Preventive Powers of Ovulation and Progesterone

Ovulation and the Heart

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We have been asking, through a series of newsletters, what we know about women's health related to normal progesterone levels and ovulation. We have discussed the fact that ovulatory disturbances (meaning anovulation and short luteal phase cycles) are common and hidden within menstrual cycles that seem perfectly normal. I speculate that at least a third of all cycles - in regularly menstruating, healthy women 10-30 years since menarche (their first period) - produce too little progesterone. (We don't really know the percentage of cycles with ovulatory disturbances in the general population because no one has studied it. CeMCOR in joint study with Norwegian scientists and funded by Canadian Institutes of Health Research is currently trying to learn what proportion of women's cycles is anovulatory.)

In previous newsletters we described how difficult it is to know if we have ovulatory disturbances. Most of the time, unless we are working to become pregnant, we think everything's fine. Thus, doctors would call ovulatory disturbances "subclinical" because they don't come to medical attention. The majority of ovulatory disturbances occur within cycles of normal length, normal flow and even with perfectly normal estrogen levels (1). However, they are lacking any (anovulation) or have too little progesterone production (short luteal phase). Thus, ovulatory disturbances provide an "experiment of nature" that allows us the opportunity to understand how progesterone alone - not just in combination with estrogen, its essential partner ovarian hormone - contributes to women's health.

Earlier we discussed that estrogen's job is to stimulate the growth of cells (i.e. proliferation) but that progesterone's role is to decrease that proliferation and induce maturation and differentiation of tissues (2). Although much of our research and treatment has focused on estrogen, which is considered the primary "woman's hormone", I believe that progesterone is an essential partner hormone to estrogen. These two important ovarian hormones are meant to work together, complementing or counter-balancing each other in every tissue and every cell of women's bodies and across our life cycles (3).

I'll say again what I believe, and what we are making progress in proving: **Regular** menstrual cycles with consistently normal ovulation during the premenopausal years will prevent osteoporosis, breast cancer and heart disease in women.

The purpose of this article is to describe new and suggestive evidence that progesterone is important for preventing women's cardiovascular diseases (CVD, heart attacks, strokes and blood clots). However, before we can make sense of any information about progesterone and CVD, we have to put what we currently believe and know into a context.

We are now ready to wrap up this review of progesterone and women's health. This final section concerns women's risk for heart disease, stroke and diseases of the blood vessels and the relationships of these vascular problems to estrogen and progesterone. Let's start with what "we" believe—by this I mean the two main cultural myths that surround women's heart disease.

Myths about women's heart disease

1. The first myth--women's heart disease is the same as men's

Obviously it is simpler for doctors, media and organizations to give one consistent message that applies to young and old, woman and man alike. It is also advantageous to pharmaceutical interests and will expand the potential customers to have a one-size fits all marketing campaign. However, these messages are fundamentally untrue. Women's heart disease first occurs at an older age than in men. Furthermore, contrary to advertising, women's heart disease rates never becomes as high as in men, and the population-adjusted death rate in women remains lower than in men (4). In addition, in a population follow-up study, men whose cholesterol levels were in the lowest quarter of the population level had higher heart attack rates than women with cholesterol levels in the highest quarter of the population level(5). Furthermore, low dose aspirin (a single 325 mg tablet a week, or 81 mg every day) doesn't prevent heart disease in women although it has been shown to prevent heart attacks in men (6). And, as opposed to men, there is no credible evidence that the popular lipid lowering drugs (such as statins) are effective at preventing as opposed to treating heart disease in women (7).

Despite this myth of women and men having similar risks for heart disease, there are sex-related disparities in the health care for women and men with acute heart attacks. According to a recent report from Ontario, women are more likely to be taken care of by a family doctor without a specialist than are men of similar income bracket and age. Women are also likely to wait longer before they get infusion of the clot-busting intravenous drugs (thrombolytic) when they come to the emergency room with a heart attack. And finally, women are less likely to have the diagnostic angiogram testing that tells physicians the extent of the cardiovascular risk. These facts are ironic given the messaging that says women and men are at the same risk for heart disease.

2. The second myth—women's heart disease is caused by estrogen deficiency

The reasoning behind this notion goes like this—young women have lots of estrogen and don't get heart attacks. Older menopausal women are "estrogen deficient" and get heart attacks. Therefore, lack of estrogen causes women's heart disease. That is like saying that headache is an aspirin-deficiency disease!

Ten years before the first Women's Health Initiative (WHI) proved me correct in suspecting that cardiovascular disease would not be prevented by estrogen treatment (8), I could "see" that this myth about estrogen therapy preventing heart disease was wrong (9). This myth has now, finally, been repeatedly tested in randomized double-blind placebo-controlled trials in both women (8;10) and men (11). In every scientific (randomized, placebo-controlled) test, this estrogentreatment-heart-disease-prevention myth has failed—and yet the myth persists (12;13).

The only possible reason for such a nonsensical idea to persist is because it serves some purpose. I can guess that its purpose is to re-enforce the "woman problem." As a culture, we fundamentally believe women to be somehow lacking (the anatomy and physiology of men—thank goodness) or that women are weak or ill. Pharmaceutical companies, some specialist physicians and those dominant in our culture appear to gain power by treating women's "deficiencies," often with estrogen.

What's the evidence for the Estrogen-Heart Disease Prevention Myth?

Large observational studies, including some of the data from longitudinal population-based studies like the Framingham Heart Study, have shown that women taking estrogen had fewer heart attacks than did women not taking so-called hormone "replacement" therapy (14). The reasons estrogen (here read pill estrogen as in conjugated equine estrogen, CEE, or Premarin) was proposed to prevent heart disease were that it increased the apparently preventative, good high-density cholesterol (HDL) level. Estradiol is also undoubtedly active in the complex nitric-oxide system through which the microcirculation (small blood vessels) is controlled (15). But we knew, even many years ago, that the women who take estrogen treatment differ in heart-protective ways from the women who don't—they are more likely to have a personal physician, to be well educated, to exercise regularly, to be non-smokers, to be of normal weight and without diabetes or high blood pressure (16).

Oral estrogen treatment increases HDL cholesterol and makes blood flow better in

small and medium sized blood vessels—this is called endothelial function because it is controlled by complex changes in endothelial lining of vessels. Estrogen treatment also doesn't appear to cause high blood pressure, diabetes or obesity. Although estrogen treatment, in general, has no effect on blood pressure, insulin resistance or obesity in randomized controlled trials—in some women it does appear to contribute to individual-specific increases in blood pressure, blood sugar and weight gain.

How could estrogen or estrogen-progestin treatment cause the increase in risk for heart disease shown in multiple randomized controlled trials (8;17)? One possible way is through its increased levels of C-reactive protein, a strong marker of inflammation, which is now considered a common pathway to many diseases including heart disease (18). CEE also increases triglycerides that are now known to be more strongly associated with causing women's heart disease than HDL levels are at preventing it. Most important of all, oral estrogen increases women's risk for blood clots(19). I believe that the formation of clots within arteries is estrogen's main negative cardiovascular effect (both on heart attacks and strokes)—we used to call heart attacks "coronary thrombosis" (meaning heart artery blood clots).

The good news about estrogen and blood clots is that estrogen applied through the skin (transdermal estrogen—as a patch or gel or cream), doesn't go from the stomach through the liver first and thus increase levels of blood clotting proteins—transdermal estrogen does not cause blood clots (20:21). I believe that no one, who needs estrogen treatment, should ever be treated with oral estrogen, given that safer transdermal bio-identical estradiol is available as a patch, gel or cream.

Progesterone, Blood Vessels and Heart Disease

I believe that ovulatory disturbances in young menstruating women cause an increased risk for heart disease in older menopausal women. This postulate is a very hard one to test—large numbers of menstruating women with frequent ovulatory disturbances would need to be given a placebo or cyclic progesterone for years and then followed for at least 10 years following the last menstrual flow. This is because ovulatory disturbances occur in young, menstruating women whereas heart disease is largely a disease of the very elderly. And heart disease takes years to develop.

Despite the difficulty in doing a definitive experiment about progesterone and heart disease, there are many heart disease risk factors that progesterone appears to decrease. We'll begin with these CVD markers, and then discuss the two experiments that strongly suggest that ovulatory disturbances cause subsequent heart disease.

Cardiovascular Risk Markers and Progestin or Progesterone

We have known since a controlled trial in 1985 that oral micronized progesterone decreased blood pressure in both menopausal women and in men (22). This means progesterone should decrease women's risk for strokes for which high blood pressure and blood clotting are major risks. Here it is worth recalling that both the Estrogen-Progestin and the Estrogen-only arms of the Women's Health Initiative trials showed higher risks for stroke with hormone treatment compared with controls (8;23). We have repeated the study of progesterone and blood pressure in a randomized double-blind trial in of progesterone for hot flushes in healthy menopausal women and expect to know the results in the next year.

Potential CVD reducing mechanisms have also been shown for medroxyprogesterone MPA (a progestin most closely related to oral micronized progesterone) although MPA is often blamed for heart disease (24). MPA may decrease CVD risk by lowering triglycerides and C-reactive protein levels (Kalyan Pharmacotherapy 2010). These data are from a randomized blinded one-year comparison of CEE and MPA that showed an important difference between estrogen and MPA. Women randomized to MPA had lower triglyceride and C-reactive protein levels at the end of the trial. Although the women on MPA also had lower HDL levels than did those on CEE, their HDL levels remained within the normal range (Kalyan Pharmacotherapy 2010). In that randomized comparison study of estrogen and MPA (the only one that has been published) there were no differences in blood pressure. We have these data about MPA, however, it is difficult to know about the effect of progesterone on cholesterol, other lipids and inflammatory markers because, to our knowledge, no study has compared placebo with oral micronized progesterone without estrogen. Again, we have collected this information in a controlled trial of progesterone for hot flushes and hope to publish the results within a year.

Another observation in the randomized blinded comparison of CEE and MPA is that women on CEE gained more weight (almost five versus about 2.5 kg) (25), and tended to increase their truncal fat more than did those women on MPA (Kalyan Pharmacotherapy 2010). It is abdominal fat that is associated with insulin resistance, diabetes and an increased risk for heart disease. We do know that most women exposed to progesterone can eat this imperceptible amount more and not gain weight. From studies in which young normal-weight women kept a three-day diet diary about a week after flow started and a week before the next flow, we discovered that the women who ovulated were eating about 300 calories more during the luteal than the follicular phase yet kept their weights steady (26). This occurs because progesterone raises our core temperature about 0.2 degrees C. and increased temperature requires increased energy. This fact makes it likely that

progesterone aids women in avoiding obesity, insulin resistance and potentially diabetes mellitus, a very important women's heart disease risk factor.

Endothelial function is another cardiovascular marker for which there are positive progesterone data. Abnormalities in the control of blood flow by the endothelium of arteries are associated with an increased risk for heart attack. Control of blood flow is a complex process through which nitric oxide is released in the endothelial lining of blood vessels. Some years ago we did a randomized study in which healthy menopausal women came once a week for the study of blood flow. During each session, blood flow in the forearm was measured following standardized stimulations when (a week apart) estrogen, progesterone, estrogen plus progesterone or just the base solution (control) were infused into the local artery (15). This study showed that progesterone was as effective or better at increasing blood flow as estrogen(15). We have repeated this study in women randomized to oral micronized progesterone or placebo and will soon be able to present our results.

Primate and Human Studies of Ovulation and Risk for Heart Disease

The most convincing studies are always those with disease outcomes—like measured blood vessel abnormalities or better yet heart attacks. There are two such studies of the potential association of ovulatory disturbances and risk for CVD—one is in colonies of female monkeys fed a high cholesterol diet, and the other a study of ovulation over three cycles in a large number of women who were followed for heart attacks in a population-based Dutch study.

The monkey study has the advantage that the animals were captive, could be studied closely and at the end their arteries could be carefully examined for the plaques that indicate a risk for heart attack (27). The scientists first observed that some of the female monkeys were groomed more, got to the food first and were dominant over other female monkeys. They then observed that, although the dominant monkeys tended to weigh more, their menstrual cycles were the same lengths but the stressed, isolated subordinate monkeys were more likely to have ovulatory disturbances. After three years of this monitoring, when they looked at the arteries they found that, although the male monkeys had the most abnormal arteries the subordinate females had similar artery disease. However, the regularly ovulatory, non-stressed dominant female monkeys had little or no artery plaque (27). Although, in this study they did not measure estrogen levels which were likely similar between groups, progesterone levels were lower and cortisol stress hormone levels were higher. Therefore, the lower progesterone levels, the higher cortisol levels or both appear to cause female monkeys serious blood vessel disease.

The study of pre-/perimenopausal women was part of a population-based breast screening programme of over 11,000 women ages 44-49 in 1986-8 who initially completed an extensive questionnaire and brought three consecutive cycle day 22 overnight urine samples to the laboratory (28). About eight years later, local hospital registers were systematically searched for women who had participated looking for those with either acute heart attack or chest pain (angina) plus at least a 50% blockage in a coronary artery on angiography (29). Women with heart disease were matched by age, screening and other variables with three women without CVD—those with heart attacks (cases) and those without (controls) were compared for things that differed. Researchers found that those with heart attacks were more likely to smoke (60%!), to have treated high blood pressure and to have diabetes. Also, although there were no differences in actual levels of estrogen, progesterone or testosterone in their urine, more of those with heart disease had low levels of progesterone designated as anovulatory levels than did controls. This suggests that those with major heart risk factors (smoking, diabetes, high blood pressure) were more likely to have a heart attack in their mid-50s if they also had been anovulatory earlier. Although this study did not take into account the great differences between ovulatory women in their metabolism and excretion of progesterone, it is suggestive that those without adequate progesterone in perimenopause have higher rates of heart attack later.

Thus both cardiovascular risk factors (like blood pressure, inflammation, triglycerides, less weight gain and improved endothelial function) and two studies of ovulation in female monkeys and women all suggest that ovulation and normal progesterone levels with normal estrogen may be protective for heart disease in women.

Summary - Progesterone Prevents Osteoporosis, Breast Cancer and Heart Disease

In this series of newsletter articles we have discussed the difficulties in making a clinical diagnosis of ovulatory disturbances (multiple blood, urine or saliva tests or serial ultrasound studies). We also assert that a motivated woman, with little equipment or cost, can know her own cycle using the Menstrual Cycle Diary and measurements of her first morning temperature analyzed scientifically and accurately using a quantitative method (30;31). We have estimated that approximately 10-20% of women's cycles are anovulatory and about a third have short luteal phases thus ovulatory disturbances occur in a high percentage of seemingly normal menstrual cycles. Thus we know that ovulatory disturbances with their normal estrogen but lower progesterone levels are both common and silent.

In this series of articles we have already shown that progesterone is important for women's bone health. Progesterone, acting through the bone-forming osteoblast

cells, is important for the increased bone gain that occurs in the first years after menarche as cycles are "growing up" to become ovulatory (32). We also know that young, healthy and regularly menstruating women with more ovulatory disturbed cycles are silently losing bone (1;33). It may be that, eventually, progesterone will be used as part of the treatment for osteoporosis and used to prevent fractures.

We have also made a strong case that progesterone may prevent breast soreness, lumpiness (sometimes called "fibrocystic disease") and breast cancer risk. We showed that progesterone is necessary for the breast to mature to its grown up, Tanner Stage V form that has a Canadian two-dollar sized darker areola surrounding the nipple (34). That progesterone can stop the excessive cell growth caused by estrogen is also shown in two randomized human trials of hormones applied daily to one breast before a breast biopsy (35:36). Finally, the latest evidence from a large prospective observational study is that progesterone (but not progestins) with estrogen decreases the risk for breast cancer caused by the estrogen alone (37).

This final article suggests that, although women's heart disease is under an unscientific cloud of myths and disadvantages in clinical care, that there are evidences that progesterone is positive for heart disease risk factors and some clinical studies suggesting normal ovulation prevents later heart attacks. All of these ideas need testing in well documented prospective studies and randomized controlled trials before they will be proven.

The data to date confirm CeMCOR's postulate that normal ovulatory cycles during the premenopausal years prevent later, menopausal osteoporosis, breast cancer and heart disease, the three major health issues for women in industrialized countries who live to become older women.

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