

# **Breast Development and Endocrinology**

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<https://breast.is>

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## Updates:

Information on aromatase enzymes and their modulation added May 3, 2018.

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# I Biology

## Breast Development

The hormones of estrogens, progestogens, and prolactin influence breast tissue through Estrogen Receptor Alpha ( $ER\alpha$ ), Progesterone Receptor B (PRB), and Prolactin Receptor (PrlR). As each receptor is positively stimulated by its respective hormone, it also becomes desensitized. There are more receptor types in the breast that cannot be ignored due to health reasons, but those mentioned above regulate breast tissue.

Positive estrogenic stimulation, or agonism, of  $ER\alpha$  causes lengthening of milk ducts. Branching of milk ducts, which increases the amount of end buds, is caused by progestogenic agonism on PRB. The initial formation of milk lobules converted from the end of milk ducts and their continued growth is caused by prolactin's effects on PrlR. Progesterone also has a role in differentiation, or conversion of end points into milk lobules, by influencing prolactin, during the luteal phase.

Of  $ER\alpha$ , PRB, and PrlR, their non-respective hormone enhances each hormone's response to its respective hormone, known as receptor upregulation. Without this synergistic action, the response to a receptor's own specific hormone dulls with quantity or potency, known as receptor downregulation. Too much of a potent hormone may possibly damage its own and other interacting receptors. An imbalance of too much of one type of hormone is a cancer risk. The breast contains more types of cell receptors, but the mentioned above are the focus here.

## Endocrinology

Outside of the luteal phase or pregnancy, progesterone amounts in the body are existent (due to the adrenal glands), but negligible. Progesterone is produced by the corpus luteum, which is a temporary organ whose function is to signal to the pituitary gland to momentarily prevent menstruation, for purposes of maintaining fertilization or pregnancy. The pituitary gland releases prolactin, which signals the corpus luteum (and if during pregnancy, the placenta) to release more progesterone, creating a feedback loop. If the egg is not fertilized, the corpus luteum dies within the ovaries, then this signals for the pituitary to release Follicle Stimulating Hormone (FSH) instead of prolactin, allowing the menstrual cycle to proceed. Luteinizing Hormone (LH) is released later to continue the egg's preparation. The ovaries also produce estrogens and progesterones during the luteal phase and pregnancy. Progesterone increases prolactin, and prolactin lowers FSH and LH.

Estrogens are formed from androgens through a process called aromatase, and aromatase enzymes occur in tissue where  $ER\alpha$  and Estrogen Receptor Beta ( $ER\beta$ ) are present. This includes ovarian, egg, bone, brain and adipose tissue.

## II Hormone Imbalances

Here is about hormone balance and some of their manifestations. Serum prolactin, progesterone and estrogen levels work synergistically for breast maintenance, and their proportion is important throughout the cycle. There are more hormones that play a role in the health of the human body.

### LH, FSH and Androgens

Prolonged or heavy periods can be explained by low prolactin and abnormally high Follicle Stimulating Hormone (FSH). FSH and Luteinizing Hormone (LH) allow menstruation and ovulation to continue. Light or a delay in menstruation can be explained by high prolactin levels.

High amounts of androgens, high amounts of LH, a presence of hirsutism, and poor insulin sensitivity are associated with polycystic ovary syndrome (PCOS). It is uncertain if a lack of aromatase (the conversion of androgens into estrogens), or if too much aromatase which is coupled with high amounts of androgens contribute to PCOS. Exercise is commonly used as a treatment for PCOS to lower abnormal amounts of androgens caused by negative feedback due to insulin insensitivity.

Androgen insufficiency in women is rare, except in late reproductive years and afterwards. A few symptoms of adrenal insufficiency are fatigue, loss of libido, loss of appetite and nauseousness. Adrenal androgens play a role in women's health, for instance, for causing growth spurts during puberty.

### Fertility

A prolonged excessive imbalance of hormones can cause reduced fertility, and that is a risk for sterility.

Low levels of LH and FSH, usually as a result of high levels of prolactin, cause diminished fertility. Both progesterone and prolactin are capable of pausing the menstrual cycle for pregnancy or nursing, as are also their roles in the luteal phase. High progesterone and prolactin, with the absence of LH, FSH, and possibly androgens cause symptoms consistent with shrinkage of the ovaries. Estrogenic compounds in the presence of high prolactin and progesterone, in the absence of LH and FSH, further reduce fertility. In cases of ovarian shrinkage, reduced fertility can often be reversed, until if sterility occurs. An imbalance of low estrogen levels is consistent with primary ovarian insufficiency (POI), and it is uncertain if this is related to what is described above.

An excess of clover, hops and possibly the mycotoxin ZEN are capable of shrinking the gonads which can eventually lead to the occurrence of sterility. Clover and hops are definitely known to raise prolactin. Lowered birth-weight of animals is anecdotal evidence of prolactin properties of ZEN, which is considered a mycoestrogen. For animals grazing on clover, the outcome of reduced fertility has been known as "clover disease." Farm animals that were fed clover and were administered estrogen had less

offspring than animals that just ate clover by itself. Based on clover's stronger effects on ER $\beta$  in the reproductive tract than hops, clover's infertility effects appear to be more potent than hops.

Infertility due to hormones are not limited to progesterone and prolactin excesses. PCOS and endometriosis (uterine tissue growing outside the uterus) are also associated with infertility.

Severe PCOS can cause damage to the ovaries. PCOS is consistent with abnormally high LH, FSH and androgen levels, which are consistent with low levels of prolactin. It is uncertain whether estrogen conversion contributes to or alleviates PCOS.

Sensitization of aromatase enzymes in granulosa cells, which are within ovarian tissue, is important for reproductive health. Miniscule amounts of certain phytohormones upregulate aromatase enzymes, while large amounts desensitize them.

Progesterone deficiency or insensitivity of the reproductive tract, and abnormally high levels of bodily estrogen contribute to endometriosis. Severe endometriosis may block passage ways needed for fertilization.

Contractions are caused by high serum levels of FSH and LH, which is a risk to an existing pregnancy.

There may be other hormonal imbalances that cause reproductive changes which contribute to lack of fertility. Not all infertility cases can be determined by symptoms of menstrual irregularity.

I have a theory that, if reproductive tract tissue is activated and upregulated, what if fertility age can be extended.

## **Theories on Cancer Treatments**

When a well intended cancer treatment works against a specific cancer, the cancer's receptors usually become desensitized. This situation is also seen in the analogies of steroid and drug use, where more and more is needed to get a desired effect to a diminished body response and diminishing ability for bodily regulation. With receptor targeted therapy, the receptor must be re-sensitized for a cancer therapy to remain effective. This often seems to be the case in receptor negative types of cancer. Otherwise, a stronger medicine is given, and it becomes less and less effective. Not all substances with a specific hormone attribute have anti-cancer properties to be used for re-sensitization of receptor responses. This idea was extended from a few studies about upregulating specific receptors for more effective cancer treatment.

It is thought that insoluble dietary plant fiber, which otherwise cannot be absorbed into the bloodstream, is digested by intestinal flora to produce anti-cancer chemicals which enter the body.

## Premenstrual Syndrome

Premenstrual syndrome (PMS) can occur during the late luteal phase. It is commonly recommended to lower salt intake and to avoid alcohol during this time.

Low levels of progestogens allopregnanolone, pregnenolone, pregnanolone and 5 $\alpha$ -dihydroprogesterone are associated with negative mood during the late luteal phase. Pregnenolone is the precursor to progesterone, which suggests that not enough progestogens were being converted for hormonal balance. Progestogens allopregnanolone and 5 $\alpha$ -dihydroprogesterone are neurosteroids formed by 5 $\alpha$ -reductase from other progestogens that help the brain cope with stress during the luteal phase. Alcohol may cause problems, because it decreases allopregnanolone levels during this time.

My hypothesis is that premenstrual syndrome is associated with the monthly disintegration of the corpus luteum during the second week of luteal phase. The corpus luteum produces the majority of progestogens in the human body, and lack of certain progesterones are associated with negative symptoms. It is during the second week of luteal phase, when progesterone levels drop due to an absence of the corpus luteum, and this perhaps help create hormone imbalances that are not fully understood.

Lowering salt intake is commonly recommended to reduce PMS bloating. Many symptoms can be attributed to high levels of the mineralocorticoid aldosterone, which is a breakdown product of progestogens formed by the adrenal gland. Aldosterone influences the body to retain liquids and sodium, but it also causes loss of potassium. High amounts of potassium salt were also surprisingly associated with PMS symptoms. These imbalances may be responsible for bodily swelling as well.

## Physical

A history of hormonal inconsistencies can be related to breast conditions. Prolactin influences mammary gland size which possibly then influences nipple or areola development. Estrogen causes the extension of ducts, which allows room for branching by other hormones. Otherwise, a hormone excess can cause fibrotic breasts. In theory, a lack of bodily prolactin, and possibly an excess of estrogen can be a cause for inverted nipple. Ductal elongation is caused by estrogen, so a consistent higher proportion of estrogen to prolactin or progesterone can explain the shape of tuberous breasts. History of menstrual irregularities may be common with tuberous breasts or inverted nipples.

## More

Prolactin or progesterone imbalances may aggravate mood disorders. For one, prolactin and dopamine influence each other. The brain also reacts to hormones on its own.

For post-menopausal women, progesterone levels are naturally negligible due to lack of menstrual cycling.

## III Appendix

### More

[breast.is/appendix/](http://breast.is/appendix/)

[breast.is/blog/](http://breast.is/blog/)

### Glossary

- $\alpha$  = Alpha
- 5 $\alpha$ -reductase = Enzyme that converts Testosterone or Progesterone into more potent forms
- Agonism = Positive activation
- Alveologensis = Creation of milk lobules
- Antagonism = Negative activation
- Differentiation = Conversion of a type of cell into another
- Endometriosis = Uterine tissue that grows outside the uterus
- ER $\alpha$  = Estrogen Receptor Alpha
- FSH = Follicle Stimulating Hormone
- Gonadotrophin = Hormone released by the pituitary gland; These include LH, FSH and prolactin
- Lactagogue = Galactagogue = Breastfeeding herb
- LH = Luteinizing Hormone
- Mycoestrogen = A fungal estrogen
- Mycotoxin = A toxin made by fungi
- PCOS = Polycystic Ovarian Syndrome
- POI = Primary Ovarian Insufficiency
- PRB = Progesterone Receptor B
- Phytohormone = Plant based hormone
- Phytoprogestogen = Phytoprogestin = Plant based progestogen; For plants, the terms phytoprogestogen and phytoprogestin are interchangeable
- PrlR = Prolactin Receptor
- Prl = Prolactin = Luteotrophic Hormone = LTH



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