Georgia Hormones, P.C.
Robert P. Goldman, MD
3400-A Old Milton Pkwy, Suite 360, Alpharetta GA 30005 770-475-0077
www.GeorgiaHormones.com
2009-05-18

Progesterone, A Central Role in Hormone Balance and Cycle Control

Today's Ignorance of Hormonal Importance:

In mid 2006 the cover article in *Contemporary OB/GYN* was on perimenopause. The management options suggested in the article were:

- Birth control pills to regulate the abnormal cycle and bleeding
- Sleeping pills for the poor sleep pattern
- SSRI antidepressants for the mood disturbance
- Mirena IUD to stop bleeding
- Endometrial ablation to reduce excess bleeding
- Uterine artery embolization to reduce bleeding.

All of these are common, contemporary modes of treatment. None of them treats the problem. All of them simply help control the symptoms of the problem. **The problem is the loss of Progesterone**.

Some common problems:

- A 14-year-old girl with PMS and irregular cycles.
- A 22-year-old woman with irregular bleeding, weight gain, facial hair and acne
- A 38-year-old woman with very heavy periods, fibroids, weight gain, dysmenorrhea and anemia
- A 45-year-old woman with occasional very heavy bleeding, hot flashes, migraines and anemia
- A 47-year-old woman s/p hysterectomy with hot flashes on Premarin and Effexor with weight gain, low libido, nervousness, poor sleep and migraines.
- A 50-year-old woman with hot flashes, occasional light bleeding, weight gain and low libido
- A 53-year-old diabetic woman with minimal hot flashes, adequate vaginal moisture and no HRT. She is at high risk for endometrial carcinoma and possibly breast cancer if left untreated.
- A 64-year-old woman on no HRT whose dermatologist has given her Premarin cream to use for the wrinkles on her face. The doctor says it won't get absorbed through the skin, so there is no risk. She is gaining weight, is bloated, has difficulty sleeping and is exhausted.

All of these are common problems. The last two patients, however, might have their problems missed altogether without physician awareness and some lab work.

Let's learn some physiology and figure out how to solve these problems safely, naturally and physiologically.

Quick Menstrual Cycle Review: (yes, this is the quick review)

1. The cycle: The lowest hormone levels are just before the bleeding begins. The falling hormones cause disruption of the blood supply to the endometrium and the tissue sloughs off.
2. The low hormone levels are recognized by the hypothalamus and pituitary.
3. In a healthy woman, both FSH and LH are produced. FSH levels are higher than LH. **This is important**.
4. LH stimulates the ovarian **Theca cells** to make **Testosterone and Androstenedione**. These two androgens diffuse out of the Theca cells into the Granulosa cells.
5. FSH stimulates the ovarian **Granulosa cells** to make the enzyme **aromatase**. It changes the Testosterone into **Estradiol** and the Androstenedione into **Estrone**.
6. FSH stimulates the increase of its own FSH receptors in the Granulosa cells.
7. FSH stimulates the Granulosa cells surrounding the growing follicles to make **Inhibin B**.
8. The most prominent growing follicle has the most FSH receptors. It makes the most Inhibin B, the most Estradiol and grows the biggest.
9. **Inhibin B feeds back on the Pituitary to inhibit FSH. LH levels continue to rise**.
10. When Estradiol and Inhibin B are high enough, LH will surge, and FSH will surge, but to a lesser degree.
11. Only if the egg is healthy, will it launch. We will have an ovulation. If the egg is not healthy, a common problem as women age, there will be no ovulation. Estrogen and LH levels continue to rise.
12. After the ovulation, the Granulosa cells surrounding the launched egg form a Corpus Luteum. Significant amounts of Progesterone are made. Remember the proportions. **There will be 20 to 100 times as much Progesterone in the blood as Estradiol.**
13. **Progesterone** in circulation reaches the brain. **It stimulates the production of brain opiates**. This has calming effects, reduces brain stimulation from the high estrogen levels, inhibits migraines, and inhibits PMS. **But most importantly here, the brain opiates lower LH**.
14. If the egg is not fertilized, there is no pregnancy. After 14 days or so, the Corpus Luteum dies off, and Progesterone and estrogen levels fall. Hormonal support for the endometrium disappears and the period begins.

IGF-I and IGF-II

What are they?
IGF stands for **Insulin-Like Growth Factor**. They are called this because of their **similarity in structure to insulin**. They are protein hormones of significant size. The gene that codes for their structure resides near that of insulin on the same chromosome and is similar to it. IGF-I is manufactured in large quantities by the liver and is carried in the blood my special carrier proteins, IGFBP-1-6. IGF-II is manufactured in the ovary and is the main IGF active within the ovary.

What do they do?
The IGF proteins are intimately involved with the **steroid hormones and the functions** they induce and promote around the body. **Insulin-like growth factors promote cellular mitosis and differentiation**. They are an intermediary between estrogen and progesterone and the effects they have in multiple locations around the body. IGF-I is involved in estrogen's effects on growth within the endometrium. IGF-II is involved in the

differentiation in response to Progesterone. IGF-I is the primary regulator of myometrial growth in response to estrogen.

Why so many IGF binding proteins? Within cells, the various binding proteins act as regulators controlling the functions that the steroid hormones stimulate. In the serum, IGF-I is mostly carried by IGFBP-1. Most of the IGF-I in the blood is bound to the carrier protein.

IGF receptors: Within the cell, IGF-I and IGF-II bind to special receptors. IGF-II, the main IGF within the ovary, binds to both its own IGF-II receptor and also the IGF-I receptor. Outside of the ovary, IGF-I is mostly active and binds to the IGF-I receptor. The activity level of the IGF hormones, regulated by their carrier proteins, is a central to the actions of the steroid hormones, estrogen and progesterone, and the levels of the hormones themselves. **All the multitude of actions of the steroids around the body happen through the intermediary actions of the IGF proteins.**

Why do I need to know about the IGF proteins? The biggest issue is their **similarity to insulin**. Insulin has the ability to bind to the IGF-I receptor. For the most part, insulin is free in the serum. Insulin resistance, high intake of sugar and insulin use by diabetics, all increase insulin in the blood. Here is the link between insulin resistance and abnormal cycles in PCOS. **Insulin, especially in excess quantities, will bind to IGF-I receptors and promote Estrogen effects throughout the body!!**

What is normal?

Under the Patient Evaluation and Work-up heading, I have several papers on "normal" values of various hormones from the laboratory. Here is a more central question. In the balance between estrogen and Progesterone, what is normal? When oral contraceptives were invented, the twenty-one day on and seven day off pattern was chosen to mimic the twenty-eight day menstrual cycle. In fact, this was fairly arbitrary. Speroff has a nice review of the developers of "The Pill". One had the hope of official Catholic Church approval if it reproduced the twenty-eight day cycle. That didn't happen. In fact, **over the course of history, few women spent their lives having periods.** Most women were pregnant from an early age. Pregnancy, although having high estrogen levels is dominated by Estriol and Progesterone. It is primarily a Progesterone dominant state. Pregnancy was followed by a year or more of breast-feeding; a low estrogen state. After a few cycles, a new pregnancy began. "**Normal" was a few months of periods followed by pregnancy and breast-feeding.**

Family Planning:
With a much lower death rate among children and new medical technology, the late Twentieth Century ushered in the era of family planning. Most women now spend their lives with pregnancy and breast-feeding a rare event. Birth control pills are progestin dominant.

Inhibin B:

The Imperfect cycle:
As women age, they are constantly losing eggs. Those eggs that remain are less likely to function properly. Fertility rates peak in the early twenties and slowly decline until age thirty-five. After age thirty-five the decline in fertility is more rapid. **Declining fertility is just a reflection of lower ovulation rates as well as poor egg quality and lower progesterone levels.** Estrogen, however, is not declining at this time.

The role of Inhibin B:
Lets go back to the review of the menstrual cycle above. As the egg matured, the granulosa cells in the ovary produced Inhibin B. This hormone fed back on the hypothalamus-pituitary to suppress FSH production. **What happens, as there are fewer viable eggs?** Inhibin B production goes down. This means that FSH will not be as well suppressed. In women in their late thirties and forties, the granulosa cells are working just fine. **FSH is rising because of reduced production of Inhibin B, not because of lower estrogen!** If you measure estrogen levels on these women with slightly elevated FSH, you will find that Estradiol and Estrone levels are frequently quite high.

Estrogen Dominance:
As women age, fewer cycles produce perfect ova and ovulation. Frequently the Progesterone levels are low or there is not progesterone produced at all. Inhibin B levels are low, resulting in **elevated FSH**. The ovary is over stimulated and makes **high levels of estrogen**. In addition, without Progesterone, LH levels are not brought back down to normal during the second half of the menstrual cycle. There is no Progesterone to induce brain opiate production. **LH levels are not brought back down**. After a few months in a row without ovulation, LH levels grow. The woman gets into a state similar to PCOS with high LH. This stimulates the **theca cells to over produce Testosterone and Androstenedione**. FSH levels are high also, because of the lower levels of Inhibin B. **The over stimulated granulosa cells have no trouble turning the excess Testosterone and Androstenedione into excess Estradiol and Estrone**. Estrogen becomes dominant and the needed Progesterone is not present to mitigate its effects.

High estrogen levels will over stimulate the endometrium. The over stimulated endometrium will grow thicker and thicker. Eventually, it will start to come apart and cause irregular, heavy bleeding. If there are fibroids, they will grow.

Before I review the roles of estrogen and progesterone and estrogen dominance, let me tell you the bottom line here.

Treating this patient with real, bioidentical Progesterone will:

- **Reduce LH**
- **Reduce intra-ovarian androgens**
- **Restore estrogen/progesterone balance**
- **Restore a normal bleeding pattern**
- **Increase the chances of a normal ovulatory cycle.**

Lets go over the physiology of estrogen and progesterone.

The roles of Estrogen and Progesterone:

Estrogen and Progesterone live in a push-pull balance in many areas of a woman's body. Many of the roles of Testosterone in men are expressed in women with Progesterone. The receptors for Testosterone, Progesterone and Cortisol are all very similar and all three hormones can attach to any of the three receptors. In many tissues, Testosterone and Progesterone have similar stimulatory effects, while Cortisol has a down regulating effect. This is true of the osteoblast cells in the bone, of muscle production and of thyroid.

Men make Testosterone on a constant basis. A young man's Testosterone level is approximately two hundred and fifty times his Estradiol level. A man in his fifties still has Testosterone approximately one hundred times

his Estradiol, unless he has excess abdominal fat or poor liver function, in which case, his estrogen levels will rise, upsetting the balance.

In women, Progesterone is only present during pregnancy and in the second half of the menstrual cycle. Progesterone levels range from twenty to one hundred times those of Estradiol during the normal cycle.

Lets look at some of the balancing differences between estrogen and progesterone.

ESTROGEN EFFECTS	**PROGESTERONE EFFECTS**
Estrogen stimulates tissue growth	Progesterone promotes maturation of tissue
Increase central body fat	Promotes metabolism of fat
Promotes salt and water retention	Diuretic, promotes salt and water loss
Brain stimulator, wakefulness	Sedative, promotes CNS endorphin production
Enhances memory and thinking	--- Testosterone enhances memory#
Inhibits REM dream sleep	Promotes REM dream sleep
Sleep not restful	Improves restful sleep
Stimulates rise in LH	Promotes reduction in LH
Suppresses thyroid on target tissues	Enhances thyroid effect on target tissue
---	Raises basal body temperature BBT
Increases carbohydrate craving	Decreases carbohydrate craving
Promotes weight gain	Mitigates weight gain
Increases libido	Also increases libido
Enhances Immunity	Quiets immune response*
Inhibits osteoclast action, Reduces bone loss	Promotes osteoblast action, Promotes bone growth
Promotes endometrial cancer	Protective of endometrial cancer
Possibly promotes breast cancer	Possibly protects against breast cancer**
Thickens Gallbladder secretions Promotes Gallbladder disease	Thins Gallbladder secretions Reduces Gallbladder disease

The hippocampus in the brain controls memory and learning. It contains aromatase. Testosterone is first converted into estrogen and thereby promotes memory.
* Women have seven times the rate of autoimmune disease that men do. Loss of progesterone after age 35 and estrogen dominance is theorized as a possible cause. Men do not lose their balancing testosterone.
** Population studies show that women with fewer pregnancies and estrogen dominant women have a higher frequency of breast cancers. Progesterone would theoretically be protective. Unfortunately, too few women are taking natural bioidentical progesterone for population studies to be meaningful. Also, breast cancers probably take over a decade to reach a detectable size. A meaningful prospective study would take decades to complete.

Estrogen Dominance Syndrome:

So, what would this estrogen dominance state look like? We see these women every day. As women age beyond thirty-five, ovulation becomes less frequent. If they don't ovulate for a few months in a row, **LH becomes persistently high**. This induces a **chronic state of elevated intra-ovarian androgens**, which inhibit ovulation. The situation becomes self-perpetuating. But wait, there's more.

Weight gain:
The excess estrogen causes increased **carbohydrate craving**. Because of this, the patient starts to **gain weight**, especially around her waistline. Intra-abdominal fat has the ability to make the enzyme aromatase. **Aromatase will convert adrenal produced testosterone and androstenedione into estradiol and estrone.** That drives estrogen excess even higher, increasing and speeding up the process. **We have a positive feedback circuit**.

The Uterus:
All this estrogen promotes the growth of the endometrium. That growth is continuous. It is not mitigated by Progesterone. Eventually, we get heavy bleeding that comes at irregular intervals. The estrogens also promote the growth of fibroids and polyps.

The Ovaries:
Even if there is a growing egg, if it is defective, a more common occurrence with age, it will not ovulate. With the extra FSH around, the follicle will grow into a follicular cyst. If anovulation is chronic, the rising LH will cause extra intra-ovarian testosterone and androstenedione. That inhibits the maturation of follicles. The stimulated follicles don't die off as easily either, a process called apoptosis. We get a bunch of follicles frozen in an intermediate state of neither growth nor apoptosis. **These strings of small follicles form the typical appearance of the PCOS ovary**.

Insulin and IGF-I:
Were you wondering why I brought up IGF and insulin earlier? Well, here it comes. With weight gain comes increased insulin resistance. **These women crave carbohydrates**. They are eating bread and sweets. **Some are drinking those dainty thirty-two ounce soft drinks that come with your fast food value meal number one.** Today's soft drinks are sweetened with high fructose corn syrup, pure, monosaccharide glucose. It is very rapidly absorbed and **drives blood glucose** levels up. This is followed by a rapid **rise in Insulin**. The insulin drives the sugar into the abdominal fat, causing an **increase in central obesity**. **This is a second positive feedback circuit.**

Remember, insulin and IGF are very similar in size and shape. **Insulin fits on the IGF-I receptor**. Insulin stimulates the receptor just as if it were IGF-I. With all that **extra insulin** around, the target tissues think there is a lot of estrogen driving IGF-I activity. So, the **target tissue does the same things it would do if there were lots of estrogen**. In the endometrium, this means grow thicker and bleed heavier. In the myometrium, this stimulates fibroids to grow bigger and endometrial polyps to grow. In the breast, this stimulates ducts and glands to proliferate, but not to differentiate. Women with insulin resistance have elevated rates of breast cancer. In the ovaries, follicular cysts are increased. **This is our third positive feedback circuit** in these women. Giving Metformin may help, but a reduction in carbohydrate and total calorie intake is essential.

The estrogen dominant women as bullet points:

- **Irregular, often heavy cycles**
- **Growth of fibroids, endometrial polyps and ovarian cysts**
- **Weight gain, especially central weight gain (apple shaped)**
- **PMS**
- **Migraine headaches**
- **Poor sleep pattern with depression caused by sleep depravation**
- **Low libido and nervousness**

- **Hot flashes**
- **Increased risk of endometrial cancer**
- **Increased risk of breast cancer**

Some common problems:

Lets go back to the common problems listed at the start of this section. For therapy instructions, see "**Hormone Workup and Therapy,** A Quick Guide to Natural Hormone Use".

- **A 14-year-old girl with PMS and irregular cycles.**

At this age, she may not have a regular hypothalamic-pituitary axis. The ovary simply responds to the stimulating hormones it sees. Without normal LH and FSH surges, luteal phases tend to be ineffective and progesterone is often inadequate. If she is not sexually active and doesn't need contraception, Progesterone cyclic therapy can work wonders with little or no side effects.

- **A 22-year-old woman with irregular bleeding, weight gain, facial hair and acne**

This is the typical PCOS patient. If she needs contraception, a low dose birth control pill is a good option. I see many women in my practice who are in their thirties and forties, have completed their families, but are still suffering with the side effects of PCOS. Progesterone cycling alone will help many of these women. Others will require special attention to hirsutism, acne or insulin resistance issues.

- **A 38-year-old woman with very heavy periods, fibroids, weight gain, dysmenorrhea and anemia**

These women respond beautifully to Progesterone given in a cyclic fashion. Their only problem is an aging ovary with aging eggs. The positive feedback nature of estrogen dominance often spins them out of control. **It is my belief that if these pre-menopausal women were treated with cyclic Progesterone, the hysterectomy rate in the U.S. could be reduced by 70-80%.** Endometrial ablation is performed on women with a normal or nearly normal sized uterus. Their problems are hormonal, not uterine. **I have not needed to perform an endometrial ablation in over three years**. It is possible that I have some patients in whom I have failed to control bleeding. If they sought help from another physician I might be unaware of it. But, until this writing, I have been able to bring bleeding under control and prevent further anemia in all these patients. This is true even for some women with large fibroids who came to me because they absolutely refuse surgery. **Of course, if cancer is suspected, that must be dealt with appropriately.**

- **A 45-year-old woman with occasional very heavy bleeding, hot flashes, migraines and anemia**

This is the typical pre-menopausal woman. She may have mildly elevated FSH but it is accompanied by a still significant level of Estradiol or Estrone. Many of these women have high Estrone, which may not be obvious if only Estradiol is measured. Some women at this age are fully menopausal. If FSH is the only hormone measured, this woman would be falsely labeled as menopausal and treatment would not be ideal. These women respond beautifully to Progesterone. Periods straighten out, hot flashes stop, migraines are reduced or stop all together and anemia is no longer a problem. Sleep is improved and that helps all of life.

- **A 47-year-old woman s/p hysterectomy with hot flashes on Premarin and Effexor with weight gain, low libido, nervousness, poor sleep and migraines.**

Without a uterus, there is no bleeding. The only way to access ovarian output is with hormone measurement. Many physicians measure only FSH. Just because FSH is elevated does not mean the patient is low on Estrogen. **Giving additional estrogen to a woman who is already estrogen dominant will only make her**

worse. I see many of these women. The constant high estrogen produces the weight gain. Insomnia and chronic sleep depravation without good REM sleep leads to nervousness and depression. It reminds me of my first year of OB residency. Sleep depravation is a terrible thing. Simply giving progesterone and restoring balance works wonders. Many of the women spontaneously stop the SSRI antidepressants once a normal sleep pattern is restored. They don't need them anymore. Of course, if they are still making estrogen, they don't need estrogen supplements.

- **A 50-year-old woman with hot flashes, occasional light bleeding, weight gain and low libido**

This woman may still be making a small amount of estrogen. **Although her estrogen levels are low, without any progesterone, she still has some symptoms of estrogen dominance**. She may need both estrogen and progesterone. Since her menopause is recent, I would cycle the progesterone to check on withdrawal bleeding. Endometrial surveillance is still appropriate as needed to rule out hyperplasia or carcinoma. Progesterone therapy will usually resolve low-grade endometrial hyperplasia.

- **A 53-year-old diabetic woman with minimal hot flashes, adequate vaginal moisture and no HRT. She is at high risk for endometrial carcinoma and possibly breast cancer if left untreated.**

Remember the lessons of insulin and IGF-I receptors. We should have all these women on natural, bioidentical Progesterone. She is on no HRT because she has plenty of estrogen (it may mostly be Estrone) and in addition, her high insulin acts as if she had even more.

- **A 64-year-old woman on no HRT whose dermatologist has given her Premarin cream to use for the wrinkles on her face. The doctor says it won't get absorbed through the skin, so there is no risk. She is gaining weight, is bloated, has difficulty sleeping and is exhausted.**

This is a real patient. She did not tell me about the facial Premarin cream. When I got back her blood work I was shocked by an Estradiol of 600 pg/ml. That was before the lab changed the test. With today's Estradiol test, Premarin would mostly show up in the Estrone level. The Equine estrogens do not appear on the test at all. I gave her Progesterone 200mg HS QD. I also gave her Biest in gradually lowered doses. I felt it would too much of a shock to reduce the estrogen too rapidly. She felt much better on much lower estrogen with matching bioidentical progesterone.