Preventive Powers of Ovulation and Progesterone

Ovulation and Breast Health

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I believe that ovulation with a normal luteal phase length – and normal amounts of progesterone to counterbalance and complement estrogen – is of key importance for women's bone, breast and heart health (1).

The five previous issues in this series have discussed what ovulation is, how it is ignored or assumed in regular cycles and that we have little solid evidence about how frequently or not ovulation occurs among menstruating women in the whole population. The little epidemiology evidence we have suggests that 17% of the time women in the population, often despite regular cycles, do not ovulate. We also have talked about how you can assess your own cycles for ovulation by taking your first morning temperature and analyzing it. This "quantitative basal temperature" (2) is much more reliable than the old fashioned BBT methods, especially when coupled with a daily Menstrual Cycle Diary (3). Finally, we discussed the many problems with how ovulation and luteal phase lengths are assessed by physicians.

In the last issue we discussed the importance of ovulation and normal progesterone for building and maintaining strong bones. Estrogen levels rise and fall during the normal menstrual cycle. When estrogen levels fall, there is a small amount of bone loss—this loss needs to be offset by an increased bone formation, caused by normal luteal phase lengths and normal progesterone in order to prevent bone loss (4;5). Progesterone's job is to stimulate bone formation. I believe progesterone could be added to a bone-loss-slowing medication to form improved fracture-preventing osteoporosis treatment for women.

Now it is time to examine the complex relationships among ovulation, progesterone and breast health. We will start by discussing the hormonal influences on breast growth and development during adolescence. Then we will look at the roles estrogen and progesterone play in normal breast cell function. Finally, and of crucial importance, we will review the new evidence that ovarian hormone therapy (OHT, menopausal hormone therapy) with estrogen plus progesterone is not associated with an increased risk for breast cancer. As every woman knows and fears, treatment of menopausal hot flushes with estrogen alone or with estrogen plus medroxyprogesterone (a cousin of natural progesterone) increases the risk for breast cancer. When we understand more we may eventually have evidence that normal ovulation and progesterone levels prevent breast cancer.

Grown up breasts

As you recall from our earlier discussion, at menarche (the first period), our ovaries are making plenty of estrogen. However, at that time our bodies have not yet learned the complex process of ovulating. There is a natural clue in how breasts look that reflects whether or not ovulation has been established (or the breasts have been exposed to the progestins in contraceptives or the standard Pill).

There are a series of reasonably orderly steps that the breasts go through in the process of becoming "grown up." These steps are called Tanner Stages, after the doctor who took pictures of girls' breast and pubic hair changes yearly from before to several years after menarche. A young child will have breasts that are Tanner Stage I (small circle of skin called the "areola," around the small nipple and both are lying flat against the chest). Around age 8-10, a small lump, made up of the glands that will eventually form the mature breast, begins to be present beneath the small areola and nipple—this gives us Tanner Stage II. At the first period we have usually reached Tanner Stage III, meaning that the breast is round and somewhat full but the areola (the now darker bull's-eye circle of skin surrounding the nipple) is still small—about the size of a nickel or quarter. You can see all the stages of breast development in this figure.

Starting about a year or so after the first period, around the time that the first cycles are ovulatory, the areola starts to balloon out and get bigger around. This awkward phase is called Tanner IV and occurs because the ducts are starting to mature under the influence of progesterone. Once ovulation is established, the areola then flattens but is now bigger (about the size of a Canadian two-dollar coin) and is now fully grown up, Tanner V. By this time the breasts will be able to make milk for nursing a baby, their fundamental purpose.

Unfortunately, doctors tend to consider breasts based only on their size—which continues to increase across adolescence, increases during pregnancy and may increase in perimenopause—while ignoring the key issue, how big around the areola is. That means that Tanner Stage III and Tanner Stage V can be mixed up. The drawback is that medicine has missed an important clue—a clear sign that tells us whether or not women have established normal ovulation (or breasts have been exposed to progesterone/ progestins).

Breasts changes with estrogen and progesterone

Have you ever noticed that your breasts get bigger or swollen before your period? Maybe you found that it was sore if you accidentally bumped your nipple at the middle of your cycle. Or perhaps you've had the experience of knowing that you were pregnant even before you'd missed a period—the clue, breasts that were too

sore to touch! All of these experiences are telling us that estrogen and progesterone are working in our breasts. What is important to understand is what changes each hormone causes and the necessity that estrogen and progesterone be in balance.

Many hundreds of studies have examined breast cells grown in dishes in the laboratory and noted the changes that occur when estrogen or progesterone are added to the cultured cells. In general these studies observe that both estrogen and progesterone stimulate breast cells to grow. Cell growth—or proliferation as it is commonly called—is associated with more chance for a mistake and overgrowth of abnormal cells leading to breast cancer. Therefore, for years it has been assumed that both estrogen and progesterone play roles in the risk for breast cancer.

However, cell culture studies often use breast tumour cell lines, or cells that are not natural (because they can continue to grow in culture). In addition, most investigators only observe the cells for a day or two. It turns out that in every tissue studied in many different animals, estrogen initially and continuously causes proliferation (6). However, although progesterone initially causes cell proliferation, it then begins and continues to stimulate cells to differentiate(7). Because more differentiated or more mature cells are less likely to be cancerous, progesterone, according to this measure, should have anti-cancer effects.

The best way to understand what estrogen and progesterone do in breast cells is to study these cells in living, breathing women. This turned out to be possible because women were scheduled for a small surgery to remove a lump that, in each case, turned out to not be cancer. Two excellent randomized, double blind controlled studies have done just that—in each trial women applied onto the breast that was scheduled for a surgical biopsy a gel containing one of four things: estrogen, progesterone, estrogen and progesterone or just the alcohol base. The first study was in menstruating women who were scheduled for the biopsy on day 11 of their cycle (8). They began applying the gel on the first day of their menstrual period and continued through day 11 when they had surgery. The second study was in menopausal women who were randomized to apply the gel for 14 days with the biopsy scheduled on the 14th day (9). Both of these studies showed that the estrogen and progesterone got into cells and in amounts that were natural; they also showed that breast cell proliferation changed in response to hormones compared with placebo. In both studies, estrogen caused proliferation, and progesterone decreased proliferation. This suggests that estrogen's job is to make breasts grow and progesterone's job is to stop the growth and allow breast cell maturation.

The next time your breasts become sore or enlarged, ask yourself if estrogen is stimulating your breast cells to proliferate. Also, you might wonder whether your

body is making enough progesterone to counterbalance estrogen.

What about history of ovulation problems and breast cancer?

On this question, we have few good answers. Remember that we said it is commonly and wrongly understood that regular cycles mean normal ovulation? We know that women with more years of menstrual cycles (earlier first period, later menopause) have a higher risk for breast cancer (10). But we also know that regular cycles can be anovulatory and without progesterone.

Two moderate sized long cohort studies from the 1980s in women with medical diagnoses associated with ovulation problems—infertility and anovulatory androgen excess (AAE, also known as polycystic ovary syndrome, PCOS)—have documented inadequate progesterone and then followed women to observe how many of these women compared with controls, developed breast cancer. The first was a study of 1083 women who were documented between 1945 and 1965 to have infertility that was presumably caused by ovulation disturbances because blocked tubes or problems with their husbands' sperm were excluded (11). Compared with controls who had other reasons for infertility all of whom were followed through 1978, women with ovulation disturbances showed 5.4 times increased risk for premenopausal breast cancer (11). The second study observed all 1270 women hospitalized for AAE/PCOS at the Mayo Clinic beginning in the 1930s (12) and compared their risk until the late 1970s with women hospitalized for other reasons. The women with chronic anovulation and androgen excess (AAE/PCOS) had a risk for menopausal breast cancer that was 3.6 times higher than their controls (12). Both of these studies suggest that chronic ovulation disturbance (especially if estrogen levels are normal or high as they are in AAE/PCOS) is an important risk for breast cancer.

Risk for breast cancer with ovarian hormone therapy

Multiple large, long observational studies from the 1940s through the 1990s showed that menopausal women who took ovarian hormone therapy, meaning estrogen or estrogen with progestins, appeared to have fewer heart attacks, to be less likely to develop dementia and more likely to live longer. There were concerns, however, that this treatment might cause breast cancer. Plus it was never clear if these women were healthier in the first place, or better at taking pills, or more likely to see their doctors regularly. To test whether menopausal ovarian hormone therapy (OHT) was causing benefit or harm, women scientists pushed the National Institutes of Health in the USA to do randomized controlled trials—the Women's Health Initiative (WHI) hormone trials.

In July 2002 the almost 17,000 women in the estrogen plus progestin (E + P) arm

of the WHI were told to suddenly stop their study drug—this was four years earlier than planned—because more women taking hormones than taking the placebo developed breast cancer and heart attacks (13). Although the estrogen only (E only) WHI trial in women who had undergone a hysterectomy continued for another two years, it, too, was stopped early. In this case, the reasons for stopping were lack of heart disease prevention and more strokes in those taking estrogen (14). Surprisingly, the E only WHI trial did not show an increase in breast cancer.

Although many had blamed the low dose medroxyprogesterone (2.5 mg/d) in the E + P arm for the increased breast cancer that arm of the WHI showed, it has been known for many years that women who have had pelvic surgery (hysterectomy, even tubal ligation) have a lower risk for breast cancer (15). It is likely that the WHI E only trial didn't have enough women in it to show a risk for breast cancer, given the lower risk in women with hysterectomy and especially since that trial had only about 11,000 women enrolled. Our best guess about why hysterectomy decreases breast cancer risk is that, for reasons not yet quite clear, the ovaries are getting less blood flow and hence make lower levels of testosterone, which, because it gets made into estrogen by our bodies, causes lower levels of estrogen itself (16).

How can it be that a cousin of progesterone, medroxyprogesterone, that, like progesterone also causes less breast cell growth/proliferation, should cause breast cancer when taken plus estrogen? Given what we know about estrogen causing proliferation and progesterone or progestins stopping that growth and causing maturation, I initially wondered if the reason for breast cancer increase with E + P might be that it was a full dose of estrogen (Premarin® 0.625 mg/d) but only a quarter luteal phase equivalent dose of medroxyprogesterone (MPA, Provera® 2.5 mg/d). The dose imbalance in the WHI E + P trial is still a probable reason, however, a recent randomized trial in monkeys without their ovaries of hormone therapy with estrogen plus MPA (2.5 mg/d) or estrogen plus progesterone (200 mg/d) for two months showed that estrogen with MPA caused markedly increased breast cell growth but that estrogen with progesterone did not (17). The MPA dose was lower in relative terms than the progesterone dose but the difference in effect was marked. In addition, although there are many guesses, none of which can be proved at the moment, one of the most recent ones is that medroxy-progesterone activates quiet or hiding breast cancer stem cells that estrogen then stimulates to grow (18). Of course, the reason everyone will understand is that breast cancer increase is just one further evidence that estrogen is good and progestins or progesterone are somehow bad.

Although observational studies and randomized ones differ (like in heart disease risk with hormone therapy), in the case of breast cancer, multiple studies have show a greater risk for cancer from estrogen with MPA than with estrogen

alone (19). A recent large, observational study from France called the E3N study of women (mostly teachers) in an insurance programme, has provided important information about the progesterone and breast cancer question. (Note that this is not a randomized, double blind placebo-controlled trial like the WHI, therefore it may well have biases we don't yet understand.) However, E3N was performed in France, a country that has had oral micronized progesterone therapy (called Prometrium® in North America or Utrogestan® in France) since the 1980s—in Canada it has been available only since the mid-1990s. The E3N study examined risk for breast cancer in about 80,000 menopausal women followed for about eight years by whether they didn't take ovarian hormone therapy (the control group), or used estrogen alone, estrogen with progesterone (about a third of those taking combined therapy), or estrogen with MPA (20). They found that estrogen alone increased the risk 29%, estrogen with MPA increased the risk for breast cancer by 79% but that estrogen with progesterone showed no increased risk (20). This study suggests that MPA differs significantly from its parent hormone, progesterone, especially in relationship to breast cancer risks.

Making sense out of progesterone and breasts

All of the evidence we have right now suggests to me that the currently unknown major risk factor for breast cancer is being exposed to enough or too much estrogen without enough progesterone. One day we may know that having normal ovulatory cycles throughout our reproductive lives is a way to prevent breast cancer. It is clear that estrogen needs to be counterbalanced by progesterone in the breast to prevent tenderness, overgrowth or cancerous growth in breast cells.

We have reviewed the evidence that our breasts need progesterone as well as estrogen to mature into organs with large areolae that have the ability to make milk. Two good randomized studies show that progesterone causes breast cells in women to become more mature and less likely to cause cancer. Yet the Women's Health Initiative randomized placebo-controlled trial of estrogen with the progestin, MPA, showed an increased risk for breast cancer not shown in the estrogen only trial, in women who had their uterus and possibly ovaries removed. Finally, a large observational study indicated that estrogen with progesterone therapy did not cause breast cancer although estrogen alone or estrogen with MPA did. Estrogen causes important cell growth that progesterone must transform into mature cells for milk production, normal soft and non-tender breasts and, most importantly, to avoid an increased risk for breast cancer.

In the next newsletter we will discuss ovulation and progesterone related to women's blood vessels, cholesterol and risks for heart disease.

Stay tuned!

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