NATURAL HORMONES, LABOR, AND BREASTFEEDING: MOLECULES THAT INITIATE LIFE

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FACULTY OF MEDICINE

INTEGRATED UNDERGRADUATE AND GRADUATE UNIVERSITY STUDY OF MEDICINE IN ENGLISH

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I. Thesis mentor and committee

Thesis mentor: Associate Professor Lara Batičić, PhD

The graduation thesis was graded on _____ in _____, before the Committee composed of the following members:

1. Full Professor Vlatka Sotošek, MD, PhD _____
2. Assistant Professor Marko Klarić, MD, PhD _____
3. Associate Professor Marin Tota, PhD _____

The graduation thesis contains 46 pages, 8 figures, 61 references.

II. Preface

I express my deepest appreciation to

my affectionate, irreplaceable, and caring partner

and our beautiful little daughter Caitlyn-Laetitia.

They always give me strength.

My partner and my parents supported me in any possible way.

They have always encouraged me in achieving my goals.

I could not have undertaken this journey without them.

Deeply grateful

III. Thesis table of contents

IV. List of abbreviations and acronyms

17αOHP 17α-hydroxyprogesterone

3β-HSD 3β-hydroxysteroid dehydrogenase, 3β-hydroxysteroid dehydrogenase

5α-DHP 5α-dihydroprogesterone
5β-DHP 5β-dihydroprogesterone

cAMP cyclic adenosine monophosphate
CL Corpus Luteum
CRH Corticotrophin releasing hormone
CYP17A1 17α-hydroxylase
CYP21A2 21-hydroxylase

DHEA dehydroepiandrosterone

FSHR follicle-stimulating receptor

$GABA_A$ gamma-aminobutyric acid type A
GnRH gonadotropin-releasing hormone, Gonadotropin-releasing hormone

IGF-1 insulin-like growth factor-1

LH Luteinizing hormone
LHR luteinizing hormone receptor

OVTA Ornithine Vasotocin Analog, Ornithine Vasotocin Analog
OxyR oxytocin receptor

PR Progesterone receptor
PR-A progesterone receptor A
PR-B progesterone receptor B

SP surfactant proteins

SPRM Selective progesterone receptor modulators

TRH thyrotropin-releasing hormone

1 Introduction

Pregnancy, labor, and breastfeeding are the most natural phenomena in the world. Sexual reproduction is the only possible way for the human species to reproduce. This is the reason why human life still exists in today's world. The possibility of the diversity of human reproduction contributed significantly to an evolutionary progress and continuous amelioration of the human species.

The desire to explore all existing phenomena in this world is one fundamental interest of every human being. Researchers have made it their task to explain all phenomena. The same is true for medical researchers. Pregnancy, birth, and breastfeeding are fundamental parts of every new life that come into this world, and they have always functioned in the same way ever since.

Nowadays there are many research approaches to find out the exact molecular mechanisms related to the human reproduction. The human body is one of the most complex organisms in the world and even after an extensive investigation of the same, some physiological and biological mechanisms remain unclear.

Maintenance of pregnancy and the interplay of various hormones is not fully understood. Otherwise, premature labor and the associated complications might be preventable. The maintenance of pregnancy merges consecutively with the initiation of labor.

The initiation of labor is also one phenomenon, where the exact mechanisms also remain unknown until today (1,2,3). Many attempts were made to get a better understanding of the hormonal involvement in correlation with their reaction of the target tissue.

Lactation is essential to nourish the new-born. Breast milk is made up of the optimal composition of fat, proteins, vitamins, and immunoglobulins. Many attempts have been made with the goal to produce formula milk with the same properties as breastmilk, but until now they have failed so far. Despite the fact, that breastmilk is the optimal nutrition for a new-born, many women refuse to breastfeed (4). Some of their arguments are, that they don’t want to share their body with a new-born, or they want to go out without being dependent on the baby. Some women even say, that only monetary poor people breastfeed, because they can’t afford formula milk. All these statements contribute to the fact, that many women take medication to inhibit the initiation of lactation. On the molecular basis, the pathway of lactation seems to be the best understood and relatively easy to control on the pharmacological level.

2 Aims and objectives

The main goal of this review is to summarize the main physiological changes of the human body in accordance with pregnancy, labor, and breastfeeding. Special attention will be paid to the major hormones involved in this topic to get an overview of the interconnection of many different factors. Four major hormones were chosen, which play an essential role in pregnancy, labor, and breastfeeding. Namely, progesterone which is a key hormone during pregnancy similar to estrogen, which supports pregnancy predominantly during the first trimester. Oxytocin, which is present in every human being but is indispensable during labor and Prolactin, whose primary role is to induce and maintain lactation.

The primary focus is to represent these three hormones during the events within the context of physiological reproduction. All other pathophysiological mechanisms in which these hormones might also play a role, are not going to be described in detail or are just briefly mentioned.

In addition, this thesis serves to give a structured overview and to understand the individual physiological processes. A structured overview of this topic assures a good knowledge, which is indispensable for the future work as medical doctor to optimally care and advice patients.

3 Hormones involved in pregnancy, labor, and breastfeeding namely progesterone, oxytocin and prolactin, estrogen..

3.1 Progesterone

"Progesterone (P4; preg-4-ene-3,20-dione) is a natural female sex hormone. It plays essential roles in female reproductive functions, including menstruation, implantation, and pregnancy as well as breast development and lactation." (5)

3.1.1 Everything starts with this hormone - Cholesterol

Cholesterol is an important lipid molecule consisting of twenty-seven carbon atoms and it is the sole precursor of all steroid hormones (6). It is produced by animal cells and "plays several important roles in the human body" (7) Both the liver and the intestines as well as the adrenal glands produce a large amount of cholesterol, and only one fourth of total cholesterol is derived from the ingestion of food from animal origin (7). "The biosynthetic pathway of steroid hormones is the same regardless of the steroid-generating organ (ovary, testis, adrenal cortex, brain and placenta), but the type and the amount of synthesized and secreted steroids depends on the expression of enzymes specific to each of these organs." (8)

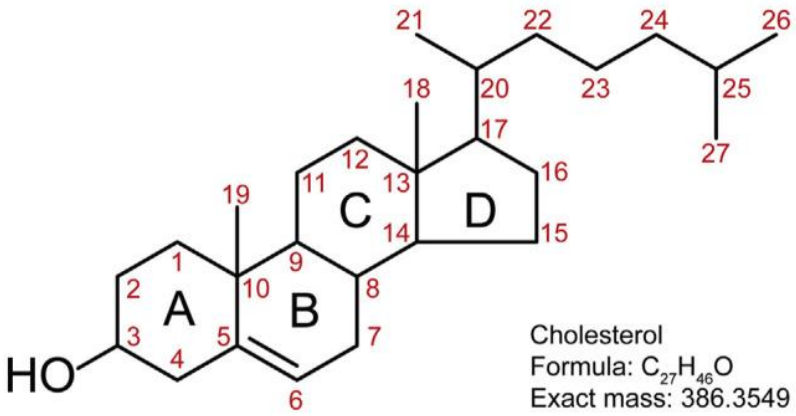

Figure 1: Molecule of Cholesterol (7)

3.1.2 Biosynthesis and chemical pathway

Progesterone belongs to the group of steroid hormones and the chemical structure is composed of twenty-one carbon atoms. From the molecule cholesterol all steroid hormones can be formed, and the further pathway is determined by the enzymes involved in the chemical reaction.

Female gonads exhibit only specific enzymes important for the production of the sex hormones, whereas the adrenal gland further transforms the hormone progesterone into glucocorticoids and androgens. (8).

The biosynthesis of progesterone is characterized by only two independent reactions. Starting with the universal hormone cholesterol, the enzyme cytochrome P450 side chain cleavage converts cholesterol to pregnenolone. The enzyme 3β-hydroxysteroid dehydrogenase (3β-HSD) is located in the smooth endoplasmic reticulum and ensures the subsequent reaction to form progesterone from pregnenolone (9).

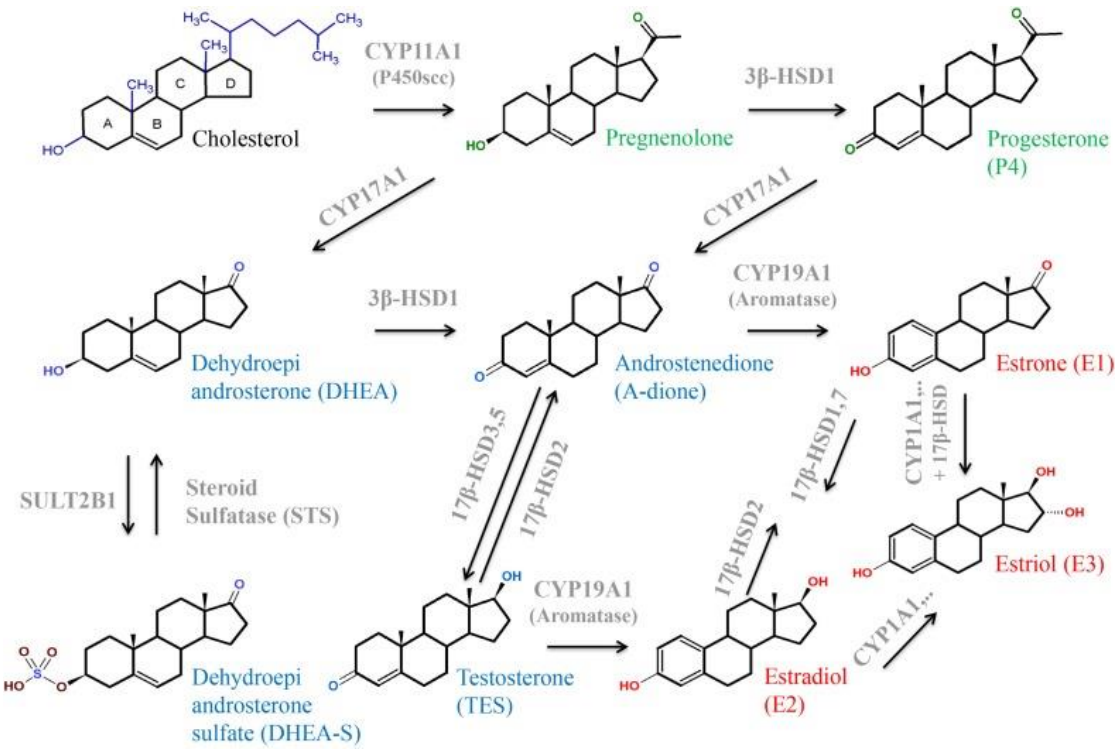

Figure 2: Interconversion of sex hormones (10)

3.1.3 Location of progesterone synthesis

After ovulation, Corpus luteum (CL) starts producing progesterone and is the main location to produce progesterone and in the occurrence of fertilization up until the end of the first trimester of pregnancy.

"Progesterone is secreted by the CL, adrenal cortex, and placenta and is necessary for implantation, the regulation of uterine development, uterine secretion, mammary gland development, and lactogenesis." (11)

Small luteal cells, which constitute a cell type of the CL, appear to be sensitive to LH by secreting progesterone subsequently. This seems to work by activating the small luteal cells with protein kinase A through the messenger pathway and releasing progesterone as a consequence. In contrast to that, large luteal cells are composed of granulosa cells and are equipped with prostaglandin receptors, whose binding will induce the degradation of corpus luteum (1).

3.1.4 Hormonal regulation

Luteinizing hormone (LH) and together with the follicle-stimulating hormone (FSH) are two hormones originating from the adenohypophysis and released under the pulsatile influence of the gonadotropin-releasing hormone (GnRH) secreted by the hypothalamus. FSH alongside LH are the main hormones acting on the gonads and thus regulating the sex hormone production. FSH and LH bind to the follicle-stimulating receptor (FSHR) and the luteinizing hormone receptor (LHR) respectively. These receptors belong to the group of G-coupled protein receptors and their stimulating leads to a rise of intracellular levels of cyclic adenosine monophosphate (cAMP) concentration (12). The exact mechanism how an increase in cAMP, as an intracellular messenger, has an impact on the uterus, is still unknown (13). High concentration of progesterone in the blood initiates a negative feedback on the hypothalamic-pituitary axis (14).

Uterine quiescence and maintenance of pregnancy is thought to be established by suppressing the production of various proteins. One representative of inducing uterine contractions being the contraction associated protein called connexin 43, which is a gap junction

protein. Connexin 43 due to its similar properties works closely together with oxytocin and prostaglandin. Progesterone is thought to maintain uterine quiescence by suppression the production of afore mentioned hormones, as well as downregulating the expression of the oxytocin and prostaglandin receptors. Additionally, progesterone seems to regulate the ion channels within the myometrium of the uterus (3).

3.1.5 Progesterone receptor (PR)

Progesterone plays a major role in various physiological functions in the human body especially female reproduction. This is the reason, why progesterone and its receptor became a major point of interest, especially due to their pharmacological importance. Nowadays progesterone is used in a form of contraceptives, as treatment for uterine bleeding and during and after menopause as hormonal replacement therapy to reduce the associated menopausal symptoms (15).

Progesterone can only exhibit its action by binding to the progesterone receptor, which is located in the nucleus to induce specific gene transcription and gene expression. Studies have shown that progesterone also has an impact on the non-genomic level and this receptor is located in the cell membrane (8,16). Meaning that progesterone has the ability to act on the genomic, as well as on the extranuclear level (8). With other words, coupling of the ligand to the progesterone receptor can either initiate the modulation of the gene, that should be transcribed or by binding to the receptor located on the plasma membrane, which induces the activation of second messenger signaling cascades (17). The non-genomic receptors react in a very fast manner compared to the genomic progesterone receptor.

The genomic PR belongs to the group of “ligand-activated nuclear transcription regulators” (17). Progesterone is a lipophilic molecule, and this characteristic facilitates the passage through the cell membrane to bind to its nuclear receptor (8). Binding to the genomic progesterone receptor initiates a cascades of events starting by activating co-regulators, which in turn stimulate the production of proteins, who then regulate the effects associated with female reproduction (8,12).

This receptor is composed of different domains with both activating and inhibitory function (17). The genomic progesterone receptor does exist in two different versions, one being the progesterone receptor A (PR-A) and the other one is called progesterone receptor B

(PR-B) (18). Structurally the two isoforms of these receptors are pretty similar except the fact, that the N-terminal of PR-B consist of additional 164 amino acids (15). Studies have shown that the PR-A is important during the development and growth of the uterus and the maintenance of the reproductive ability, whereas PR-B is essential for the physiological development of the mammary gland (17).

3.1.6 Pharmacological agonist

5α-dihydroprogesterone is one potent agonist of the progesterone receptor with a high affinity, whereas the 5β-dihydroprogesterone only has a very low affinity for the same (19,5). 17αOHP represents another agonist of the PR, but with a lower affinity compared to progesterone (5).

Progestins belong to the group of synthetic hormones that act as progesterone receptor agonist (20). Pregnanolone and allopregnanolone are metabolites of progesterone, belong to the group of neurosteroids, do not bind to the PR but do have a potent allosteric modulatory effect on the $GABA_A$ receptors (21,5). These neurosteroids act on the $GABA_A$ receptors by increasing the hyperpolarization (14), meaning that the stimulation of this type of receptor inhibits uterine contraction (22).

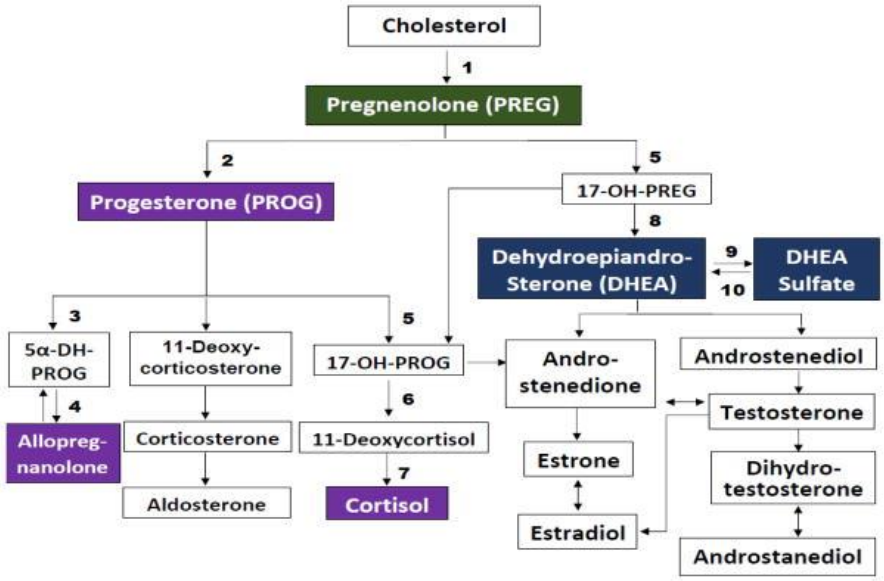

Figure 3: Pathway from pregnanolone to allopregnanolone (23)

1= cytochrome P450scc enzyme (or CYP11A1), 2=3β-hydroxysteroid dehydrogenase, 3= 5α-reductase, 4=3α-hydroxysteroid dehydrogenase, 5=17α-hydroxylase, 6= 21-β-hydroxylase, 7= 11-β-hydroxylase, 8= 17,20 lyase, 9= sulfotransferase, 10= sulfatase

3.1.7 Pharmacological antagonists

Progesterone antagonists are used primarily to terminate pregnancy. One representative of this group is mifepristone (16).

Selective progesterone receptor modulators (SPRM) are compounds with mixed properties meaning both agonistic and antagonistic characteristics (15). SPRM are not suitable for the termination of pregnancy due to their mixed mechanism of action. One representative of SPRM is the compound asoprisnil (15,5). Area of application is primarily in the gynecological and oncological setting. In some cases, this new class of drug is already used in clinical practice whereas in other fields further research is needed (5).

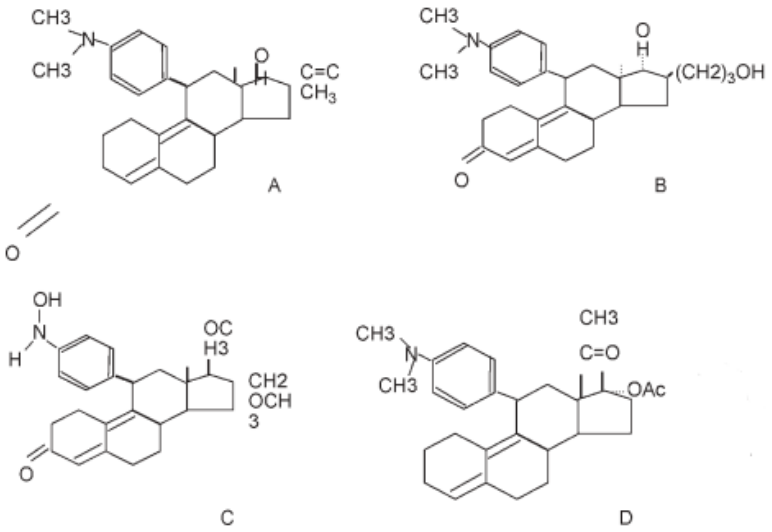

Figure 4: Chemical structure of progesterone antagonists and SPRM (15)

(A) mifepristone, (B) onapristone, (C) asoprisnil, CDB 2914 (D) CDB 2914

In general, stimulation of $GABA_A$ receptors result in an inhibitory subsequent signal (24). A study on rabbits proved that the stimulation of peripherally located $GABA_A$ receptors inhibits uterine contraction (22). It is known, that progesterone already has an inhibitory action on the uterine myometrium, but additionally some progesterone metabolites have an impact on the $GABA_A$ receptors and act as positive allosteric modulators and thus further enhance the inhibitory effect (21). In contrast, oxytocin triggers the desensitization of $GABA_A$ receptors (21). Allopregnanolone, as a metabolite of progesterone, has an opposite effect than oxytocin,

meaning that the decrease of allopregnanolone towards the end of the last trimester induces the rise of oxytocin levels and favor the contractility of the uterus (22).

3.1.8 Physiological function

Progesterone is a hormone playing a major role during the menstrual cycle, especially during the secretory phase to prepare the endometrium and thus promoting implantation of the fertilized egg. The name pro-gesterone derives from the Latin words *pro* and *gestationem*, meaning that its main task is to support and maintain pregnancy in case fertilization has occurred (8). Corpus luteum produces progesterone and correspond to its main source during the second half of menstrual cycle as well as during the first twelve weeks of pregnancy. Serum concentration of progesterone during pregnancy varies in the range of 100 to 500 nmol/L (24). Additionally, progesterone is involved in the growth and further development of the glandular breast tissue. Apart from the reproductive system and secondary female characteristics, progesterone as well has an impact on the central nervous system, have a protective effect on bones and not to forget the positive effect on the cardiovascular system (8).

The impact of progesterone on the central nervous system is by acting on the hypothalamus and altering the LH release. This influence changes the feedback mechanism and the subsequent steroid hormone production. (8)

Allopregnanolone seem to have a neuroprotective ability after brain injury by reducing oedema and restoring the function of the blood brain barrier. Moreover, it may slow the progress of Alzheimer's disease as well as preventing aggressive behavior. (8)

Progesterone also has an impact on the development of the secondary sexual characteristics in both sexes, influences the salt and water balance and regulates blood pressure. It also protects against tumors and promotes thermoregulation. (24)

3.1.9 The role in pregnancy

Progesterone, as already mentioned above, plays an essential role during implantation of the blastocyst and maintenance of pregnancy (24).

CL generates the largest amounts of progesterone during the first trimester of pregnancy. After the regression of corpus luteum, the trophoblast of the placenta takes over and produces progesterone. After the regression of corpus luteum, the trophoblast of the placenta takes over and produces progesterone. Demonstrating the importance of this hormone during pregnancy is the fact that the deficiency of the corpus luteum and the resulting decreased levels of progesterone are present in about one-third of the miscarriages (8). Progesterone originates from maternal cholesterol and the enzymes located in the placenta catalyze the reaction to produce progesterone. With the end of pregnancy, the progesterone concentration decreases to the concentration before conception (25). Premature drop in circulating progesterone concentration during the second or third trimester, may lead to a preterm delivery.

In the recent past, progesterone became progressively more popular as a possible agent for the prevention of premature birth (25).

Furthermore, it is known that steroid hormones have a positive impact on the neural development. Progesterone receptors are expressed in several pathways during development (26). An investigation showed correlating progesterone levels of the fetus compared to the levels of the mother, indicating that progesterone is derived from the same source. “An immunochemical approach demonstrated that progesterone from maternal circulation not only reaches fetal circulation but binds to nuclear PR within fetal brain. “ (25) This indicates that the fetal neural development is positively influenced by progesterone.

During pregnancy progesterone together with the insulin-like growth factor-1 (IGF-1), encourage the proliferation and differentiation of the breast tissue. Progesterone inhibits lactation during pregnancy and the sudden drop of the progesterone concentration after pregnancy ensures lactation (24). Stored progesterone in adipocytes may interfere with lactation by either delaying its onset or inhibiting lactation completely (24). This might raise the suspicion, that overweight people are more prone to develop difficulties in regard to lactation.

3.1.10 Indication for administration of exogenous progesterone

Various indications justify the usage of progesterone administration. Progesterone is used in assisted reproduction as well as in recurrent pregnancy loss. Women at risk for giving birth prematurely may profit from progesterone substitution (24). Most contraceptives contain progesterone, either as progesterone-only pill or in combination with estrogen (24,15).

Progesterone is also widely used in hormonal replacement therapy. The associated benefits of progesterone are also utilized in oncology (24).

3.1.11 Pharmacokinetics of exogenous progesterone

Progesterone reaches its target organs primarily via the bloodstream, where progesterone is either attached to the cortisol binding globulin or to serum albumin. The time that elapses before only half the amount of the active substance is present in the human body, better known as half-life, is only 5 minutes for progesterone, which can be considered relatively short. The liver is the main organ metabolizing progesterone, which is then excreted via urine. The optimal pharmacokinetic properties are shown during the intramuscular administration, because transdermal administration won´t reach the adequate blood concentration and if applied orally a huge percentage of the administered drug is already metabolized by the first pass liver before reaching the circulating blood stream. (8)

3.1.12 Progesterone metabolism and degradation

The liver is the primary location for progesterone metabolism. The enzyme 5α-reductase metabolizes progesterone to form dihydrogenated 5α-dihydroprogesterone (5α-DHP) and the enzyme 5β-reductase enables the conversion of progesterone to form 5β-dihydroprogesterone (5β-DHP). 5α-DHP and 5β-DHP are furthermore converted into tetrahydrogenated allopregnanolone, and into other compounds such as pregnanolone, isopregnanolone and epipregnaninole catalyzed by the enzymes 3α-hydroxysteroid dehydrogenase and 3β-hydroxysteroid dehydrogenase (3β-HSD). (5)

Another possible pathway of metabolizing progesterone is to be hydroxylated by the enzyme 17α-hydroxylase (CYP17A1) to form 17α-hydroxyprogesterone (17αOHP) or by the enzyme 21-hydroxylase (CYP21A2) to form 21-hydroxyprogesterone (27,5).

3.2 Estrogen

Estrogen levels, just like progesterone levels, are increased during pregnancy. By the end of pregnancy, the value can be increased up to 8-fold. Progesterone and estrogen, because they are both steroid hormones, have some common features. (10)

3.2.1 Physiological function

Estrogen has various function in relation to pregnancy such as to stimulate and maintain the utero-placental blood flow, myometrial contractions and proliferation of the mammary gland. “Estrogens regulate growth, development, and behavior associated with reproduction”. (28) Various endogenous hormones control the synthesis of estrogens namely hormones like cortisol calcitriol, human choriogonadotropin and insulin. (10)

The estrogen receptor also belongs to the ligand gated receptors, which are situated on the surface of the nucleus, which activate certain genes that initiate the production of the hormone. During the menstrual cycle, follicles produce estrogen and progesterone to promote ovulation. LH and FSH as the main regulator of steroid hormone production also influence the estrogen synthesis (12). Estrogen seems to affect both the estrogen receptor itself and the progesterone receptor. The presence of estrogen causes the number of estrogen receptors to increase and, in contrast, progesterone receptors to be downregulated. Conversely, this means that estrogen both upregulates its own receptor but also ensures that progesterone genes are expressed. Estrogen does this at different levels, both transcriptional and posttranscriptional. In conclusion, an increased estrogen concentration is accompanied by a concomitant increase in progesterone. (28)

3.2.2 Estrogen synthesis

Like all steroid hormones, cholesterol is the common precursor of both progesterone and estrogen and is also produced in the gonads. The chemical pathway from cholesterol to estrogens involves several reactions to ultimately produce an 18-carbon molecule derived from a 27-carbon molecule. Estrogens comprise a group of hormones consisting of 18-carbon atoms, namely estrone, estradiol and estriol, of which estradiol is the most abundant. (1)

Estrogen can be produced by different pathways. Its synthesis begins with the same chemical reactions as the synthesis of progesterone. However, estrogen production can then be achieved by different reactions. Instead of converting pregnenolone into progesterone, it is possible to convert pregnenolone into 17α-hydroxypregnenolone with the help of the enzyme 17α-hydroxylase. This in turn can be converted into dehydroepiandrosterone (DHEA) with the help of the enzyme 17,20-lyase. However, it is also possible to form estrogen from progesterone. In this pathway, the two enzymes mentioned above also facilitate the reactions. Then progesterone is also converted by the enzyme 17α-hydroxylase into 17α-hydroxyprogesterone, which in turn enables androstenedione with the aid of the enzyme 17,20-lyase. Up to one third of the estrogen production during pregnancy is thought to derive from the reaction of pregnenolone with the placenta-derived enzymes with 17a-hydroxylase and 17,20-lyase activities. Studies have shown that dehydroepiandrosterone is produced by both the maternal and fetal adrenal glands. Dehydroepiandrosterone can be metabolized to androstenedione by the enzyme 3β-HSD, which in turn might be transformed to estrone by the enzyme aromatase. Aromatase is also able to transform testosterone into estradiol. Pregnancies with reduced aromatase concentrations in the placenta are more likely to be affected by preeclampsia than pregnancies with physiologic levels. Estriol is the last step in the reaction chain and results from the conversion of either estrone or estradiol. The enzyme 16a-hydroxylase is essential in this last step of reaction. (10)

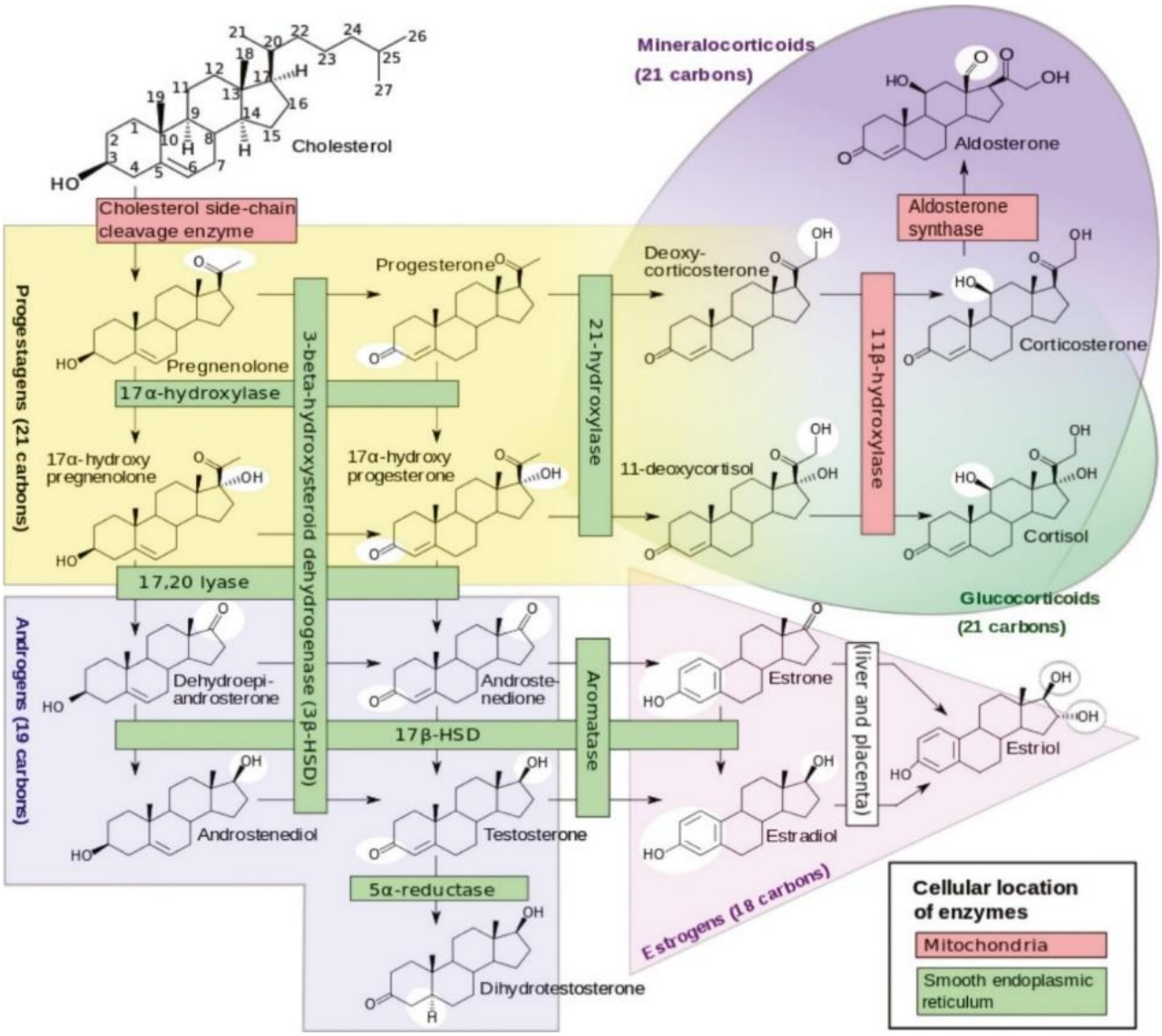

Figure 5: Steroidogenesis (8)

3.3 Oxytocin

Oxytocin is a molecule containing a nine amino acid sequence and is known for its crucial role in the event of labor and lactation. This hormone and its properties were already discovered in 1906 and it was given the name “Oxytocin”, which figuratively means “initiation of childbirth” derived from the Greek language. Induction of uterine contraction and the ejection of milk during breastfeeding are the main properties, which were also discovered before 1910. (29)

3.3.1 Involvement of physiological function

Oxytocin is a molecule, which is known for its function to induce contraction during labor, as well as playing a role during milk ejection while breastfeeding (29).

Apart from its action during labor and breastfeeding, oxytocin is also involved in several other physiological functions. This hormone is thought to influence the behavior of learning, anxiety, and pain perception along with sexual behavior, aggression, and social attachment (29,30).

The transition to motherhood is accompanied by extreme hormonal changes, social and familial challenges, and physical pain due to uterine contraction and tissue stretching. Being confronted with a completely new situation of life, caring for an infant, establishing an emotional bond and breastfeeding the new-born, this is all part of the new stage of life (31). Bonding and social attachment is especially prominent during the intimate phase shortly after birth and thus strengthening the interpersonal connection and trust between mother and the child (29).

Oxytocin is the molecule involved in nearly all of these events (31).

3.3.2 Chemical pathway

The molecule oxytocin consists of nine amino acids and its structure is very similar to vasopressin, because they only differ by two amino acids (29).

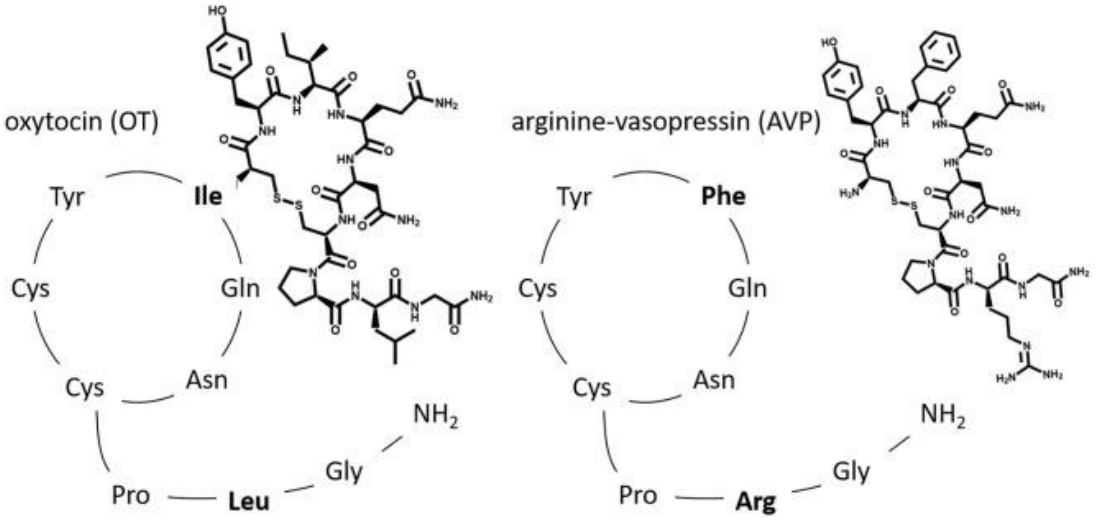

Figure 6: Amino Acid Sequence of Oxytocin in comparison to Vasopressin (32)

The hypothalamus consisting of several areas, important to mention in this context are the paraventricular nucleus, which is together with the supraoptic nucleus the main location for oxytocin synthesis (29). To be more accurate, oxytocin is produced inside magnocellular cells, which are situated in the nuclei of the hypothalamus (29). There are also other areas in the brain synthetizing oxytocin, but the hypothalamus secreting the largest amounts (30). Inside the hypothalamus, an inactive form of oxytocin is produced together with neurophysin I, which serves as a carrier protein. After its synthesis inside the magnocellular cells, oxytocin is transported to the neurohypophysis via the axons of neurons located in the paraventricular nucleus and the supraoptic nucleus (29,30). At the level of the posterior pituitary gland, oxytocin is discharged into the circulation through the capillary plexus of the posterior pituitary gland (30). During pregnancy oxytocin is stored in the posterior pituitary gland. At the end of pregnancy inhibitory mechanisms disappear to initiate parturition (31). Oxytocin is degraded inside the target tissue with the help of aminopeptidases (30).

3.3.3 Hormonal regulation

Oxytocin is discharged by the hypophysis in a pulsatile manner, primarily in response to stimuli. The release of oxytocin during lactation is mainly caused by mechanical stimulation of the mammilla (33). Oxytocin in the breast binds to myoepithelial cells and induces their contraction, thus leading to the ejection of the milk, which was stored inside the alveolar cells

(34). During the period of breastfeeding, oxytocin levels physiologically increase, and cortisol levels decrease (29).

Estrogen has a huge impact on the oxytocin synthesis itself, as well as altering the oxytocin receptor. Investigations revealed that a rise in estrogen concentration leads to a simultaneous increase in oxytocin concentration. Moreover, estrogen potentiates the effect of oxytocin by upregulating the oxytocin receptors. Progesterone and other steroid hormones are known to have an impact on oxytocin too. Progesterone is thought to alter the expression of oxytocin receptors on the cell surface by interfering with the cholesterol metabolism (30). Thyroid hormones and estrogen, both promote the oxytocin synthesis (29).

Gonadotropin-releasing hormone has a direct interaction with oxytocin meaning that GnRH positively interacts with oxytocin. Conversely, oxytocin antagonists will decrease the frequency of the GnRH release. The concentration of circulating oxytocin starts to rise shortly before parturition (35).

Oxytocin rises in response to stressful events, allowing to handle the situation with less anxiety, due to its anxiolytic properties (29). This mechanism explains, why decreased levels of oxytocin are associated with depression and anxiety. Increased circulating oxytocin levels induce a negative feedback loop to decrease the secretion of stress hormones by the hypothalamic pituitary axis (29).

3.3.4 Oxytocin receptor

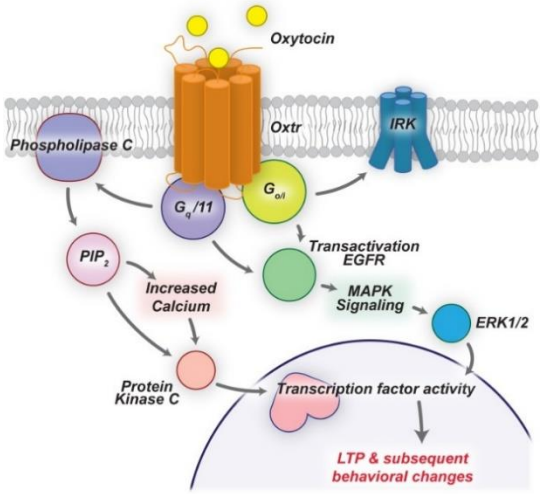

Figure 7: G coupled-protein Oxytocin receptor (36)

Until today, only one oxytocin receptor (OxyR) has been discovered (29). This receptor belongs to the family of G coupled- protein receptors and works by coupling to the phospholipase C. Binding to this receptor promotes the likeliness of uterine contraction (35,3). Most oxytocin receptors are found in the uterus with an upregulation of oxytocin receptors towards the end of pregnancy (30,31). Oxytocin receptors are also found on the smooth muscle cells of the stomach and inside the central nervous system regulating the appetite despite various other fields of activities (30).

Oxytocin receptor expression increases greatly during pregnancy primarily in the uterus and in the myoepithelial cells of the breast (29). Binding of oxytocin to its own receptor induces a downstream cascade resulting in the production of prostaglandin precursor, which in turn induces the increase of oxytocin receptors (35).

3.3.5 Oxytocin agonists

Agonist of the oxytocin receptor is the synthetically produced hormone oxytocin, which is used to induce labor, support prolonged and protracted labor and managing placental period of labor to prevent postpartum hemorrhage. Contrary to the current stage of knowledge and the fact that endogenous oxytocin promotes lactation, a study in Sweden showed, that synthetic oxytocin administration during labor resulted in prolonged onset of lactation. Another study expressed the possibility that oxytocin receptors downregulate in response to high amounts of oxytocin. These new findings raise the question of whether active management in the form of administering exogenous high levels of oxytocin is appropriate as treatment of prolonged delivery. The logical conclusion would be, that high amounts of oxytocin resulting from the combined amounts of exogenous and endogenous oxytocin will lead to a downregulation of oxytocin receptors and further exacerbate the problem of protracted labor. Oversaturated or internalized oxytocin receptor possess the risk that in case of a postpartum hemorrhage effective treatment is impossible, because oxytocin cannot work adequately. Free and unbound oxytocin without functional receptor can´t exert its physiological action and thus the opposite effect than the medically intended effect will occur. The patient will suffer from these devastating consequences. (31)

Estrogen and oxytocin agonists are also known to have similar properties. Estrogen works through two different mechanisms; one is the direct stimulation of the oxytocin receptor

and the other one by acting directly on the oxytocin gene itself (29,30). A rise in estrogen concentration shows a simultaneous increase in binding of oxytocin receptor (30).

Prostaglandin and oxytocin are not the only and most important hormones initiating parturition, but both are playing an important role as they do promote the contractile ability of the uterus (35). An optimally and regularly contracting uterus is the prerequisite for physiological labor to avoid prolonged or even undesired obstructed labor.

3.3.6 Oxytocin antagonists

During the last decades, two antagonists of oxytocin were discovered. One being Atosiban and the other one being Ornithine Vasotocin Analog (OVTA). The primary application of Atosiban is to treat and delay imminent premature birth. Due to the molecular similarity to vasopressin, oxytocin antagonist may interfere with the vasopressin receptor. (29,31)

Progesterone is able to attach directly to the oxytocin receptor and thus inhibiting the action of the same (35).

3.3.7 Corticotropin releasing hormone as competitor to oxytocin

Corticotrophin releasing hormone (CRH) is described as another hormone responsible for initiation of parturition. CRH is produced by the placenta and its concentration rises towards the end of pregnancy. It is thought that CRH induces uterine quiescence throughout the pregnancy (3). At the end of pregnancy, the binding protein for CRH decreases and thus the bioactive form of CRH increases and might even support the action of oxytocin (3). High levels of CRH induce the release of cortisol by the adrenal gland. Cortisol stimulates the surfactant production of the fetal lung during the third trimester. Surfactant lining of the fetal lung is essential for extrauterine survival. Without surfactant, the fetal lung might collapse with high risk of developing the respiratory distress syndrome. There might be a connection between the presence of surfactant protein A and the initiation of parturition (3,2,35). “It has been proposed that the surfactant proteins (SP) secreted from the maturing fetal lung into the amniotic fluid may provide the key signal for parturition at term.” (35)

3.4 Prolactin

The words *pro* and *lactin* already indicate the main function of this hormone. Prolactin initiates and promotes milk production and lactation after labor to nourish the newborn. Afore, prolactin, together with progesterone and estrogen, initiate the growth of the breast during early pregnancy to optimally prepare the breast for the time after parturition (37). The hormone Prolactin is essential for physiological lactation. Hyperprolactinemia is also present in some pathological conditions, but these cases are not going to be consolidated in this review.

3.4.1 Involvement in physiological functions

Prolactin is known for its several functions in the human body, not only related to the preparation of breastfeeding during pregnancy and breastfeeding itself.

Apart from playing a major role during reproduction and the associated events that come along with it, it is known that prolactin also promotes the development of obesity and the metabolic syndrome, as wells as disturbing the insulin and lipid metabolism (38). Additionally, prolactin seems to have an impact in the development of breast cancer (39).

Serum prolactin levels in non-pregnant females range from 2 to 30 ng/ml and during pregnancy the levels rise to levels between 10 to 210 ng/ml (40). Hyperprolactinemia in the event of motherhood is a physiological condition and is associated with lactation to nourish the newborn as well as amenorrhea (37).

3.4.2 Chemical pathway

The anterior pituitary gland produces prolactin inside of lactotrophic cells (39,12). This molecule is polypeptide consisting of 199 amino acids, which has a similar structure compared to the growth hormone and the placental lactogen hormone. Apart from being produced by the pituitary gland, prolactin is also produced by the central nervous system and the immune system. Also, the uterus as well as the glandular tissue of the breast have demonstrated to produce prolactin. “Lastly, the decidua-layer of the placenta has been found to synthesize prolactin as well.” (40)

3.4.3 Hormonal regulation

Many factors have an impact on the secretion of prolactin, but the frequency and duration of nipple stimulation by the sucking newborn being one of the most influencing factor (31,37). Nerve fibers from the mammillae carry the signal to the hypothalamus and thus preventing the secretion of dopamine (40). The absence of dopamine indicates the absence of the inhibitory function and therefore stimulating the prolactin secretion. The oxytocin synthesis in the hypothalamus is stimulated by the same mechanism and the release of oxytocin by the neurohypophysis has an additional inhibitory effect on dopamine (40,37).

Any changes in the prolactin levels may lead to significant disturbances in the homeostasis (38). Hyperprolactinemia, not only in breastfeeding women, will induce amenorrhea, due to the fact, that prolactin inhibits the secretion of the gonadotropin-releasing hormone (GnRH), which is produced by the hypothalamus (40). The main role of GnRH is to induce the release of FSH and LH by the hypophysis, which will induce, among other things, ovulation of the mature follicle from the ovary. In the absence of adequate concentrations of LH and FSH, the hormonal regulation is disturbed and will lead to anovulation, amenorrhea and concomitantly infertility. (37)

The thyrotropin-releasing hormone (TRH), antagonists of dopamine and estrogen are all stimulating the production of prolactin. In hypothyroidism, the negative feedback loop stimulates the hypothalamus to secrete a higher amount of TRH to compensate the lack of thyroid hormone and thus simultaneously stimulating the prolactin secretion. Therefore, it is not surprising, that hypothyroidism may present with galactorrhea and infertility due to the suppression of ovulation. (40)

3.4.4 Prolactin receptor

The prolactin receptor belongs to the “lactogen/cytokine receptor superfamily”, which acts by activating the KAJ/STAT pathway, as well as the MAPK and SRC kinases, thereby stimulating the associated genes (39). The transcribed genes after stimulation of the prolactin receptors are essential for the milk synthesis inside the breast tissue (37).

3.4.5 Pharmacological agonist and antagonist of prolactin

Dopamine is produced and released by the hypothalamus and binds to the lactotrophic cells, which are located in the adenohypophysis, to induce intracellular signaling and therefore inhibiting the production of prolactin (40). This inhibition of prolactin synthesis is physiologically present in all non-pregnant female adults (40). Dopamine agonists are used to prevent or to stop the production of milk after delivery in women who refuse to breastfeed (38). In contrast, dopamine antagonists are sometimes used to increase the amount of milk in breastfeeding women (38).

Increased progesterone concentration induces the downregulation of the prolactin receptors, which is the case during pregnancy (40).

Estrogen also acts like an agonist and thus stimulating the prolactin synthesis plus promoting the upregulation of prolactin receptors (37,28).

Direct prolactin receptor antagonists are still under research. Primarily these direct prolactin receptor blockers are thought to be beneficial in the anticancer treatment of breast cancer (41). Due to their excellent pharmacological effect, dopamine agonists and antagonists are primarily prescribed in the everyday life to either stop or promote lactation respectively (38).

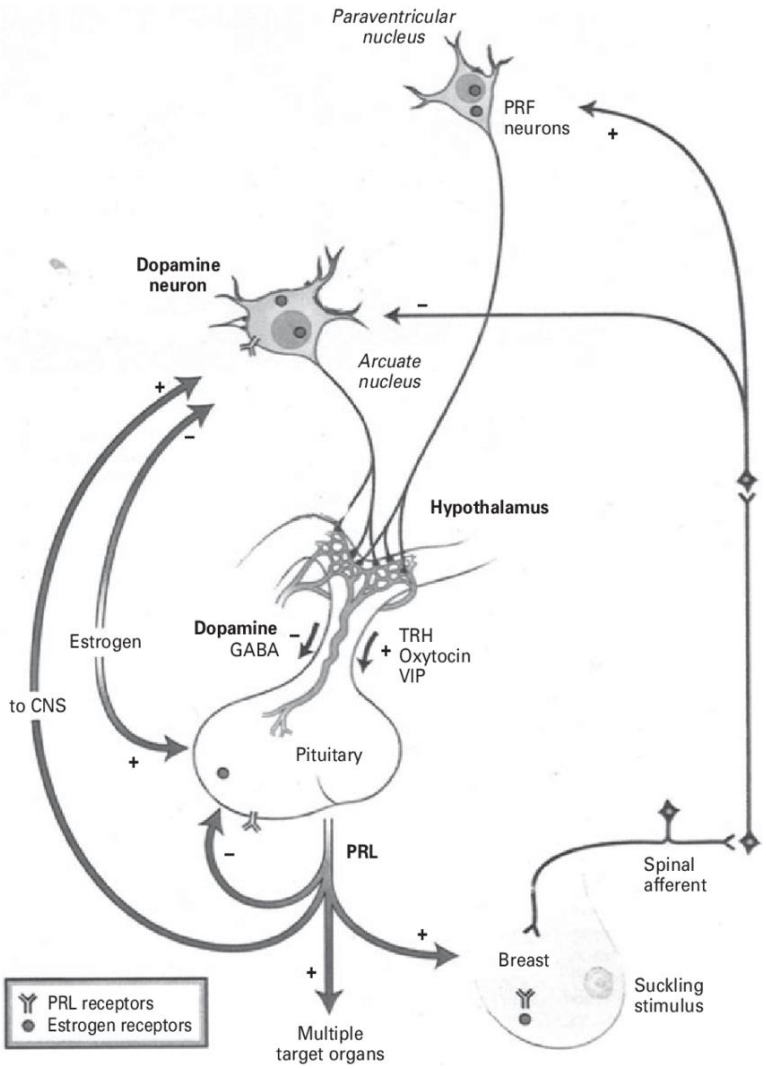

Figure 8: Prolactin production and secretion (42)

3.5 Physiological functions and pathophysiological changes during lactation

Delivery is an event accompanied not only by major physical but also by various hormonal changes. Shortly before and during delivery, progesterone levels start decreasing and subsequently the prolactin levels start to rise to encourage lactation. The levels of prolactin stay not constantly elevated during the period of breastfeeding, but they rather spike during the mechanical stimulation of the mammilla and slowly decline in the period without stimulation. As soon as the mother stops breastfeeding her child, the prolactin concentration will decrease to a non-pregnant state within the next week or two. (40)

Disturbances of any kind in the serum prolactin levels may have severe consequences. Hypoprolactinemia in pregnant women and young mothers will lead to the failure to lactate. In

contrast Hyperprolactinemia, in either men or women, will induce galactorrhea and infertility regardless of breastfeeding or not. Pathological conditions in which hyperprolactinemia is present are prolactinomas and the consumption of first-generation antipsychotics, which block dopamine. The Sheehan Syndrome is another pathological condition caused by pituitary ischemia due to hypovolemia and hypoxia shortly after delivery. These consequences are due to a massive postpartum hemorrhage. The Sheehan Syndrome is presented by severe panhypopituitarism. (40,43)

3.5.1 Positive effects of breastfeeding:

The nature designed this optimal nourishment for the infants. Nowadays there is a trend not to breastfeed due to various reasons (4). Centuries ago, this was the only possible way to nourish a child and it is the only reason why the human species has survived (4). Several studies proved, that breastmilk has beneficial effects in regard to the general and especially brain development of the newborn (44). The optimal concentration of fat, proteins and carbohydrates enable an optimal growth and development according to the current needs. Breastmilk changes its composition according to the demands. Apparently, breastmilk also changes its composition in special situations like an infection or a growth spurt to optimally supply the child with valuable and necessary nutrients, which are particularly important in these situations to compensate the demands (4).

Breastmilk additionally has major protective properties toward various diseases. Many infectious diseases can be prevented due to the immunoglobulins, which will be transmitted to the infant through the breastmilk. Breastfeeding exclusively has beneficial and protective effects for mother and child. Breastmilk protects the child from almost all pathological changes just to name some examples like leukemia, necrotizing enterocolitis, and cardiovascular diseases. Intellectual benefits are also attributed to breastfeeding and thus associated with an increased intelligence quotient. Aside from the eco-friendly features, breast milk feeding is undeniably the best for mother and child. Breastfeeding speeds up the postnatal regression and involution and enables a quick return to the pre-pregnancy body weight. Breastfeeding should be better promoted for the benefit of both mother and child, but instead the major food manufacturers advertise their formular food to boost sales. The health aspect is ignored. It is the task of the physician and of all people working in the health system to provide adequate information to enable optimal care and a good start in life for the child. (4)

4 Discussion

Calik-Ksepka *et al*. claim that in approximately 82% premature labor is accompanied by delayed initiation of lactation (37). An analysis by Chrustek *et al*. revealed that the composition of breastmilk of women who gave birth before term differs compared to the composition of the milk, which came from term births. (45). The result showed no significant differences in the basic components such as fat, carbohydrates and proteins. But the study revealed elevated levels of cortisol in the breastmilk in women who gave birth before the 37 weeks of gestation. This result fits perfectly with the previously mentioned possibility that elevated cortisol levels will induce premature labor. This elevated cortisol levels may be persistent for a longer period of time and thus influencing the composition of breastmilk. This may also be mainly due to the fact that mothers generally experience more stress, so that cortisol is elevated anyway. But the fact that cortisol is especially elevated in breastmilk of premature babies has the optimal side effect that the susceptible child is better protected. Cortisol has both anti-inflammatory properties, has protective effects on the gastrointestinal tract and has an impact on the neurological development. (45)

The data and the scientific paper regarding the hormonal composition and changes during lactation in preterm infants is scarce. It is primarily reported that preterm birth is often accompanied by problems during lactation (37). Based on the egg events described above, at least one possible explanation can be derived. Whether preterm birth is due to psychosocial stress and the associated increase in cortisol, or whether preterm birth is due to other causes, in either case, the task of delivering a child before the due date is stressful and comes along with worries about the health consequences. Bloomfield *et al*. demonstrate that elevated cortisol levels will in any case, influence and promote the release of dopamine (46). Dopamine has antagonistic properties to prolactin. This simple correlation can already explain the pathophysiological mechanism of delayed or absent lactation. A weak suckling reflex of the premature infant can additionally complicate the problem.

Chrustek *et al*. represent the overall opinion, that breastmilk is with no doubt the optimal nutrition for newborns and especially premature infants will profit from its protective properties (45).

Dieterich *et al*. nicely show the protective effects for infants. Breastmilk supplies the infant with optimal nutrition, protects the child from infections and illness and protects the intestine (47). Breastfeed children show a better neurological outcome but Der *et al*. argue that this is

primarily due to the socioeconomic status and the environment (48). An analysis performed by Bartick *et al*. calculated that 911 death would have been prevented if more than 90% of infants would have been breastfeed exclusively for the first 6 months (49). Sudden infant death syndrome is in the United Stated still the leading cause of death. Breastfeeding contributes significantly to the prevention of the same, which was proved by two different meta-analysis studies performed by Hauck *et al*. and Ip *et al* (50,51).

Opinions differ on atopic allergies, Gdalevich *et al*. claim that breastfeeding has a protective function in regard to allergies whereas Sears *et al*. mention an elevated risk of allergy (52). An investigation by Li *et al*. rules out, why breastfeeding may protect from childhood obesity. Bottle fed children eat at certain times certain amounts and lean to finish the whole bottle at once. In contrast, the breastfed children cannot be controlled regularly regarding their exact drinking volume, so they drink more as needed and do not tend to be overfed (53). In Germany we use the Latin words *ad libitum*. Owen *et al*. analyzed the data of 7 different meta-analysis studies and proved, that breastfeeding reduces the cardiovascular and metabolic risk by nearly 40% in relation to formula nutrition (54).

Apart from the previously mentioned positive effects for the child, various studies have observed additional positive long-term effects for the mother. Dieterich *et al*. also displays nice and clear the maternal long-term beneficial effects of breastfeeding (47). Bonding is thought to be supported by breastfeeding although the evidence is inadequate. In contrast, Kim *et al* found out, that brain activation in breastfeeding women is higher with the consequence, that these mothers react more sensitive, adequate and promptly to the reaction and needs of the child (55). An investigation directed by Baker *et al*. proved, that both the intensity and duration have an impact on the amount of weight loss after pregnancy (56). Also, the mother benefits from a reduced metabolic and cardiovascular risk which was proven by Schwarz *et al*. (57). The decreased risk of developing diabetes type II was observed by Aune *et al*. (58). Song *et al*. observed that breastfeeding has a positive impact on the postmenopausal bone density (37). Groër *et al*. stated, that breastfeeding improves maternal sleep duration, which in turn makes the mother more resilient and less irritable during the day (59). Chowdhury *et al* and Dieterich *et al*. claim that breastfeeding decreases the incidence of developing breast cancer and also ovarian cancer (60,47).

Health authorities should strongly recommend breastfeeding on the basis of all short- and long-term benefits for mother and child. Promotion of breastfeeding should be primarily by educating the parents. The final decision to breastfeed should be made by the parents

themselves on the basis of their own convictions, rather than forced decisions pressured by relatives or medical staff.

5 Conclusion

Maintenance of pregnancy is primarily supervised by the delicate concentration of numerous hormones. Progesterone as main representative of promoting physiological pregnancy is a hormone with various functions. It is not only a gestational agent, but it is also the precursor of various important steroid hormones. “Although several studies prove the importance of progesterone in various essential physiological processes, we are far from completely understanding the key role of progesterone in the miracle of life.” (24)

Initiation of parturition seems to be controlled by various different components. It’s a mixture of chemical and mechanical factors induced by the mother, the fetus, and the placenta, which work as a functional unit. The regulatory factors, which coordinate this complex interplay still need to be identified. (35) These regulatory factors seem to have the ability to synchronize the physical processes to facilitate an optimal outcome.

The causes of preterm birth should be investigated more specifically. Subdivided into the anamnestic history should simplify the search for causes, with the idea that the women are better comparable on the basis of their anamnesis. Regardless of the cause, in the end elevated cortisol levels will be present in each case. Cortisol appears to play a significant role in the occurrence of preterm labor. Therefore, future therapeutic approaches, both prevention and therapy should start focusing on keeping cortisol levels at normal physiological levels.

As far as we know, prolactin is primarily involved in the process of lactation in physiological condition. On the pharmaceutical level, dopamine agonists and antagonists have proven to manipulate prolactin levels significantly to be prescribed in the everyday manner.

From a medical point of view, there are no disadvantages of breastfeeding, on the contrary, it has only advantages for mothers and children in the long run. Apart from the individual benefits, breastfeeding also has a tremendous impact on the health care system and could relieve it financially by reducing the incidence of chronic diseases.

In conclusion, the most important aspects have been highlighted. These information will be useful and relevant for the future medical work. Optimal recommendations and patient education with helpful and logical explanations are essential to provide ideal medical care.

6 Summary

All events connected to reproduction are multifactorial and complex. Many hormones come into play. Some hormones play a more important role, others only a subordinate one.

This review has limited and focused on the most significant hormones. However, depending on the scope and complexity of each individual hormone, it was still not possible to present them in an all-encompassing manner. This is mainly due to the fact that further research is needed in many areas in order to make more concrete conclusions.

However, it is exactly this interaction of all hormones, each in its specific amount, which makes the human body work perfectly when reached its optimal hormonal composition. Apart from the hormonal component, mechanicals factors seem to play an equally significant role.

The larger the functional range of a hormone, the more complex and diverse and far-reaching are the involved chemical reactions. This complexity makes it difficult for researchers to investigate every single interaction. In this review, the four most important hormones that appear to have the greatest influence on pregnancy, birth and lactation have been selected.

Key words: breastfeeding, estrogen, labor, oxytocin, pregnancy, progesterone, prolactin

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VI. Curriculum Vitae

Anna Katharina Quint was born on the 26.10.1992 in Berlin in Germany. She started going to primary school in 1998 and after a regular duration of 13 years, she finished high school with the Abitur in 2012.

Directly after high school, she started working as a nursing assistant in an old people´s home as well as in a hospital in Husum. In September 2013 she received a commitment for an apprenticeship to become a midwife. After the successfully completion of the same, she worked fulltime as a midwife in a hospital in the close proximity to Cologne.

In 2017 she started studying medicine in Rijeka/Croatia.

In her free time and during the semester break she is still working as a midwife.