

## Preventive Powers of Ovulation and Progesterone

### Ovulation and Bone 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 (see [Ovulatory Disturbances: They Do Matter](#)) (1).

The four previous issues in this series have discussed what ovulation is, how it is ignored or assumed to be present in regular cycles and that we know little about the prevalence of ovulation from population-based studies. In fact, in the less than 400 women in epidemiology studied for ovulation, the information suggests that in any given regular cycle you may not ovulate once or twice out of a year’s worth of 13 cycles. We also talked about how you can assess your own cycles for ovulation by taking your first morning temperature and analyzing it. [Quantitative Basal Temperature](#)(QBT), that you can assess yourself, is much more reliable than old-fashioned BBT method, especially when QBT is coupled with a daily [Menstrual Cycle Diary](#)®. In the last issue we discussed how medical doctors assess ovulation using a series of expensive and somewhat embarrassing vaginal ultrasound tests, a painful and invasive endometrial biopsy or an inconvenient and not cheap series of blood tests for progesterone in the latter half of the cycle.

With this background, it is now time to begin discussing what consistent, normal ovulation means for specific aspects of our health. The above overview from my 1997 article (1) says that I believe ovulation is important for bone, breast and heart health for women. This article will discuss what we know of ovulation and progesterone for building strong bones and preventing osteoporosis and fractures.

#### **How Bone Renovates Itself to Prevent Fracture**

Before it will be clear why progesterone and normal ovulation are important for bone health and osteoporosis prevention we need to discuss how bone renews itself. To keep the bone strong, old bone must be removed (by cells called osteoclasts) and replaced with new bone (created by cells called osteoblasts). Estrogen slows the action of osteoclasts and thus prevents bone loss. Progesterone directly stimulates osteoblasts to make new bone.

Our bone has a natural life cycle. We build bone size and strength starting in utero and continuing until the early teen years. Bone then reaches a high point called “peak bone mass.” After that, women’s bone is ideally kept steady through the

premenopausal years until bone loss occurs when skipped periods start in perimenopause. It is normal to lose bone at about 2% a year beginning when irregular periods start in perimenopause and continue at that high rate until one year after the last period. From menopause for the first four years, we lose bone at a rate of about 1%. Then bone loss is normally slowed to about half a percent a year because osteoblasts can't keep up with the loss caused by osteoclasts.

### **How Progesterone Works with Bone Cells and Bone Tissue**

We all know that estrogen is important for bones and prevents bone loss (although it acts indirectly rather than by talking to osteoclasts) What is clear, but most physicians and even some bone experts don't know is that progesterone sits on specific receptors on osteoblasts and stimulates the formation of new bone. There are numerous papers showing that osteoblast cells cultured in a lab grow rapidly and make bone and bone enzymes when progesterone is added to the culture ([2-4](#)).

### **Ovulation and Building Strong Bones in the Teens and Twenties**

As we discussed in the second part of this series, it takes a number of years after the first period (called menarche) before the brain, pituitary and ovary learn to have regular ovulation. In fact, the first year after menarche estrogen levels are normal or high and cycles may be regular or irregular but ovulation almost never occurs. In a study of pre-teen and teen growth, bone density, exercise and nutrition performed by UBC nutrition professor, Susan Barr, with assistance from my laboratory ([5](#)), we found that the first of these young women to develop an ovulatory cycle was 11 months after menarche and the majority were over one year. When we tracked bone gain, the maximal increase in bone occurred after ovulation first began, rather than with menarche, suggesting that progesterone was important for teen bone growth (Kalyan, J Bone Min Research 2007, abstract).

### **Ovulation and Keeping Strong Premenopausal Bones**

As I mentioned earlier, my first research studied exercising women and tracked their menstrual cycles. We got funding to study women ages 20-40 for one full year and measure their spine bone density at the beginning and the end of that year. We enrolled 66 healthy, normal weight women who were all proven to not only have regular menstrual cycles but to ovulate normally on two cycles using the QBT method ([6](#)). However, when we followed these women's cycles and ovulation across a year, although all women continued to have regular periods, only 13 women had normal ovulation every cycle, 13 had at least one cycle in which they did not ovulate, and 28 women had more than one short luteal phase cycle. This study showed that the length of the luteal phase (the time of high progesterone

production) explained over 20% of the one-year change in bone (calcium or caloric intake explained only 2%). Said another way, these healthy women with enough estrogen and regular cycles but who didn't ovulate for even one cycle were losing bone, while those who ovulated every cycle during the year were maintaining bone (7). This was the first study to show that progesterone and ovulation, not just regular cycles and normal estrogen levels were necessary to prevent premenopausal bone loss (7).

Since that study, two further investigations of bone in premenopausal women have shown that ovulation disturbances are related to loss of bone (8;9). One of these studies showed that the urinary progesterone peak, and the total amount of progesterone were significantly lower in women from a random sample of the population with the lowest bone density compared with cycles from women in the same study with normal bone density (8). The other study assessed ovulation using progesterone levels in saliva and monitored women over 2 years (9).

### **Progesterone for Preventing Premenopausal Bone Loss**

Those studies of bone loss in healthy premenopausal women who have regular cycles but don't ovulate normally raised real concerns about bone loss in premenopausal women who have obviously abnormal menstrual cycles (long cycles as well as skipped periods for months at a time). In addition to recommending regular exercise, stable weight, good intakes of calcium and vitamin D, women with abnormal cycles need something to stimulate new bone to grow (see "[ABCs of Premenopausal Osteoporosis Prevention](#)").

We wanted to test the idea that progesterone builds bone by performing a randomized trial of [cyclic progesterone](#)[pdf] in premenopausal women with abnormal cycles but who were otherwise well. Because, before 1996 natural oral micronized progesterone called Prometrium® was not available in Canada, we designed a trial using the closest cousin of progesterone, the progestin called medroxyprogesterone acetate (MPA, Provera) for the last 10 days of the menstrual cycle if it was regular, or for the month if it was not (10). We enrolled healthy, normal weight women ages 20-40 with amenorrhea (no periods for six months or longer), women with cycles farther apart than 36 days, those with regular cycles but who were not ovulating, or with regular cycles and ovulation but short luteal phases. Women were randomized to cyclic MPA or placebo. The results showed that women with abnormal cycles given cyclic MPA had a significant gain in bone (2-3%/year) while those on placebo MPA lost about 2% of their spinal bone—the effect of cyclic progestin was very highly significant (10). This study proves that progestin (which, like progesterone stimulates osteoblasts through the progesterone receptor) not only prevents bone loss but also builds new bone in women with disturbed menstrual cycles or ovulation.

To date no study has given cyclic progesterone to perimenopausal women with abnormal ovulation. It is very clear that perimenopausal women with irregular cycles need increased vitamin D and calcium intakes (see the "[ABCs of Midlife Osteoporosis Prevention](#)").

## **Progesterone's Role in Osteoporosis Treatment**

Typically menopausal women who have osteoporosis have had a broken bone with a minor fall or are at high risk for breaking bones. Because such women not only have low bone density but are losing bone, the primary treatments are those medications that slow bone loss (such as estrogen, calcitonin or bisphosphonates). One early clinical study of menopausal women taking estrogen plus 5 mg MPA daily showed a greater gain in bone in these women than menopausal women only taking estrogen therapy (11). In addition, we documented that women with osteoporosis treated with the bisphosphonate, Etidronate, plus 10 mg of MPA daily had a greater gain in bone than women on Etidronate alone (12). Neither of those two clinical studies was randomized or placebo-controlled, however.

More convincing evidence that progestins add to the positive effects of estrogen on bone came from a randomized double-blind placebo-controlled study that compared women on standard doses of estrogen with 2.5 mg of MPA daily and on only estrogen (if they had undergone a hysterectomy). These controlled results showed about a one percent greater bone gain on estrogen with MPA than on estrogen alone (13). To date no study has shown that adding progesterone or MPA to a therapy that slows bone loss can prevent fracture more effectively than the bone-loss-preventing osteoporosis therapy alone. We are planning a randomized two-year study of a bisphosphonate plus Prometrium (300 mg/day) compared with the same bisphosphonate plus placebo progesterone. That study will provide the information needed to plan a larger fracture prevention study. All women in any such trial will be treated in the standard way (see "[ABCs of Osteoporosis Treatment](#)") in addition to their bisphosphonate and randomized progesterone therapy.

## **Summary: Progesterone is a Bone-building Hormone**

To summarize what we've covered about bone in relationship to ovulation and progesterone, we can say that progesterone sits on specific receptors on the bone-building osteoblast cells. Therefore, women with regular cycles but ovulation disturbances, despite having normal estrogen levels, will continue to lose bone. However treatment with cyclic progestin (and probably progesterone, ideally given for days 14-27 of a 28 day cycle) will significantly increase bone density. Although a few studies in menopausal women have shown that the progestin, MPA, adds to

the benefits of bisphosphonate or estrogen treatment, no study has yet been designed to show that progesterone therapy prevents fractures.

In our next newsletter we will cover issues related to progesterone and breast health plus the risk for breast cancer.

Stay tuned!

*Reference List for "Is Ovulation (and are normal Progesterone levels) Important for the Health of Women?"*

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