received a single report of an adverse event in more than 40 years of estriol use. The castigation of estriol in recent years did not seem to be because it is at least as safe and effective as current estrogens on the market, but in response to what was considered unsupported claims that estriol was safer than current forms of estrogen replacement and because there is no standardized dose.

As stated above estriol has unique physiologic properties associated with a reduction in the risk of breast cancer, and combining estriol with estradiol in hormone replacement preparations would be expected to decrease the risk for breast cancer; and even moreso when combined with progesterone and not progestins.

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