Breast Development and Endocrinology

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This information is not meant to substitute medical advice, and it is not meant to treat or cure any condition. It is not intended to diagnose, treat, prevent, or cure any disease. While the author has striven for this book to be accurate at the time it was written, there are many gaps in knowledge about endocrinology, and the understanding of endocrinology is also evolving. The reader of this pdf is responsible for taking care of their well-being. Please research and check with local relevant authoritative guidelines, and/or with your practitioner. The author of this pdf is not liable or responsible whatsoever for injury or loss by accident, error, omission or any other cause occasioned with information or suggestions in this book. This pdf makes no claims of efficacy.

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I Biology

Breast Development

The hormones of estrogens, progestogens, prolactin and androgens influence breast tissue through Estrogen Receptor Alpha (ERα), Progesterone Receptor B (PRB) and Prolactin Receptor (PrlR). ERα, Estrogen Receptor Beta (ERβ) and progesterone receptors (PR) in the reproductive tract are important for estrogen balance and fertility. As each receptor is positively stimulated by its respective hormone, it also becomes desensitized. There are more receptor types in the breast and body that cannot be ignored due to health reasons.

Positive estrogenic stimulation, or agonism, of ERα causes lengthening of milk ducts. Branching of milk ducts, which increases the amount of end buds, is caused by progestogenic agonism on PRB. The 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 secretory phase.

Endocrinology

Of ERα, ERβ and PRB, mild potentencies of their non-respective steroid hormone enhances each hormone receptor's response to its respective hormone, known as receptor upregulation. Without compatible synergistic action, the response to a receptor's own specific hormone dulls with quantity or potency, known as receptor downregulation. Upregulation and downregulation also applies to non-steroid hormone receptors like PrlR. Too much of a potent hormone can damage its own and other interacting receptors. An imbalance of too much of one type of hormone is a cancer and fertility risk. The breast and reproductive tract contain more types of cell receptors, but the mentioned above are the focus so far.

Estrogens are formed from androgens through a process called aromatase, and aromatase enzymes are located within tissue where ERα and ERβ are also present. ERβ is located in ovarian, egg, bone, brain and adipose tissue. Within the ovarian follicle or corpus luteum, androgen production by theca cells, and estrogen production by granulosa cells are together important for reproductive health.

Estrogens, progestogens, androgens, glucocorticoids and mineralocorticoids are steroid hormones which are fat soluble. Steroid hormones react with their respective receptors within cells.

Follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (Prl), anti-müllerian hormone (AMH) and inhibin are amino acid based hormones that regulate the menstrual cycle. These hormones do not last as long in the body as steroid hormones, and these hormones interact with receptors at cells walls. Balance of these non-steroid hormones, and the health of their corresponding receptors is also important.

Menstrual Cycle

The menstrual cycle will be divided into the following 4 phases to simplify timing: menses (menstruation), proliferative, secretory and premenstrual. Follicular phase has been divided up into menses and proliferative phases. Menstruation is when the uterus lining is shed. The proliferative phase is when the uterus rebuilds to prepare for potential pregnancy, and this lasts from the end of menstruation until ovulation. Ovulation is an intermediate time between proliferative and secretory phases. The luteal phase has been divided into secretory and premenstrual phases. The corpus luteum, which produces progesterone, is present during the secretory phase. Premenstrual phase begins after the corpus luteum disintegrates, and it lasts until menstruation starts.

During menstruation, FSH increases menstruation intensity, and prolactin decreases menstruation intensity. Estrogen is not a dominant hormone during menstruation. FSH develops the follicle, but it also causes follicles to be released. During proliferative phase, one or few follicles continue to develop which raises inhibin and estrogen. Inhibin signals the pituitary to not release FSH, and for new follicles not to be released. Rising estrogen levels prepare the reproductive tract for egg implantation. Estrogen suppresses LH at first, but a buildup of estrogen eventually causes the body to release LH. LH allows ovulation to occur, releasing the egg from the follicle, leaving behind the corpus luteum in the ovary. The sequential rise of LH, then FSH initially matures the corpus luteum within the ovary during ovulation. FSH then pushes the egg towards the uterus. 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. Lower amounts of estrogens than progestogens are produced during the luteal phase and 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. Progesterone increases prolactin, and prolactin lowers FSH and LH. If the egg is not fertilized, the corpus luteum dies within the ovaries. Once progesterone levels drop during premenstrual phase, the pituitary gland begins to release FSH, allowing menstruation to begin. Outside of the secretory phase, early premenstrual phase or pregnancy, progesterone amounts in the body are existent (due to the adrenal glands), but negligible.

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.

FSH and Prolactin

Prolonged or heavy periods can be explained by low prolactin and abnormally high FSH. Light or a delay in menstruation can be explained by high prolactin levels.

Prolactin imbalances may aggravate mood disorders. Dopamine and prolactin influence each other. The brain also reacts to hormones on its own.

Premenstrual Syndrome

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

Low levels of progestogens allopregnanolone, pregnenolone, pregnanolone and 5α-dihydroprogesterone are associated with negative mood during the late luteal phase. Pregnenolone is the precursor to progesterone, which suggests lack of progestogen conversion for hormonal balance. Progestogens allopregnanolone and 5α-dihydroprogesterone are neurosteroids formed by 5α-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 premenstrual phase.

Premenstrual syndrome is associated with hormonal changes due to the monthly disintegration of the corpus luteum at the end of secretory phase. The corpus luteum produces the majority of progestogens in the human body, and lack of certain progesterones are associated with negative symptoms. During premenstrual phase, progesterone levels drop due to an absence of the corpus luteum, and this likely contributes susceptibility to premenstrual syndome.

Lowering salt intake is commonly recommended to reduce PMS bloating. Many symptoms can be attributed to high levels of mineralocorticoids, which regulate salts and are breakdown products of progestogens. The mineralocorticoid alderosterone 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.

Androgens and LH

Androgenic symptoms like hirsutism, alcopecia and poor insulin sensitivity are associated with polycystic ovary syndrome (PCOS) and high LH. Estrogen deficiency occurs when insufficient

estrogen is converted from androgens, and it contributes to a buildup of other steroid hormones, including androgens. 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. Androgens play a role in women’s health, for instance, for causing growth spurts during puberty.

Fertility

A hormone imbalance can cause reduced fertility, and a prolonged excessive imbalance is a risk for sterility. Hormone receptor insensitivity can result from an excess of any particular hormone which can contribute to lowered fertility. PCOS, uterine fibriods, ovarian shrinkage, primary ovarian insufficiency (POI) and endometriosis are associated with reduced fertility.

Progesterone deficiency or insensitivity of the reproductive tract, and abnormally high levels of bodily estrogen can contribute to endometriosis (uterine tissue growing outside the uterus). A past history of heavy menstruation that spreads uterine shedding can also contribute to endometriosis as in retrograde menstruation. Severe endometriosis may block physical passageways needed for fertilization. Progesterone with estrogen, likely by offering antagonist or opposing actions, have reduced endometriosis in a study.

PCOS is consistent with abnormally high LH and androgen levels, which is consistent with low estrogen levels. Severe PCOS can cause damage to the ovaries.

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

In cases of ovarian or fallopian tube shrinkage, reduced fertility can often be reversed, until if sterility occurs. The fallopian tubes, like the breasts, are affected by ERα, and the ovaries are affected by ERβ.

An imbalance of low estrogen, high FSH and low AMH levels is consistent with diminished ovarian reserve (DOR). POI is a similar condition to DOR that is also marked by low estrogen and high FSH levels. Symptoms of POI are similar to those of low estrogen and low androgen levels. Estrogen insensitivity could possibly be associated with POI and DOR. Low levels of inhibin are also associated with reduced fertility.

An excess of clover, hops and 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 ERβ in the reproductive tract than hops, clover's infertility effects appear to be more potent than hops.

High prolactin, coupled with low levels of FSH, can cause symptoms consistent with diminished fertility and shrinkage of the ovaries. Progesterone and prolactin are capable of pausing the menstrual cycle for pregnancy or nursing, as are also their roles during the luteal phase.

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.

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

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 fibriotic 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.

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.

III Appendix

Glossary

- α = Alpha
- β = Beta
- 5α-reductase = Enzyme that converts Testosterone or Progesterone into more potent forms
- Agonism = Positive activation
- Alveologenesis = Creation of milk lobules
- Antagonism = Negative activation
- Anti-müllerian hormone = A hormone that gives an indication of ovarian reserve
- Differentiation = Conversion of a type of cell into another
- DOR = Diminished Ovarian Reserve
- Endometriosis = Uterine tissue that grows outside the uterus
- ERα = Estrogen Receptor Alpha
- ERβ = Estrogen Receptor Beta
- FSH = Follicle Stimulating Hormone
- Gonadotrophin = Hormone released by the pituitary gland; These include LH, FSH and prolactin
- Inhibin = ovarian hormone that reduces FSH secretion
- 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
- PR = Progesterone Receptors refering to any subtype
- PRB = Progesterone Receptor B
- Phytohormone = Plant based hormone
- PrlR = Prolactin Receptor
- Prl = Prolactin = Luteotrophic Hormone = LTH

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