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Women's Health

Women's Reproductive System as Balanced Estradiol and Progesterone Actions—A revolutionary, paradigm-shifting concept in women's health

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Purposes This review is to illustrate current concepts of women's reproduction with its cultural over-emphasis on estrogen and positive actions, while progesterone tends to be ignored or associated with negative effects. To explore the physiology, and the clinical implications of understanding that progesterone and estradiol interact in counterbalancing and complementary ways within a complex system that is Women's Reproductive Health.

Data synthesis in the context of this paradigm shift Fundamental, descriptive, quantitative and experimental data all show that estradiol's important cellular action is to promote growth and proliferation; by contrast, despite short-term proliferative effects, progesterone's dominant actions are to inhibit proliferation, to enhance differentiation and promote maturation. Estradiol and progesterone variably interact in every cell and tissue in women's bodies and across the life cycle.

Incorporation of the new paradigm into clinical and/or research relevance Since ovulation and thus progesterone's presence is subclinical in normal-length cycles, we urgently need a convenient, home, once/cycle, inexpensive test of *normal ovulation*. Major funding is needed for ovulation-testing cycle-by-cycle over months or years in large population-based cohorts of adolescent, premenopausal and perimenopausal women. These women need to be followed for their later-life experiences of osteoporotic fracture, myocardial infarction, breast and endometrial cancers. In addition, all research with menstruating women participants and female mammals needs cycle-phase specific testing.

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Conclusion It is difficult to perceive, much less to change, a current paradigm. With this journal issue, however, we have begun the important tasks of transforming concepts about women's health, and setting the research agenda to advance the innovative understanding that women reproductive and overall health becomes optimal when premenopausal menstrual cycle estradiol and progesterone actions are balanced within this complex system

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The concept of women's reproduction as a complex system

Women's reproductive health research often focuses on a particular characteristic, for illustration, let's say ''age at menarche'' and how that variable is (linearly) related, say, to age at menopause. That design ignores the likelihood that both menarche and menopause ages may relate to a common (often unmeasured) variable and may be differentially influenced by nutrition, genetic or epigenetic backgrounds, social stressors, having a father at home, or childhood sexual abuse [1]. It is important to view Women's Health as a *complex* ovarian *system* [2] rather than, in a reductionist manner, as a phenomenon simply dominated by estrogen. Changing our view of women's reproduction into one that it is a nuanced and complex system, has the potential to importantly advance our physiological knowledge.

What do I mean when I say a ''complex system''? It is not just *complicated*, as most medical students believe women's menstrual cycles to be, rather, a complex system is multidimensional, interactive, dynamic, non-linear, and multiply balanced with many feedback loops [2]. In addition, women's health is ecologically embedded in a given woman's social, emotional and physical environment [3]. Within a complex system, the notion that the actions of estradiol and progesterone are balanced becomes not only sensible but necessary. To set the stage for what we will discuss in detail later, let me give you two examples of the tightly linked estradiol-progesterone inter-relationship: the estradiol midcycle peak is needed to trigger a luteinizing hormone (LH) peak; the LH peak stimulates ovulation, corpus luteum formation and luteal phase high progesterone production; estradiol in needed in every tissue to facilitate production of progesterone receptors (PR) so that progesterone can act to decrease estrogen's proliferation and cause cell differentiation and cell maturation.

Before we can get to the that physiology, we need to know where we start in our cultural concepts.

The cultural focus on estrogen as *THE* woman's hormone

As a society, we generally consider a woman *healthy* if she has sufficient estrogen, or *unhealthy* if she is considered ''estrogen deficient'' [4]. Although, like most paradigms, it is hard to ''see'' what culture accepts as normal or natural [5]. Currently estrogen (or *estradiol*, its menstrual cycle form) is the primary focus/symbol/emblem of women's reproduction and even health. A simple way to investigate the relative roles of estradiol and progesterone is to search the medical literature. My Google Scholar search was perfectly parallel: ''women's reproduction AND *estrogen*'' resulted in 223,000 citations; ''women's reproduction AND *progesterone*'' yielded only 88,300 (accessed 2020/11/04).

The word ''estrogen'' is derived ''from the Greek οστρος (*oistros*), literally meaning 'verve or inspiration' but figuratively sexual passion or desire, with the suffix *-gen*, meaning 'producer of'" (https://en.wikipedia.org/wiki/Estrogen accessed 2020/11/03). Thus, the word ''estrogen'' itself means ''producing passion.'' Most estrogen-related scientific and lay literature tends to be favorable, attributing many positives to this ''estrogen-based trio'' of hormones (estrone, estradiol and estriol). However, a recent paper describes estradiol as a ''necessary evil''; attributing importance to estrogen, but linking increasing obesity and sedentary behavior with higher estrogen levels and then to increased risks for PCOS, infertility, ovarian and breast cancers in women and gynecomastia in men [6].

Whether positive or negative, is accurate physiology reflected in this major focus on estrogen?

You might think so if you uncritically viewed common depictions of the menstrual cycle. The reproductive lifespan of 30–50 years during which women typically have menstrual cycles, is dominated by ovarian hormones. As shown in Fig. 1-**A**, moderate-high estradiol levels are present throughout almost all of the cycle. Estradiol reaches a large mid-cycle peak with a secondary, smaller luteal or premenstrual plateau. Progesterone, by contrast, is low for the entire first half of the cycle only eventually reaching a moderate plateau following ovulation. We are so used to this image (replicated by hundreds of ''Google images'') that we don't even notice that neither estradiol nor progesterone *has any reported units of measurement*.

Fig. 1-**B** shows a more accurate picture (both literally and figuratively) of menstrual cycle hormonal levels [7]. In this diagram based on serum levels in healthy women, the low levels during menstruation for both estradiol and progesterone are used as their respective baselines [7]. The Y-axis shows the percentage changes across the cycle in levels of estradiol and progesterone above that baseline [7]. This figure looks

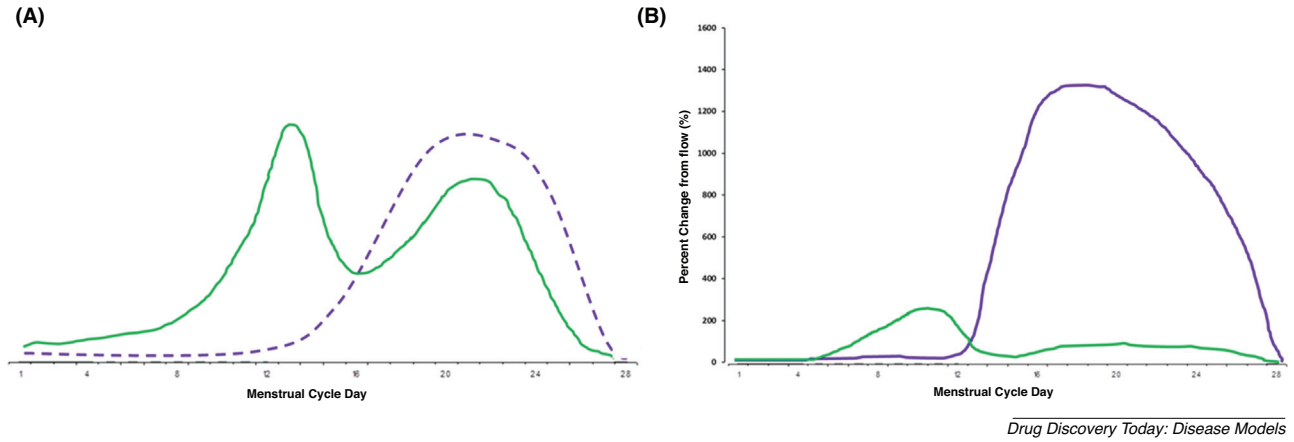

Fig. 1. A. This is a very typical simple depiction (as often seen in Google Images) of the levels of estradiol and progesterone across the menstrual cycle. **B.** This line drawing is based on a study of estradiol and progesterone across a normal, ovulatory menstrual cycle in healthy premenopausal women [7]. It shows estradiol and progesterone levels as their percentage changes from their respective low levels during menstruation in the early follicular phase. Redrawn from Ref. [7].

quite different than Fig. 1-**A**! To further understand the absolute and relative quantities of these two steroids it is also necessary to know that estradiol is reported in *pmol/L* units, while progesterone is reported in *nmol/L* units; a single *nmol* is 1000-fold larger than a single *pmol*.

With Fig. 1-**B** we can now "see" how large a quantity of progesterone the corpus luteum produces during a normally ovulatory menstrual cycle. Given generally parsimonious steroid hormone production, this suggests ovarian progesterone must be important; it must do more than assist with reproduction. Further, given this more accurate understanding of the relative menstrual cycle levels of estradiol and progesterone, it is egregious to "forget" to include progesterone, as did international experts in publishing a menstrual cycle diagram in *Nature Reviews Disease Primers* in 2015 [8].

Now we need to answer a historical, cultural question: how did we come to see estradiol as women's dominant (or only) important hormone?

What are the origins of the current cultural emphasis on estrogen/estradiol?

That is not entirely clear, but perhaps it was because investigation of the "follicular hormone" [9] was begun earlier and the chemistry of *estrone* (women's menopause-dominant form of estrogen) was documented earlier (in 1929) [10] than that of *progesterone* (in 1934) [11]. Already by 1929, Dr. Frank, who later suggested ovarian irradiation would be a good treatment for the premenstrual syndrome (!), had published a monograph, *The Female Hormone,* describing the exciting discovery of estrone [12]. Ironically, *estradiol*, the dominant *menstrual* form of estrogen, was not purified and chemically documented until 1940 [10].

However, Professor Oudshoorn, reports that estrone, extracted and purified from the urine of pregnant patients as provided to biochemist by physicians in the Netherlands, immediately began to be used by those specialists as a treatment for women [13]. Furthermore, she also observed that the estrogen-discovering scientists, the estrogen-treating clinicians and the estrogen-making pharmaceutical manufacturers all worked together [14]. In North America, the pregnant mare's urine purification into conjugated equine estrogen (CEE, brand name Premarin®) became highly lucrative in the 1940s and 1950s; CEE-related pharmaceutical donations led to the founding of the first departments of academic gynecology. Thus, for gynecologists, estrogen appears to be an affair of the heart [15].

How did progesterone come to be devalued or ignored?

That question is the flip side of the evidence for estradiol's prominent role in our cultural understanding of women.

Primary Gonadal Steroids			
	ESTRADIOL	TESTOSTERONE	
Animal	Female	Male	SEX
Human	Woman	Man	SEX & GENDER

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Fig. 2. This simple diagram shows the dichotous concept of human sex and human hormones. It wrongly assigns estrogen as woman's (only) hormone and rightly views testosterone as man's hormone. The concept in this figure likely influences understanding of women's reproduction to the present.

Here again, social scientist, Professor Oudshoorn, provides a suggestion: we knew that testosterone was men's unique hormone; it made sense that estrogen was women's hormone. This was the perfect dichotomy of testosterone for men and estrogen for women [16] (Fig. 2). Descartes' philosophy of dualism was particularly prominent during that era.

There are likely several further contributions to progesterone's current lack of stature as a woman's reproductive hormone: 1) progesterone was initially inactive by mouth, in stark contrast to estrogen that was quite orally absorbable and active [11]; 2) synthetic progestins were soon created, became used as a ''replacement'' for progesterone, and were wrongly equated with, and even called, ''progesterone'' (as we have seen); 3) progesterone was available in the mid-1900 for parenteral use (a painful, intramuscular injection), but was not micronized and marketed as a bioavailable, readily accessible, oral therapy until 1980 [11]; Prometrium® was not approved in Canada until 1996, and in the USA until 1998; and 4) ovulation, and thus progesterone production, is silent within clinically normal menstrual cycles; normal-length, predictable menstruation came to be understood as 'ovulatory' and irregular or long cycles (wrongly) as 'anovulatory.'

Subclinical ovulatory disturbances—estradiol is normal but progesterone low/absent

Some experts in women's reproduction disbelieve that regular, normal-length menstrual cycles (often called 'eumenorrheic' meaning 'true menstruation') could *possibly* have abnormal ovulation [17]. ''Ovulatory disturbances'' is a broad term to include a variety of situations in which progesterone production is low or absent. Ovulatory disturbances include insufficient luteal phases (egg release but lower progesterone levels), short luteal phases (egg release with decreased duration of high progesterone production) or anovulation (no egg release and no increase in progesterone above follicular phase low levels) [17]. When ovulatory disturbances occur, as they commonly do [18], within clinically normal cycles, they are called ''silent'' or ''subclinical'' ovulatory disturbances.

Despite the common belief that 'a regular cycle is an ovulatory cycle', there is robust, population-based serum progesterone level evidence that regular and clinically normal menstrual cycles have a high likelihood of subclinical ovulatory disturbances [19]. Again, despite general belief to the contrary, there is also recent evidence that short luteal phase cycles are associated with (at least temporary) subfertility [20]. We hypothesize, based on integration of the literature and prospective [18,21] and controlled [22–28] studies in women, that estradiol and progesterone need functionally balanced actions equivalent to a normal-length normally ovulatory cycle during the majority of the reproductive lifespan for optimal current health and wellbeing. In addition, we postulate that a majority of normally ovulatory cycles across a woman's long reproductive life span is needed to prevent osteoporosis and fracture [29], heart attacks [30,31] and breast [32,33] and endometrial cancers [34] during women's older years.

To assess the plausibility of these hypotheses, we must examine the interacting actions of estradiol and progesterone at the cellular and the tissue levels in various organs and systems.

Biological and physiological activities of estradiol and progesterone

We have discussed hormone *quantities* in section 2, but now need to investigate the *activities* of estradiol (E2) and progesterone (P4). These are summarized graphically in Fig. 4.

Fundamental estradiol and progesterone activities—cell proliferation and differentiation

The fundamental (now classical paper), is by Clarke and Sutherland published in 1990, in *Endocrine Reviews* [35]. (Note that these authors wrongly used the word ''progestin'' for progesterone. Progesterone is an endogenous ovarian hormone; progestins are a man-created ''knock-offs'' of progesterone [36], that, to be so classified are only required to transform the endometrium from proliferative to secretory and to preserve an early pregnancy.) In this important, 1990 review, by examining various tissues *in vitro* from females of many species and in women, the authors outline the dynamic and interacting effects of estradiol and progesterone [35]. *We can summarize what they found*: estradiol causes cell proliferation, both initially and in perpetuity. Proliferation is necessary for growth, is powerful and important, but unchecked, it increases the risks for genetic 'mistake' and malignancy [35]. By contrast, the main effect of progesterone is to cause cell differentiation and maturation while also *inhibiting proliferation* [35]. However, in the short term (in cell cultures, and for a few days) progesterone, like estradiol, has proliferative or growth-inducing effects.

Uterine endometrium and effects of estradiol and progesterone

The classical scenario described above plays out very typically in the human endometrium: estradiol thickens the uterine lining during the follicular phase creating a proliferative endometrium. During the luteal phase, however, progesterone inhibits proliferation and causes differentiation of the endometrium into a secretory organ into which a fertilized ovum could implant.

Uterine cervix and counterbalancing effects of estradiol and progesterone

The cervix is another reproductive tissue in which the counterbalancing actions of estradiol and progesterone are straight forward. Estradiol stimulates the cervical glands to

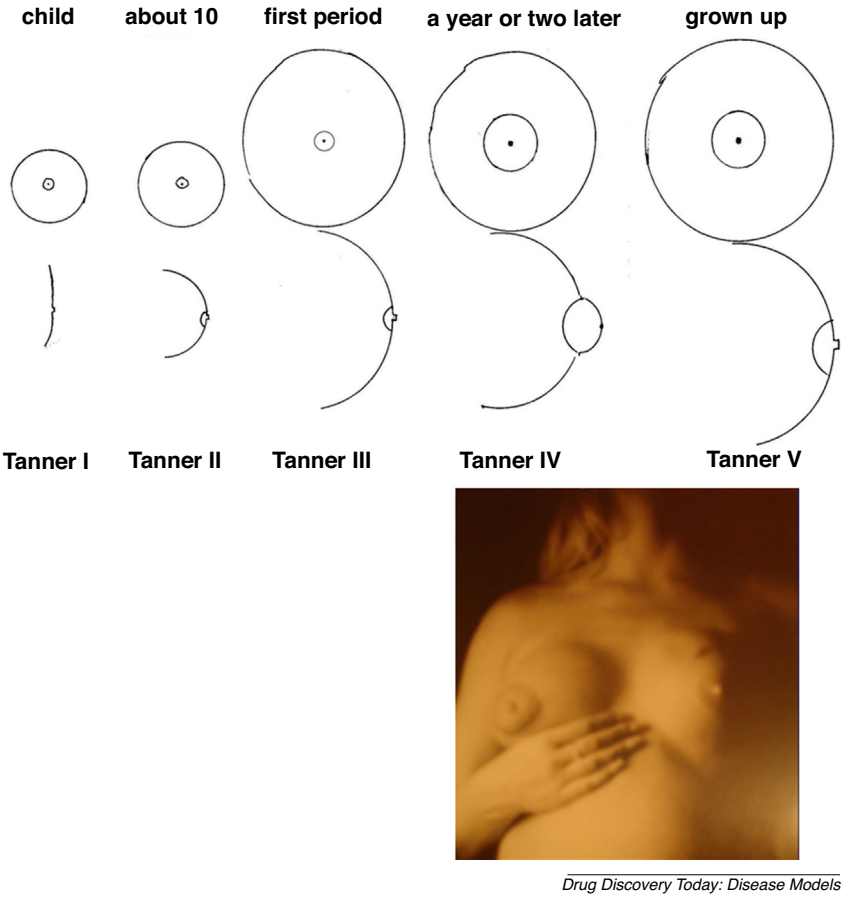


Fig. 3. This line drawing of the Tanner Stages maturation of women's breasts [42] from absence of a breast bud in childhood to estrogen's effects to increase breast size in adolescence to a small-moderate size at the time of menarche (Tanner Stage III). The breast size/volume continues to increase through Tanner Stages IV and V but the contribution of progesterone to lobular-alveolar growth is visible in changes in the size and shape of the areola, the darker circle surrounding the nipple. The line drawings are by J. C. Prior. The photograph is anonymous but shows a woman in early pregnancy with Tanner IV maturation of her right, and mature Tanner V Stage of her left breast.

make a clear, stretchy mucus that is maximal in volume and stretch around the estradiol peak [37]. This serves as a facilitator of sperm transit for fertilization of an egg. However, following ovulation, progesterone inhibits cervical mucus secretion [38], likely to prevent further sperm arriving in the fallopian tubes when they are no longer needed.

Breast epithelial tissue and the activity balance of estradiol and progesterone

Variations, on the main theme we've been discussing in which estradiol (E2) causes proliferation and progesterone (P4) causing maturation, however, occur in breast and some other of women's tissues. There are numerous, mostly *in vitro* reports of progesterone (more commonly progestins) being associated with breast cell proliferation [39]. Two randomized controlled trials (RCT) examined normal human breast epithelial tissue after transdermal steroid applications of E2, P4, E2 and P4 or identical vehicle to a single one of woman's breasts for 11 days before it underwent an open breast biopsy [40,41]. Both RCTs showed E2 caused increased epithelial cell nuclear antigen (K_{i67}) levels that indicated increased cellular proliferation; P4 caused decreased K_{i67} levels both when given alone and when in co-therapy with E2 [40,41].

Breast lobuloalveolar tissue and estradiol and progesterone actions

The human breast goes through both overall and areolar and nipple growth at varying times during puberty; the latter is especially dramatic during Tanner Stage IV [42]. From studies of pubertal girls before and just after menarche, it appears that estradiol alone can increase breast size. However, the growth of the areola and nipple and their underlying lobular and alveolar structures appears to need both estradiol and progesterone. Clarke and Sutherland reported that, ''progesterone causes ductal side branching and lobuloalveolar development'' [35]. Thus, progesterone causes growth-stimulating/proliferative actions we can visualize as increasing areolar size (Fig. 3). However, growth in lobular and alveolar tissues leads to milk production; thus, progesterone causes not only proliferation but also tissue differentiation and maturation.

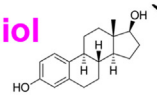
	Estradiol E2 	 Progesterone P4
Cells and Tissues	**Growth with Proliferation**	**Maturation with ↓ Proliferation**
Uterus–Endometrium	Proliferative	Secretory
Uterus–Cervix	↑ Mucus Volume and Stretch	↓ Mucus Volume and Stretch
Breast–Epithelial	Proliferation	↓ Proliferation, Maturation
Breast–Lobular Alveolar (Areola and Nipple)	↑ Breast Volume	↑ Areolar Size
Bone Remodeling	↓ Resorption	↑ Formation
Cardiovascular—Vascular Endothelial Function	↑ FMD	↑↑ FMD
Cardiovascular—Electrical Function, QT	↑ QT Interval	↓ QT Interval
Brain	Excitation/Activation	Excitation/Calming
Sleep	?	↑ Deep Sleep
Central NE	↑	Likely ↓

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Fig. 4. Women's Reproductive System as Balanced Estradiol and Progesterone Actions.
This model compares the fundamental, complementary and counterbalancing effects of estradiol and progesterone at the cell and tissue levels in which estradiol causes cell growth and proliferation while progesterone causes inhibition of proliferation and cell differentiation and maturation [35]. It then shows some variations on this them in specific reproductive and non-reproductive tissues and organs.
FMD = 'flow mediated dilatation' that is a way to assess the intrinsic arterial endothelial system functioning. NE = central brain norepinephrine levels.

Although there are many confusions about the roles of ovarian hormones in breast cancer, a truly non-sensical assertion is that *estrogen decreases breast cancer risk*, based on the results of Women's Health Initiative Estrogen-only (WHI-CEE-only) arm that documented a *non-significant* trend toward decreased breast cancer risk versus placebo [43]. The WHI-CEE-only RCT, according to its published design, had only 55–83% power (depending on assumption) to show breast cancer, provided investigators enrolled *25,000 women* [44]. Since WHI-CEE-only enrolled just under *11,000*, this trial clearly did not have power to show breast cancer risk, even with their anticipated 14-year follow-up [44]. That means the current touting of *estrogen as preventing breast cancer* is totally inaccurate [4]. In an underpowered study you cannot scientifically document *anything* about the outcome, in this case, breast cancer risk, no matter who protests to the contrary [4,45].

The various reports of progesterone increasing breast stem cells and (usually progestins) causing breast cell proliferation persist, raising concerns about progesterone and breast cancer. However, a large prospective observational study showed no increased breast cancer risk over no hormone use when estradiol and progesterone were taken by menopausal women, versus estrogen-alone (29% increased risk) and estrogen-*progestin* (69% increased risk) [32]. A recent breast basic investigation that showed the progesterone receptor (PR) transformed the estrogen receptor alpha (ERα) from a proliferation-stimulating signal to one that no longer causes breast epithelial cell proliferation [46]. Finally, a 2019 comprehensive review by an important basic scientist with years of breast cancer-related fundamental research, concluded that progesterone does not cause breast cancer [33].

Bone remodeling and the balance of progesterone and estradiol

I have spent many years studying changes in bone mineral density related to subclinical ovulatory disturbances after our one-year observational study in healthy, ovulatory premenopausal women showed that over 20% of the variance in volumetric cancellous bone change was related to the mean annual luteal phase length [18], a surrogate for progesterone exposure. For example, in adult bone remodeling, stable estradiol levels (typical mean menstrual cycle levels) decrease bone resorption (thus preventing bone loss). Luteal phase progesterone levels acting through specific PR on osteoblasts, stimulate new bone formation [29,47]. However, *decreasing* estradiol levels (*i.e.* a dynamic downward change), including

the decrease from E2's peak to the low levels during flow (Fig. 1**B**), cause an *increase* in bone markers of resorption [48]. It is for this reason that, in women with normal-length menstrual cycles and thus normal estradiol levels, subclinical ovulatory disturbances are associated with important bone loss [18,49].

Cardiovascular arterial endothelium and estradiol-progesterone balance

In cardiovascular tissues, estradiol is still generally believed to have net positive effects (despite the outcomes of the WHI-CEE-medroxyprogesterone [WHI-CEE-MPA] [50] and WHI-CEE-only [43] RCTs and that CEE and oral estradiol increases venous and arterial thromboembolic phenomena). Arterial endothelial function, whose purpose is finetuning of blood flow, is a fundamental, cardiovascular protective function. It is measured by assessing ''flow mediated dilatation'' assessed as increased arterial blood flow following temporary occlusion (as with a blood pressure cuff) of an artery. Such a test assesses the release and action of nitric oxide within the vascular endothelium. Estradiol is the classical stimulant of ''flow mediated dilatation'' (FMD) [51]. We now know, however, that *both* E2 and P4 amplify the actions of endogenous nitric oxide release to increase forearm blood flow [52]. In a random ordered, week apart, cross-over trial of FMD in healthy women early in menopause, we infused the brachial artery with physiological levels of E2, P4, E2 plus P4, or identical vehicle/placebo. Although all hormonal infusions caused similar increases in FMD, only the increased flow with P4 infusion was significantly greater than vehicle [52].

Cardiovascular electrical activity and balance of estradiol and progesterone

Another fundamental heart variable is electrical activity and the repolarization following the electrocardiogram's (ECG) T-wave. If the QT interval becomes unduly prolonged, this can lead to serious and often fatal arrhythmias, called the ''long QT syndrome'' [53]. Human gonadal steroid hormones (and many commonly used medications) affect the QT interval [54]; in general estradiol lengthens it while progesterone and androgens shorten it [55]. However, in an RCT in rabbits with genetically long QT intervals, therapy with estrogen was associated with near-universal death of the animal; all progesterone-treated females rabbits, however, survived [56].

Brain actions on central norepinephrine and on sleep of estradiol and progesterone

There are numerous studies of the brain effects of estradiol in rodents but fewer studies of progesterone. In general, and the specific mechanisms are not necessary here, estradiol acts as a brain activator; healthy men treated for a few days with an estradiol patch had an amplified stress-elevation of norepinephrine levels. By contrast, progesterone may decrease central stress hormone responses and has central calming effects [57]. Progesterone raises core temperature [58] while estradiol appears to suppress this elevation [59], again showing counterbalancing E2-P4 effects.

Progesterone, based on numerous human controlled polysomnographic studies, increases deep sleep in both men [60] and women [61]. In the latter study, after 21 days of taking oral micronized progesterone at bedtime, menopausal women showed no differences in manual function, memory or cognition [61]. In addition, progesterone, while having little effect on normal sleep, prevents sleep disruptions in women [62]. Estradiol, however, does not appear to have much effect on sleep [63].

The above sections (Fig. 4) include discrete examples of situations in which estradiol and progesterone interact and together result in balanced and healthy physiology for women.

Future implications—integration of estradiol and progesterone actions within women's complex reproductive system

Fig. 4 summarizes the cell, tissue and organ-specific, currently known, balanced and coordinated estradiol-progesterone actions. Why is it that we still only think about estrogen when we consider women's health? Earlier we mentioned a review that considered the potential negatives consequences, for both women and men, of too much estrogen [6]. What is fascinating is that the authors appropriately described as necessary steps to curb estrogen effects, improved diets and increased exercise [6]. Shortly after they discussed using drugs such as selective estrogen receptor modulators, making almost no and only passing reference to progesterone which is physiologically designed to counterbalance and correct the negatives from high estradiol exposures [6].

If we diagnose subclinical ovulatory disturbances, it is physiological to replace the deficient or missing progesterone with cyclic progesterone therapy (oral micronized progesterone 300 mg at bedtime for 14 days a cycle) http://www.cemcor.ubc.ca/resources/cyclic-progesterone-therapy. Cyclic progesterone therapy (the RCT was of medroxyprogesterone that acts through the osteoblast PR) caused gain in bone mineral density in normal weight premenopausal women with hypothalamic amenorrhea, oligomenorrhea and subclinical ovulatory disturbances [22]. There is also evidence that progesterone has benefit for bone in addition to the bone gains related to anti-resorptive therapy with estrogen [64] and perhaps with a bisphosphonate [65].

Subclinical ovulatory disturbances are the most prevalent imbalance of estradiol and progesterone for premenopausal women [18]. They are strongly increased related to high cognitive dietary restraint, a social stressor documented by elevated cortisol excretions [21]. In addition, hypothalamic amenorrhea is effectively treated by cognitive behavioral

therapy [66,67]. Therefore, we are starting to now appreciate the important connections among women's social, emotional and physical environments, nutrition and exercise and illness as adaptively relating to all aspects of physiology [68]. Women's reproduction, especially decreased progesterone production is a very sensitive marker of undue duress [69]. There is good evidence for progesterone's actions to decrease sleep disturbances and increase restful sleep [61]. There are no serious and virtually no side effects with oral micronized progesterone therapy [70].

The first step, in furthering this new model of women's healthy reproduction as a balance of estradiol and progesterone, is to make visible progesterone's menstrual cycle presence or absence. Although there are validated methods to document ovulation and luteal phase lengths such as the Quantitative Basal Temperature© [71,72], performing it is tedious and most women will not consistently collect this data. What is needed is a home test that women could conveniently and inexpensively perform once a cycle over many months or years that would determine the presence or absence of normal ovulation. Only when that new test has been collected by large numbers of women in the population in many locales and countries, will follow-up of those women for later life risk of osteoporotic fracture, early-in-menopause heart attacks, breast and endometrial cancers allow us scientific evidence for whether or not prevalent subclinical ovulatory disturbances are associated with these diseases of aging.

Even before the definitive research tying ovulatory disturbances to later life women's diseases, this new model opens the door to increased use of cyclic progesterone therapy, especially if correcting nutritional issues and providing social/emotional support have not improved the menstrual cycles and ovulation for a given woman. As another example, a menopausal woman who has undergone hysterectomy, and is suffering with hot flushes and night sweats, in contrast to current practice guidelines, would be treated with both estradiol and progesterone. This new model illustrates that progesterone does more for women than prevent endometrial cancer.

This is just the beginning of a major thought-change that needs to occur before we can develop a comprehensive understanding and appropriate treatment for problems in women's complex reproductive system. Although difficult, this fundamental paradigm shift to understanding that progesterone as well as estradiol is an important player in women's reproductive and overall lifetime health, will likely result in a number of positive downstream outcomes:

1) This model changes how we understand every woman's menstrual cycle, pregnancy, post-partum, perimenopause- or menopause-related experiences [69];
2) It poses new questions about the origins of reproductive symptoms, conditions or diseases, such as endometriosis and post-partum depression [73];
3) It provides new solutions or treatments for many woman-only or dominantly woman-experienced problems, conditions or diseases [74];
4) It connects the integrated premenopausal menstrual cycle's physiological experiences (related to their various factors in the social/emotional/physical environment [75] and interactions with genetic endowment) with age-related conditions in later life; and
5) Since so many women's health and life stories are reproduction-focused, it changes the fundamental cultural and scientific narrative about who Women truly are.

Conflict of interest statement

I have no commercial connections.

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