



DOES OSTEOPATHIC TREATMENT INFLUENCE THE HORMONE  
LEVEL OF HYPERANDROGENAEMIC INFERTILE WOMEN?

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Part of requirement for M.Sc. (Osteopathy)

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December 2007

## Declaration

This thesis is the result of my own work and includes nothing which is the outcome of work done in collaboration except where specifically indicated in the text.

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## Abstract

Background: In Europe about 14% of the couples have difficulties to conceive. In about 25% the reason for infertility is found in the hormonal system. A main pathology of the female hormonal system is hyperandrogenaemia. On the one hand, an androgen excess leads to distortions of the menstrual cycle, oligo-/amenorrhoea and anovulation. On the other hand women suffer from the apparent external changes due to hyperandrogenaemia: hirsutism, acne, alopecia and android fat distribution.

Research question: Does osteopathic treatment influence the hormone level of hyperandrogenaemic infertile women?

Study design: with-in subject design

Methods: A pilot study comprising 10 test persons was conceptualised, but only a case series of 3 subjects could be gathered. Appropriated and reasonable in- and exclusion criteria were applied. Each woman got 6 treatments every 2 weeks. Blood samples (testosterone, LH, FSH, TSH) were taken before, during and after treatment including an observation period of at least one month during which no treatment occurred. Additional questionnaires were filled in by the subjects before and after the treatment period.

Results: The testosterone level of two women deduced to a normal value. The one of the third woman remained unimproved, but she became pregnant after 4 treatments. Of note, this woman could not be considered as infertile referring to the definition of the WHO ("Infertility: failure to conceive after at least one year of unprotected coitus"). The LH-FSH-ratio was normal ( $<2$ ) throughout all measurements in two patients. Only in subject 3 the LH-FSH-ratio was abnormally high (3.4), and normalised after three treatments and remained normal after further three treatments. It should be noted that the same patient had shown normal LH-FSH-ratio two years before. TSH values were normal in all subjects at the beginning of the study, suggesting normal thyroid functioning.

Discussion: Due to the problem of the recruitment of infertile hyperandrogenaemic women, only this small number of 3 test persons could be recruited. None of these women with pathological elevated testosterone level was infertile.

Blood measuring should have included the SHBG level (sex hormone binding globulin) in order to estimate the free testosterone level as only the unbound free testosterone can exert a hyperandrogenaemic effect.

Conclusion: The results of these three cases after osteopathic treatment do not allow any statement on the effectiveness of osteopathic treatment on the hormone level of hyperandrogenaemic women. Further studies are needed to be conducted on a large scale. These

studies should be proceed in two steps: preferably first including hyperandrogenaemic women and afterwards hyperandrogenaemic and infertile women. If once it is proven that osteopathic treatment reduces testosterone levels, infertile hyperandrogenaemic women will be recruited more easily.

Key words: osteopathic treatment, infertility, hyperandrogenaemia, hirsutism, polycystic ovary syndrome (PCOS)

# Contents

1.	Introduction .....	8
2.	Physiology of the female Reproduction .....	13
2.1.	Overview of the Hormone System .....	13
2.1.1.	Biosynthesis, Transport, Effectiveness and Metabolism .....	13
2.1.2.	Regulation of Hormone Systems.....	15
2.2.	The Female Cycle.....	16
2.3.	The interaction of Hypothalamus, Pituitary and Ovary .....	17
2.3.1.	Gonadotropin Releasing Hormone (GnRH).....	19
2.3.2.	Follicle Stimulating Hormone (FSH) and Luteinising Hormone (LH).....	19
2.3.3.	Oestrogen and Progesterone.....	21
2.4.	Steroid Hormones.....	21
2.4.1.	Androgens .....	22
2.4.2.	Regulation of Steroids by Adrenocorticotrophic Hormone (ACTH).....	25
3.	Pathologies of Hormoneal Systems.....	27
3.1.	Hyperandrogenaemia .....	27
3.1.1.	Hirsutism .....	28
3.1.2.	Acne .....	30
3.1.3.	Alopecia .....	31
3.1.4.	Android Fat Distribution .....	32
3.2.	Polycystic Ovary Syndrome (PCOS) and Insulin Resistance .....	33
3.3.	Hyperprolactinaemia and Hyperthyreosis.....	36
3.4.	The Influence of Stress and Cortisol.....	37
4.	Conventional Treatment .....	40
4.1.	Medical Ovulation Induction .....	40
4.1.1.	Clomiphene Citrate .....	40
4.1.2.	Metformin.....	41
4.1.3.	Dexamethason .....	42
4.1.4.	Gonadotropins .....	42
4.2.	Surgical Ovulation Induction .....	43
4.2.1.	Laparoscopic Ovarian Drilling.....	43
4.2.2.	In-Vitro Fertilisation and Embryo Transfer .....	43
4.3.	Success Rate and Side-Effects of the Standard Medical Treatment .....	44
5.	Possible Models Explaining the Osteopathic Approach of Treatment.....	46
5.1.	The Cranial Concept.....	46
5.2.	Fluids: Blood, Cerebrospinal Fluid and Lymphatic Fluid.....	49
5.2.1.	The Blood .....	50
5.3.	The Cerebrospinal Fluid.....	51
5.3.1.	The Lymphatic Fluid.....	54
5.4.	Fascia.....	55
5.5.	Neurophysiologic Mechanisms, Somatic and Visceral Dysfunctions .....	59
5.6.	Neuroendocrine Mechanism and Emotional Influence .....	60
5.7.	Osteopathic Manipulative Treatment and Visceral Manipulations.....	61
6.	Methods.....	67
7.	Outcome .....	71
7.1.	Summary of the Questionnaires according to Tabelle 3 .....	71
7.2.	Results of Medical Documentation and Hormonal Measurements.....	74
8.	Discussion .....	76
8.1.	Problems in Patient Recruitment.....	76
8.2.	Quality of Osteopathic Treatment .....	76

8.3.	Methodology of the Series of Case Studies .....	77
8.4.	Blood Samples and Confounding Effects of Hormones .....	77
9.	Summary and Conclusion .....	80
10.	Acknowledgement.....	82
11.	List of Abbreviations.....	83
12.	Table of Figures .....	84
13.	Bibliography.....	86
14.	Appendix .....	93
14.1.	Documentation by the Doctor .....	93
14.2.	First Questionnaire .....	94
14.3.	Second Questionnaire.....	98

# 1. INTRODUCTION

Since a regional gynaecologist reported that hyperandrogenaemia (hormonal disorder) is one of the main causes for female infertility in his practice and medicamentous treatment is not always effective or wanted by these women, I look for a possible osteopathic approach to this topic. There are only few osteopathic studies known to me that investigate the effect of osteopathic treatment in case of gynaecologic phenomena such as unexplained infertility (Kirchmayr, 2006; Kapper, 2006) and uterus myoma (Kaschowitz et al., 2004) or in case of metabolic disorder such as type 2 diabetes (Kiegerl, 2006). Evidently, qualitatively valuable information and knowledge on the effectiveness of osteopathic treatment with respect to hormonal disorders is missing up to now. By searching the literature about hyperandrogenaemia and its conventional therapy, by thinking about possible models of how osteopathic treatment can influence the hormonal system and by conducting a clinical study I investigate in the present work: Does osteopathic treatment influence the hormone level of hyperandrogenaemic infertile women?

Due to an increased life expectancy and a decrease of the birth rate – it has dropped to 1.7 children per woman in 1981 to 1.4 in 2006 - the raised percentage of old people in our society represents an important topic of our today's world (Statistik Austria 1, 2007). The reasons for a childless life are manifold. On the one hand female emancipation has progressed to an extent that nowadays most women learn a profession and prefer to work for several years before becoming pregnant. Some even want to make career and to be successful instead becoming a mother. This entails on average an older age of the primiparous women which increased from 25.1 years in 1991 to 27.9 years in 2006 (Statistik Austria 2, 2007). On the other hand having a profession has made women financially independent of men. Additionally binding willingness between pairs has declined which is mirrored by the high divorce rates. The overall divorce rate increased from 26.5 in 1981 to a historical high-value of 48.86 in 2006 (Statistik Austria 3, 2007). The matrimony is not prerequisite for giving birth to children but mostly seen as the ideal environment. The rate of children born by unmarried women increased from 24.8 % in 1991 to 37.2 % in 2006 (Statistik Austria 4, 2007). The classic picture of family has survived throughout generations and has been established as ultimate life form of adults. It is also supported by state and church in order to provide a secure future to newborns and also to mothers. A stable partnership providing protection and financial security plays a certain role in the decision for offspring. Childlessness may be triggered by stress in addition to the modern style of cohabitation. Stress e.g. in professional life can reduce sexual lust. Other people are simply too tired and exhausted from working so that sexual intercourse becomes almost unfeasible after such a long day. Stress can

result from psychological pressure in the professional, social or private life, from noise or shift work to mention the main causes. In stress situations the body succeeds in maintaining its homeostasis by adaptation of the neural and hormonal system. If this adaptation does not happen at all or anymore, allostatic load i.e. the cost of adaptation to stressors occurs. Stress related diseases pertaining the autonomous, central nervous system, neuroendocrine and immune system activity are the consequences (Mc Ewen, 1998; Schulz et al., 2005). The stress hormone cortisol (a glucocorticoid) increases and therefore the hormonal balance is changed which can lead to unwished infertility. This will be explained in detail in chapter 3.4.

Considering the decreased birth rate it seems to me eminently important to help those pairs who could not realise their child wish. "Infertility" is the term for the cause of failure, missing, or absence of pregnancy despite regular unprotected sexual intercourse. Its definition will be clarified in the following.

"Infertility" is actually defined by the World Health Organization (WHO) as "inability to conceive; usually assumed to exist if pregnancy is not achieved after 12 months of regular sexual intercourse, without the use of any form of birth control" (WHO, download 23.01.07). In this definition it is furthermore differentiated between infertility in a couple that has never conceived (Primary Infertility) and infertility in a couple that has previously conceived at least once (Secondary Infertility).

A previous definition by the WHO from 1975, found in a study of Habbema et al. (2004), may cause confusion compared to the more recent definition: "A threshold of 2 years, however, is used in many epidemiological studies: a WHO scientific group recommended the operational definition of primary infertility as: 'the woman has never conceived despite cohabitation and exposure to pregnancy for a period of two years' (WHO, 1975)" (Habbema et al., 2004, p. 1498).

The term "Subfertility" describes any form of reduced fertility with prolonged time of unwanted non-conception, whereas infertility is synonymously used with sterility with only sporadically occurring and spontaneous pregnancies (Gnoth et al., 2005).

"Sterility" is irreversible according to Stedman's Medical Dictionary, infertility however is reversible (Habbema et al., 2004).

Because of the ambiguous confusing current terms - infertility, sterility, fecundity - Habbema et al. "recommend that fertility investigation of a couple should consist of statements concerning description, diagnosis and prognosis" (Habbema et al., 2004, p. 1497).

The European Classification of Infertility Taskforce (ECIT) was built by European Society of Human Reproduction and Embryology (ESHRE) under Jenkins et al. 2004. They agreed with Habbema's proposal regarding the weakness of current terminology. Although they agreed to an extension of terminology, they warned to use familiar terms in the wrong context which may lead to greater than less confusion. They suggest using computerised statements to retain and extend

current terms (Jenkins et al., 2004). Among the recommendations of ECIT is the following short definition: "Infertility: failure to conceive after at least one year of unprotected coitus" (WHO; download 24.07.2007). (This glossary was generated by the International Working Group for Registers on Assisted Reproduction and was further developed and used during a meeting.)

In conclusion I can say, that in the literature and most publications infertility is determined with at least one year of unwanted non-conception as well as this terminology is preferred to the terms subfertility and infecundity.

Medical Subjects Headings (MeSH) database "is the U.S. National Library of Medicine's controlled vocabulary used for indexing articles for MEDLINE/PubMed. MeSH terminology provides a consistent way to retrieve information that may use different terminology for the same concepts" (MeSH 1, download 12.08.2007). This means that MeSH is acknowledged by medical journals as common reference basis and is therefore being used as a binding terminological classification throughout this work. According to MeSH infertility is defined as "inability to reproduce after a specified period of unprotected intercourse. Reproductive sterility is permanent infertility.", whereas female infertility is less specifically defined in the same dictionary, namely as "diminished or absent ability of a female to achieve conception" (introduced in 1983) (MeSH 2 and MeSH 3, download 12.08.2007). Subfertility and infecundity are not directly contained in the database, but these terms seem to refer to the same topic, i.e. infertility.

As published recently approximately 14 % of couples in Europe have difficulties to conceive (ESHRE, 2007; Evers, 2002). Among various reasons 25 % are due to the hormone system as shown in Fig. 1 (Breitach, 2007).

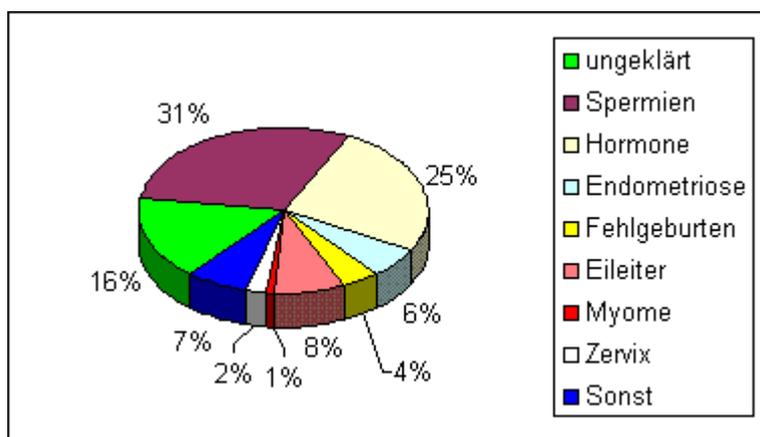


Fig. 1 Frequencies of different causes of infertility in Europe 2006 published by Dr.med. E. Breitach, see also <http://www.wunschkind.net/theorie/ursachen-der-unfruchtbarkeit/>.

One of the most frequent hormonal causes for infertility of women is hyperandrogenaemia (Wagner, 2007). This term is generally used to describe an increased level of androgens in the serum because of an elevated production in the gonads or adrenal gland (Pschyrembel, 1990). An increased level of androgen related hormones (testosterone and oestradiol) leads to disturbed maturity of the oocyte (Costa et al., 2004). hyperandrogenaemia can be caused by the polycystic ovaries syndrome, pituitary failure, and/or hypothalamus failure (hypogonadotropic hypogonadism), dysfunction of the thyroid gland, weight problems or weight changes in short time (Freytag, 2003; Hamilton-Fairley and Taylor, 2003; Wagner, 2007).

Of note, women with hyperandrogenaemia can have some additional problems. On one side they can suffer from their masculine appearance, which are not conforming to the society's sense of an attractive woman with clean, hairless and tender skin. Often a cosmetician is consulted for removing e.g. the moustache using laser methods or wax. On the other side they can suffer from being infertile because of their hormonal situation.

In recent years the influence of psychological disorders on the therapy of endocrine disease has become more and more a point of interest. A close association of psychopathology to the full recovery of patients treated for endocrine disorders is stated in several studies (Fachinetti et al., 1992; Fava et al., 1993; Sonino and Fava, 1998; Sonino et al., 2007a). Sonino et al. (2007a) found a prevalence of psychiatric diseases similarly high in pituitary patients as well as in non-pituitary endocrine patients, but not present in healthy controls. Fava and Sonino (1998) suggested a conceptual shift from the biomedical to a psychosomatic consideration of a person to improve the therapeutic effectiveness in endocrine disorders. This request can be realised with an osteopathic approach that by definition includes body, mind and spirit. It remains to prove the effectiveness of osteopathic treatment on endocrine disorders in a representative controlled trial.

In order to offer hyperandrogenaemic women that suffer an alternative to medical and surgical treatment, originally I sought to investigate whether the osteopathic treatment could reduce hormone level of androgens. Due to unaccepted problems in acquiring women with hyperandrogenaemia and infertility a clinical study could not be conducted. A case series of three women with hyperandrogenaemia is reported. Osteopathic treatment includes the structural, craniosacral and visceral techniques. By the help of theoretical, osteopathic, biochemical and bioneurological models it is explained how osteopathy could influence the hormonal system with regard to hyperandrogenaemia and infertility.

Originally I planed to examine the question of regaining fertility and achieving pregnancy Only the extent to which clinical symptoms disappear was investigated. Osteopathic treatment could be proved as a suitable, soft and well-tolerated therapeutic alternative in the field of disturbed

hormone levels (Riepler-Reisecker, 2007) and could hence offer great relief to the affected women.

The outline of this work is as follows: Substantial knowledge about the physiology and components of the female reproduction system and the corresponding hormonal system, including the origin of androgens are given in chapter 2. Chapter 3 is dedicated to the clinical picture of hyperandrogenaemia concentrating on the external appearance and possible associated pathologies. In chapter 4 classical pharmacological treatments of hyperandrogenaemia and infertility as well as effectiveness and risks are presented. The surgical interventions such as in vitro fertilisation are described as well. In contrast, chapter 5 highlights possible models explaining the approach of osteopathic treatment in a critical way. The set-up of the clinical study is presented in chapter 6 and its outcome in chapter 7. Finally the problems and difficulties of the study are discussed (chapter 8). Chapter 9 concludes the consequences for the osteopathic treatment of hormonal dysfunctions and gives an outlook to further possible studies on this problem.

## 2. PHYSIOLOGY OF THE FEMALE REPRODUCTION

### 2.1. Overview of the Hormone System

The phenomenon of hyperandrogenaemia is closely linked to the female cycle which presents a feedback control system of multiple interacting hormones. For better understanding of these interaction and regulation principles of the endocrine system some general information about hormones is given initially. Literature used for this overview is Klinker and Silbernagel (1996), Pschyrembel (1996) and Frick et al. (1987).

#### 2.1.1. Biosynthesis, Transport, Effectiveness and Metabolism

Hormones are classified according to their chemical composition in three groups: peptides, lipids (steroids) and analogues of tyrosine (hormones of thyroid gland and catecholamines). Corresponding to this classification they differ obviously in their routes of biosynthesis as illustrated below.

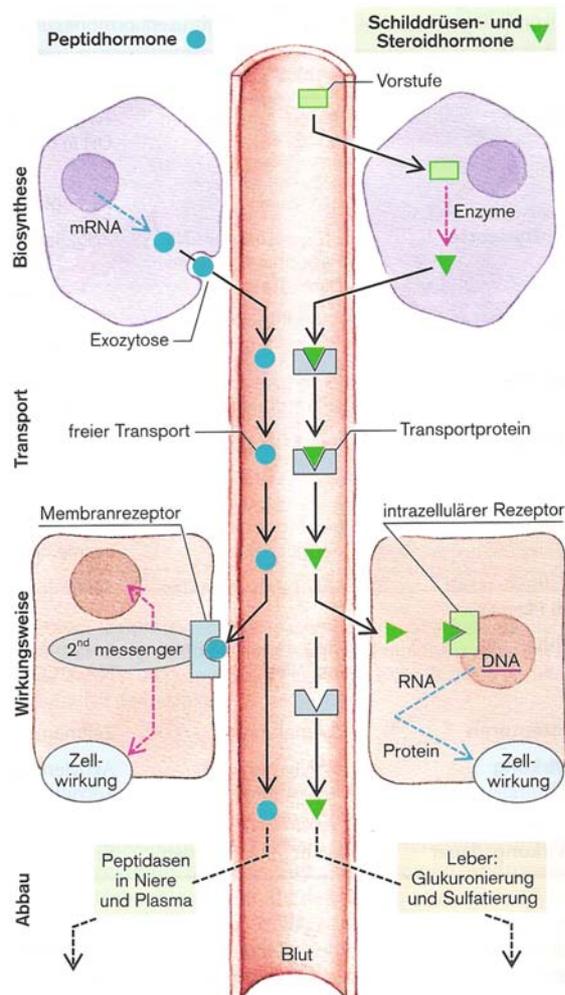


Fig. 2 Biosynthesis, transport and mechanism of effectiveness of peptides (proteo) hormones on one hand and steroid hormones and hormones of the thyroid gland on the other hand (Klinker and Silbernagel, 1996, p. 442).

Peptides are directly generated from their genes following the general principles of peptide biosynthesis over prepro- and pro-hormones. They are synthesised among others in the central and autonomic nervous system, the pituitary, and the gastrointestinal tract. In contrast steroids, hormones of thyroid gland and catecholamines derive from cholesterol by enzymatic modification of precursor molecules. The steroid synthesis takes place in the adrenal cortex, the testis, the ovary and the placenta. The biosynthesis will be completed if the active hormone is existent. Mostly it is secreted of the endocrine gland in the active form immediately or will be activated later in the blood, tissues or the target organ. The latter applies to the transformation of testosterone to dihydrotestosterone that is the most effective of androgens. For more information to the biological effectiveness of androgens see also section 2.4.1 and Fig. 8.

The secretion of both main hormone groups is correspondingly different. The pro-hormones of peptides are packed in secret granules and stored as such. After an adequate impulse only a small part of them is secreted through exocytose. Compared to this the steroid hormones diffuse after their enzymatic synthesis directly to the cell periphery being exported there. This happens in a so far unknown manner but definitely not by being packed in secret granules.

Furthermore the two big hormone classes differ also in their mechanism of effectiveness. Receptors are used in order to be identified by their target cell. Such receptors for peptide hormones are located in the cell membrane and induce, after having bound the hormone extra cellular, second messengers in the cell which provoke the hormonal effect. Steroid receptors bind in contrast on specific sequences of deoxyribonucleic acid (DNA) and influence directly the transcription. The difference between both hormone groups is mainly based on the dimension of their hydrophilicity. Peptides are hydrophilic, steroids and hormones of the thyroid gland are hydrophobic. A more exact explanation to the chemical processes would go beyond the scope of this work and can be gleaned from Klinke and Silbernagel "Lehrbuch der Physiologie", 1996, pp. 439 ff.

Finally the hormone groups differ in their half-life time, transport and metabolism. The half-life time in the plasma terms the period after which 50 % of the hormone concentration is eliminated from the plasma. This occurs through metabolism, elimination and/or through internalisation of the hormone in its target cell. Peptides have a short half-life time (some minutes to hours) since they are quickly inactivated by peptidases in the kidney or inactivated by proteolysis in the plasma. Thus, only a small part of secreted peptides reaches the target organ. Therefore the plasma concentration of peptide hormones mirrors the secretion activity of the respective cells with only a little time lag. Steroids and hormones of the thyroid gland bind on specific transport proteins in the blood and are hence protected against fast metabolism and elimination. Since only the free unbound hormone is bioactive the hormone bound on protein can be observed as

circulating storage form. Corresponding to this, the half-life time of these hormones is hours to multiple days until they are inactivated by reduction and conjugation to sulphates and glucuronic acid in the liver. This makes them less hydrophobic and prepares them to elimination through the kidney and the gall bladder. The concentration of hormones is significant for clinical diagnostic but underlies a certain secretion dynamic depending on circadian or other rhythms (e.g. menstrual rhythm). Hormone levels are therefore only significant if the part of free and bound hormone (steroids and hormones of the thyroid gland) and the conditions of the blood sample's drawing (e.g. time of day) are known.

Steroids can pass the blood-brain-barrier in contrast to peptide hormones which need additional transport mechanisms to pass it. The anatomical location of hypothalamus and pituitary (3<sup>rd</sup> ventricle, limbic system) marks the connection between central nervous system and hormones.

### 2.1.2. Regulation of Hormone Systems

The effectiveness of hormones has to be regulated precisely and according to the requirements of the organism. Regulation occurs in all levels of hormone synthesis, secretion, receptor binding and expression, effectiveness, transport and metabolism. The secretion of hormones is regulated mostly by a negative feedback of the hormones themselves and by endogen specific rhythms, which change over the years (ageing), over weeks (menstruation cycle), circadian (cortisol) or in even shorter intervals (e.g. pulsatile rhythm for gonadotropin releasing hormone).

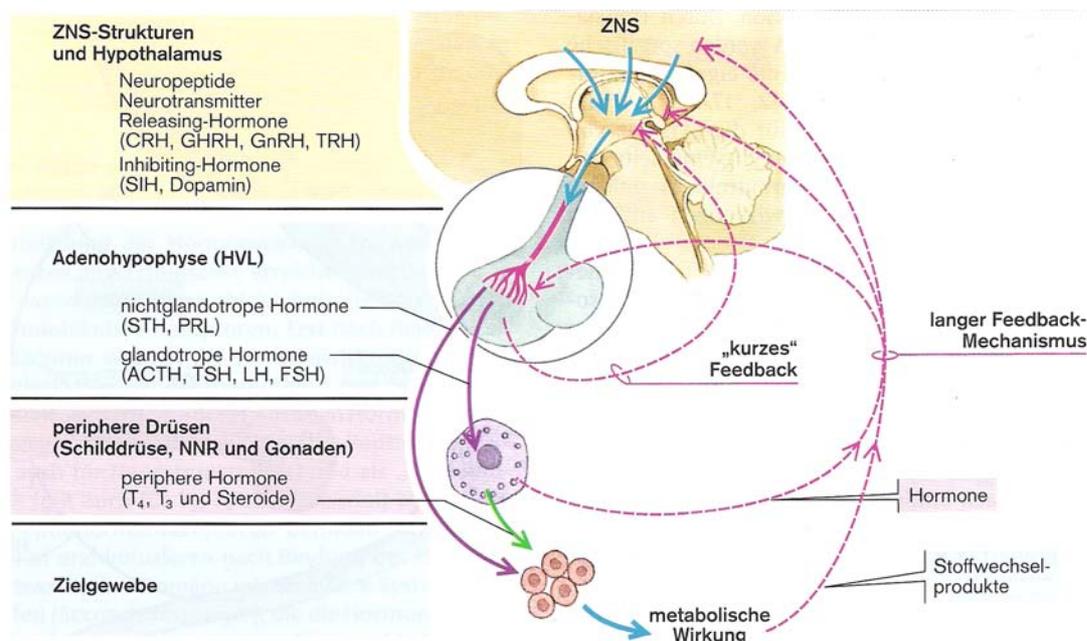


Fig. 3 Regulation in neural-endocrine systems (Klinke and Silbernagel, 1996, p. 444).

Within the present thesis the term pituitary is used substitutionally for adenohypophysis which is the anterior part of the pituitary. As illustrated in Fig. 3, the neural-endocrine systems are

regulated at the three levels hypothalamus, pituitary and endocrine glands. The hormones of the peripheral glands mostly inhibit the secretion of hypothalamic and hypophyseal hormones by a negative feedback mechanism along their hormone axis (Klinke and Silbernagel, 1996; Pschyrembel, 1990). It is distinguished between a short and a long feedback loop.

The feedback-mechanism between gonadotropins and ovarian products (oestradiol, progesterone, inhibin) is differentiated in a positive, in terms of stimulating, and a negative, in terms of inhibiting, feedback (Kaiser and Leidenberger, 1996). A positive feedback to the hypothalamus and the pituitary comes first to cause ovulation. Then a negative feedback of these hormones prevents another ovulation. Thus the possibility of multiple pregnancies, often accompanied by complications, is reduced (Klinke and Silbernagel, 1996; Pschyrembel, 1990).

These feedback loops are explained in detail in the following sections, where the single hormones are displayed according to their function in the menstrual cycle and their relations.

Additionally to the feedback on the humeral pathway some of the endocrine systems are regulated by afferent nerves of receptors, e.g. the stimulation of the acromastium augments the secretion of the lactation hormones prolactin and oxytocin.

## 2.2. The Female Cycle

Every 28 days one oocyte grows in the ovaries of the pubescent woman. After ovulation this oocyte travels down the fallopian tube to the uterus. During this period the plasma concentration of sexual hormones is changing. An ovulation of multiple oocytes would result in a multiple pregnancy, e.g. fraternal twins.

The menstrual cycle begins with the first day of bleeding and ends with the day which is the day before the next bleeding. The average menstrual cycle can be divided in several phases (Bischof, 2007).

name of phase	days
follicular phase (also known as menstrual and proliferative phase)	1-13
ovulation (not a phase, but an event dividing phases)	14
luteal phase (also known as secretory phase)	15-26
ischemic phase (some sources group this with secretory phase)	27-28

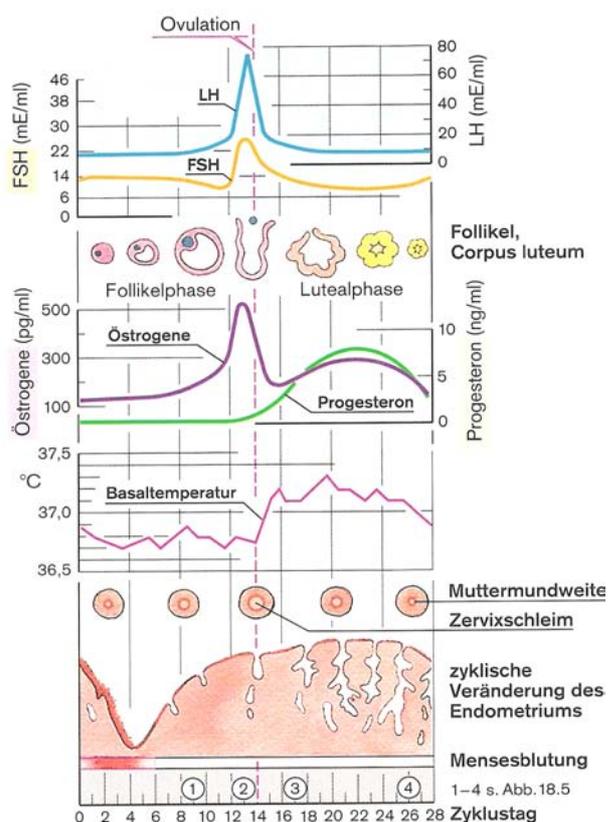
*Tab.1 Phases of the female cycle, extracted from Bischof (2007).*

The length of the cycle varies from woman to woman and from cycle to cycle. If the difference between cycle lengths is more than 2-3 days, the follicle will probably not develop regular. These presumably anovulatory cycles occur up to 20 % of the cycles in healthy women but are more

common in women with polycystic ovary syndrome. This syndrome will be explained further in section 3.2.

The basal temperature increases about 0.5° C 1-2 days after ovulation and decreases at the end of the cycle after a plateau phase of hyperthermy as illustrated in Fig. 4. The increased basal temperature in the middle of the cycle is used as an indicator for ovulation that has taken place (Klinke and Silbernagel, 1996). It provides information about the length of the follicular and the luteal phase (Kaiser and Leidenberger, 1996). However, the National Collaborating Centre for Women's and Children's Health (2004) pointed out that the use of basal body temperature charts to confirm ovulation does not reliably predict ovulation and is therefore not recommended for cycle control.

The coherences are displayed in the following graphic (Fig. 4).

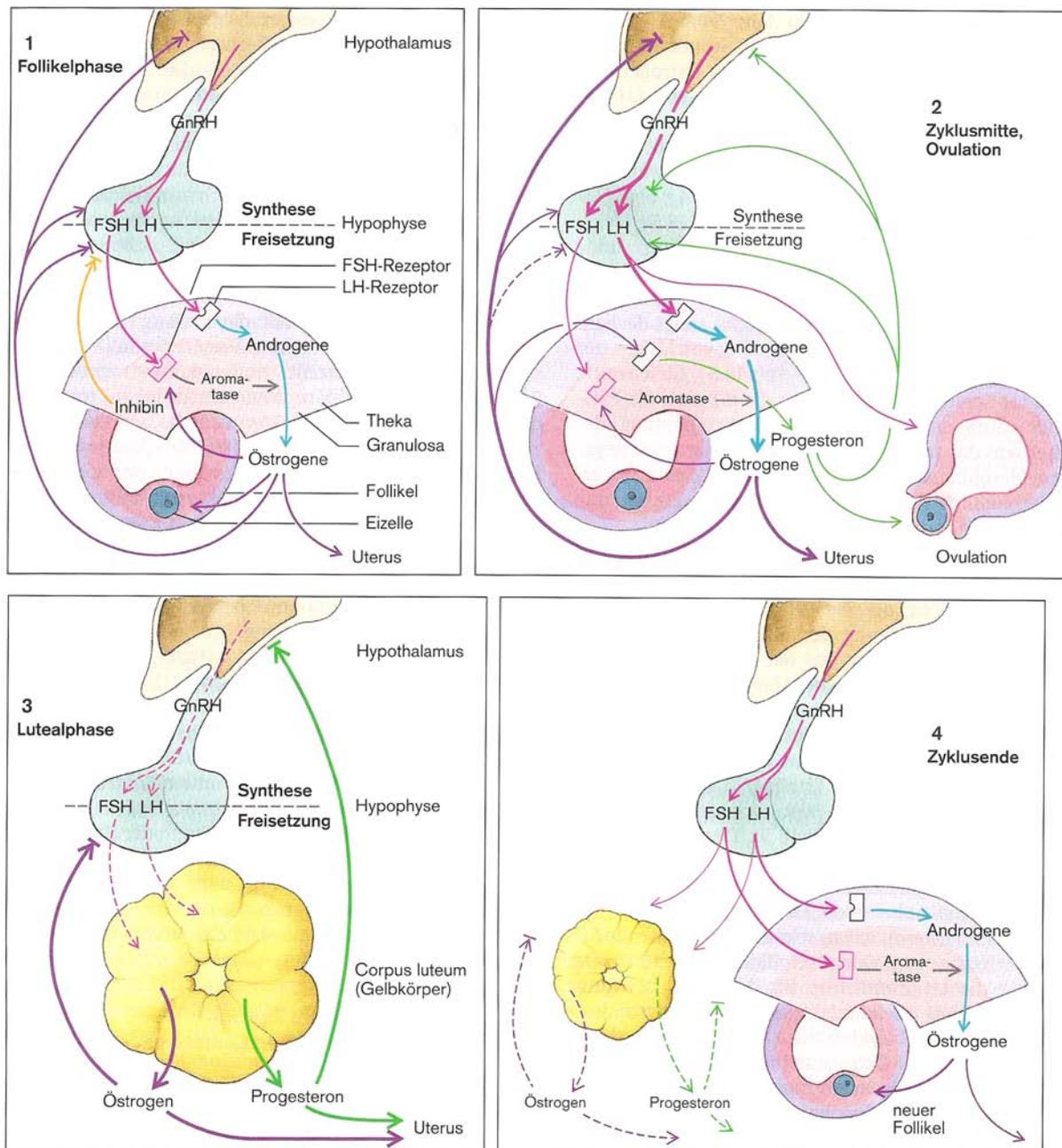


*Fig. 4 The menstrual Cycle.* Concentrations of the hormones in the plasma are illustrated simultaneously with the ovarian function, the change of the uterus and the basal temperature (1, 2, 3 and 4 mark the points in time 1-4 of Fig. 5) (Klinke and Silbernagel, 1996, p. 486).

### 2.3. The interaction of Hypothalamus, Pituitary and Ovary

Initially the interaction of the hormone axis hypothalamus-pituitary-ovary is explained. The relevant hormones of this axis involved in the reproductive system are the hypothalamic gonadotropin releasing hormone (GnRH), the hypophyseal gonadotropins follicles stimulating hormone (FSH) and luteinising hormone (LH), additionally the hormones of the ovaries, namely androgens, oestrogens and progesterones. The interaction between the glands and organs and the

regulation of the hormone synthesis and secretion is illustrated in the figure Fig. 5. The synthesis and role of the individual hormones are explained in the following sections.



*Fig. 5 The hormonal interaction between hypothalamus, pituitary and ovary. During the follicle phase (1) the gonadotropins cause the growth of the follicle and the release of oestrogens. In the middle of the cycle (2) LH is increasingly released by the pituitary and effects the ovulation. In the luteal phase (3) the corpus luteum releases oestrogen and progesterone which cause now a recurrent inhibition of the hypothalamus and the pituitary increasingly. Hence, the corpus luteum is less activated and stops finally its function. The negative feedback of oestrogen and progesterone disappears, the end of the cycle (4) is reached and a new one can begin. (Klinke and Silbernagel, 1996, p. 489)*

### 2.3.1. Gonadotropin Releasing Hormone (GnRH)

The ovarian cycle is part of an integrated system which involves the hypothalamus, the pituitary, the adrenal gland, the ovary and the uterus.

The releasing and inhibiting hormones of the hypothalamus control the biosynthesis and secretion of all hormones of the anterior part of the pituitary, which is called adenohypophysis. The pulsatile hypothalamic secretion of gonadotropin releasing hormone (GnRH) is responsible for the rhythmicity of the cycle. GnRH is secreted every 90 minutes (Breckwoldt et al., 1994; Kaiser and Leidenberger, 1996; Klinke and Silbernagel, 1996). This 90-minute-rhythm is also found in the basal activity of other physiological systems, e.g. the vegetative nervous system, and is termed as basic rest activity cycle (BRAC). The rhythmic emission of GnRH depends not only on the external events (psychological factors or the circadian rhythm) which reach the hypothalamus from the cortex through the limbic system. It also depends on the ovarian events through the feedback of the sexual steroids to the hypothalamus and the pituitary (Fig. 3 and Fig. 5). This modulated secretion of GnRH controls the release and synthesis of pituitary gonadotropins, or more precisely speaking of the follicle stimulating hormone (FSH) and the luteinising hormone (LH). Both hormones influence proliferation and hormone production of ovarian cells.

Except GnRH which generates both FSH and LH another realising hormone, that enhances only the secretion of FSH, is assumed but still not found (Klinke and Silbernagel, 1996).

In the database pubmed, there was no published article or review found which would confirm this theory.

### 2.3.2. Follicle Stimulating Hormone (FSH) and Luteinising Hormone (LH)

The FSH, which is released from the pituitary, allows recruitment and growth of the ovarian follicles as well as the selection of the dominant follicle. At the beginning of the cycle approximately 20 follicles start to grow, but only one of them will grow further. The reason therefore is the lowered secretion of FSH. If a certain level of oestrogen in the blood is reached, the pituitary will reduce the FSH production and only one follicle survives. The other follicles are degraded. In the exceptional case that two or more follicles enhance and are fertilised - or the fertilised oocyte bisects completely-, twins or multiples occur.

The chemical processes will be explained more precisely below.

As shown in the first image of Fig. 5, the ovarian follicles are composed of an outer layer of theca cells and an inner layer of granulosa cells which engulf the oocyte. The theca cells have LH receptors and produce androgens (testosterone and androstenedione) in response to LH. Androgens and their way of function will be explained more precisely in section 2.4.1. The

androgens cross the basement membrane to reach the granulosa cells where aromatase transforms them into oestrogens (oestradiol and oestrone respectively). Aromatase is an FSH-dependant enzyme; the FSH receptors are located on the granulosa cells (Bischof, 2003; Breckwoldt et al., 1994; Klinker and Silbernagel, 1996). The consequence of these processes is an increased release of oestrogens which cause a decreased release of FSH in the pituitary by a negative feedback to the pituitary. Oestrogen increases the reactivity to FSH in the follicles by proliferation of the receptors. At day 5-7 of the menstrual cycle only the follicle with the highest level of oestrogen is selected to further maturation. The production of oestrogen in the other follicles will be reduced because the other with-grown follicles (secondary follicles) are less responsive to FSH. In consequence of the negative feedback mechanism the FSH level will reduce as well. The androgen level in the secondary follicles increases further since androgens are produced at unchanged LH-secretion. Androgens induce the degeneration and atresia of the non-selected follicles. The selected follicle releases inhibin, illustrated by the yellow arrow in the first image of Fig. 5. Inhibin, as its name already says, inhibits additionally the FSH secretion of the pituitary so that the FSH level reaches its minimum at day 11 (Klinker and Silbernagel, 1996). The dominant follicle is stimulated continuously by FSH due to its large density of FSH receptors and its good vascularisation. Therefore, between the 9<sup>th</sup> and 11<sup>th</sup> day, the oestrogen concentration in the plasma increases rapidly until it reaches its peak 24 to 36 hours before the ovulation. Since under the influence of oestrogen only the release, but not the synthesis of LH is inhibited, a maximum of LH is stored. In the following the inhibition of LH release begins to weaken until the stored LH is released fast and the LH concentration in the plasma increases rapidly to a high level. This high LH level is called LH peak and is illustrated in Fig. 4. These high levels of oestrogens and LH effect the transformation of follicles into the corpus luteum (luteinising), where progesterone is produced. As a consequence of the steady rise of progesterone in the plasma, the pituitary continues to release LH (Fig. 5, second image). Contemporaneous to the LH storages (see above LH peak) the FSH storages are also emptied quickly. The FSH peak induces the completion of the first meiosis of the oocyte on the verge of ovulation. The empty storages and the negative feedback of the increased progesterone level to GnRH secretion of the hypothalamus explain at last the rapid decrease of the gonadotropins LH and FSH from the 14<sup>th</sup> day on (see Fig. 4). About 10 hours after the LH peak ovulation takes place (Klinker and Silbernagel, 1996). After the ovulation LH stimulates the cells of the burst follicle to produce progesterone. See also the following section.

The relation of LH and FSH is the so-called LH/FSH-ratio which is used for diagnostic methods. Normally, in healthy women the quotient is less than 1. If the LH/FSH-ratio is more

than 2, it indicates the so-called polycystic ovaries syndrome (PCOS), which will be explained exactly in section 3.2.

### 2.3.3. Oestrogen and Progesterone

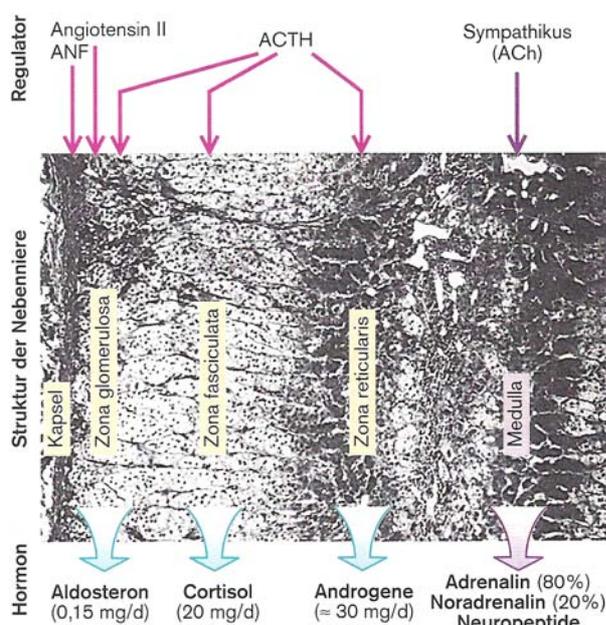
According to the previous section, oestrogen results from androgen through the enzymatic reaction of aromatase. Triggered by LH the ovulated follicle (corpus luteum) produces progesterone during the luteal phase, the so-called corpus-luteum-hormone. This is illustrated in Fig. 5, third image. Progesterone levels rise until the 22<sup>nd</sup> day and decrease afterwards again. Parallel to this oestrogens are released. In addition, progesterone is thermogenic and therefore responsible for the elevation of the basal body temperature which is visible in Fig. 4, (Scott et al., 1989).

Oestrogen exists in different high effective forms: oestradiol, oestrone and oestriol. Oestriol is the most effective one and is secreted almost exclusively by granulosa cells of the dominant follicle. Oestrone, in contrast, derives from the conversion of androstenedione or from the metabolism of oestradiol. Oestrogens circulating in the female body are produced less than the half in the ovaries, the rest is synthesised in the periphery (Scott et al., 1989). Oestrogen and progesterone are responsible for the changes of the endometrium during the cycle. The endometrium is the mucosa of the uterus. First, the endometrium grows due to the increasing concentration of oestrogen. Then, under the influence of progesterone, it will be prepared for the nidation of the embryo.

If fertilisation does not occur, a negative feedback of oestrogen and progesterone to the hypothalamus will take place. This causes a cumulative decrease of GnRH and subsequently of gonadotropins. In consequence, LH stimulation is too low and the corpus luteum cannot be activated longer and finally stops its function. Comparing to Fig. 5, fourth image, the negative feedback of oestrogen and progesterone is interrupted and the cycle reaches its end. Now the release of GnRH increases again and stimulates a new follicle phase. A new cycle can begin (Breckwoldt et al, 1994; Klinker and Silbernagel, 1996).

## 2.4. Steroid Hormones

After describing how the female cycle is influenced by hormones along the hormonal axis "hypothalamus-pituitary-ovary", the axis "hypothalamus-pituitary-adrenal" is described. The final products of this peripheral gland are steroids. For a more detailed description of general differences between steroids and peptide hormones and their secretion, please refer to the introductory section.



*Fig. 6 Structure and function of the adrenal gland.* The three layers of the adrenal cortex synthesise each its characteristic final product: mineral corticoid, glucocorticoid and androgens. Adrenocorticotrophic hormone (ACTH) of the pituitary stimulates all three zones, but the mineral corticoids are mainly under control of angiotensin II. The adrenal mark is controlled by the sympathetic nervous system (Klinke and Silbernagel, 1996, p. 463).

The adrenal cortex surrounds the adrenal mark and is divided in three layers of which each layer produces different hormones and therefore has a different function. The outer layer is the zona glomerulosa; its final product is aldosterone (a mineral corticoid). The layer below is the zona fasciculata, which synthesises cortisol (a glucocorticoid). And finally the inner layer, named zona reticularis, secretes androgens (e.g. testosterone). Further steroid hormones are oestrogens (e.g. oestradiol) and gestagens (e.g. progesterone). Each zone has its specific enzymes resulting in the characteristic final products for each synthesis (see Fig. 7), but all zones are stimulated by the same hormone of the pituitary, the adrenocorticotrophic hormone (ACTH) (Klinke and Silbernagel, 1996). More information to ACTH is given in section 2.4.2.

All steroid hormones derive from cholesterol. They are generated in the mitochondria by cholesterol containing enzymes. Gestagen is produced in the first and at an intermediate stage. In a next step gestagen is turned into glucocorticoid, mineral corticoid and androgen. Finally androgens can be transformed into oestrogens. The transformation order is only possible in this direction. Gestagens cannot be transformed directly in oestrogens. Therefore steroid hormones are also called precursor hormones (Klinke and Silbernagel, 1996; Rüscher, 2007).

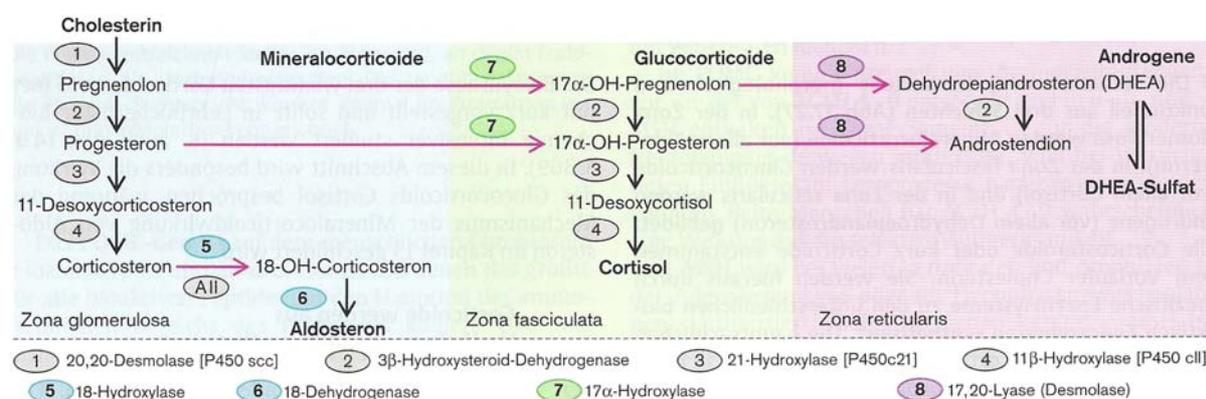
The next sections are dedicated to androgens and their regulation.

### 2.4.1. Androgens

Androgens are male sexual steroids which can exist and be metabolised in different high effective forms as shown in Fig. 8. In women, androgens of the adrenal cortex resemble the main part of male sex hormones, being dehydroepiandrosterone (DHEA) the principal androgen. A smaller part is synthesised in the ovaries, especially androstenedione. About 30-50 % of the free

circulating testosterone emanates half-and-half from the adrenal cortex and the ovaries. The other 50 % are converted primarily of androstenedione. About two-thirds of androstenedione are synthesised in the ovaries, the other third in the adrenal cortex (Breckwoldt et al, 1994; Klinke and Silbernagel, 1996; Scott et al., 1989).

Androgens, built in the female body, act mainly at any age as precursors for oestrogen synthesis, as already explained in the previous chapter. The hormone concentration of androgens in the blood varies only little, if a normal ovary function and regular menstruation occurs. The androgen excess becomes more obvious with the weakening and finally absence of the menstrual period before menopause. Pathologic androgen excess in women becomes apparent in the clinical picture of hyperandrogenaemia, which will be explained in detail in section 3.1. However, the actual level of androgens depends not only on the increased secretion and production, but although on the aggregation with their binding proteins (sexual hormone binding globulin SHBG), the enzymatic conversion and the elimination in its metabolism (Breckwoldt et al, 1994). Androgens are composed in the zona reticularis of the adrenal cortex. Based on cholesterol, pregnenolon is generated. Pregnenolon represents the initial compound for the biosynthesis of steroid hormones.



*Fig. 7 Synthesis of corticoids.* Based on cholesterol, the final products of each adrenal zone underlie several enzymatic reactions. Therefore the enzymes 5 and 6 are characteristic for the aldosterone synthesis and contained in the zona glomerulosa, enzyme 7 in the zona fasciculata (cortisol synthesis) and enzyme 8 for the zona reticularis (Klinke and Silbernagel, 1996, p. 464).

As a first option, with the assistance of different enzymes, pregnenolon can become testosterone via the intermediate molecules progesterone, 17 $\alpha$ -OH-progesterone and androstenedione. Testosterone represents the initial compound of oestradiol and thus for the other molecules of oestrogen, like oestrone and oestriol (Breckwoldt et al., 1994; Klinke and Silbernagel, 1996). In a second way, pregnenolon can be converted to the glucocorticoid cortisol (zona fasciculata), in a third to the mineral corticoids progesterone and aldosterone (zona glomerulosa). One of the main androgens of the zona reticularis is dehydroepiandrosterone (DHEA). Its main part exists as

sulphate (DHEAS). DHEA and DHEAS are predominantly of adrenal origin and show the highest serum concentrations of androgen molecules. DHEA is a relatively weak male sexual steroid as shown in Fig. 8. One part is metabolised to the more effective testosterone and dihydrotestosterone by enzymes in the intended tissues (Klinke and Silbernagel, 1996). For example, dihydrotestosterone is mainly built in the dermal fibroblasts by an enzymatic reaction of  $5\alpha$ -reductase. It is 2.5 times more effective than testosterone. If the enzyme activity of  $5\alpha$ -reductase is elevated, the synthesis of the high effective dihydrotestosterone from less effective precursor molecules is catalysed. Through these more effective molecules DHEA has an androgenic influence on the skin, the growth of hair and the muscles, which can consequently cause a male appearance in women. In men, the androgens of the adrenal cortex are less important due to the high production of testosterone in the testis (Breckwoldt et al, 1994; Klinke and Silbernagel, 1996).

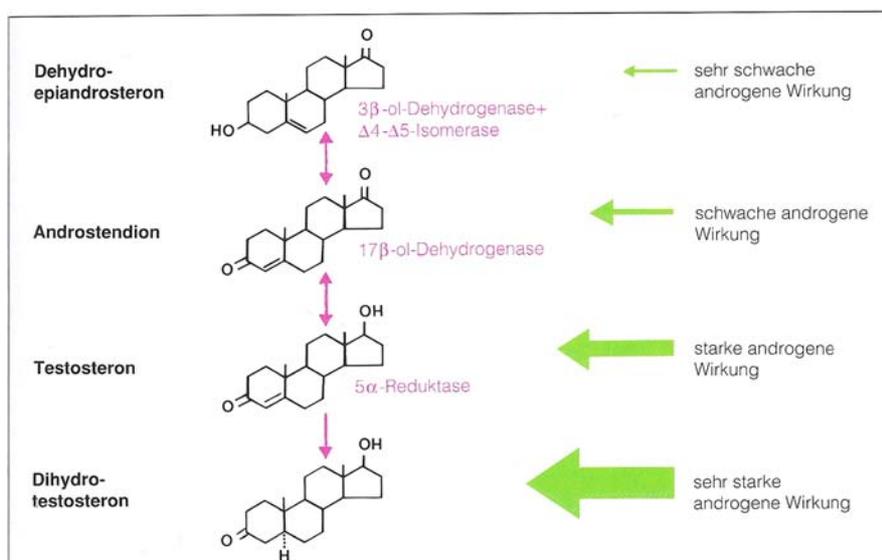


Fig. 8 The grading of effectiveness of the different androgen molecules (Breckwoldt et al., 1994, p. 59).

The effectiveness of androgens depends not only on the amount, which is produced and the activity of enzymes, which convert them into high effective molecules, but also on their binding to transport proteins as mentioned above. Sexual hormone binding globulin (SHBG) is one of the most important. Built in the liver, this transport protein binds very specific, especially testosterone. In consequence, the protein binding effects a neutralisation of androgens and reduces their bioavailability. In cause of hyperandrogenism the secretion of SHBG or the binding capacity is reduced. Thus the level of free testosterone increases (Breckwoldt et al, 1994). The production of SHBG is also stimulated by the T3 and T4 of the thyroid gland as explained in section 3.3 (Breitach, 2007; Rabe et al., 1992).

Finally the importance of subcutaneous tissue for the metabolism of hormones needs to be mentioned. A big part of enzymatic transformation of testosterone and androstenedione into oestrogens by aromatase happens in the adipose tissue. The aromatase enzyme is rather detected in stroma cells than in adipocytes, so that the extent of transformation depends on the quantity of stroma cells but not to the adipose mass of the individual adipocyte. The adipose part simply serves as a medium where the lipophilic androgens can be solved and assembled. This means that other organs except the classical endocrine organs are significantly involved in the synthesis of steroid hormones from their precursor hormones. In addition to the adipose tissue, the skin and the liver belong to those organs. It is assumed that this synthesis of biologic active hormones in non-endocrine organs is an important biological modulation mechanism (Breckwoldt et al., 1996).

The steroid metabolism begins in the liver, where steroids are inactivated and made water-soluble through hydroxylation, conjugation and methylation. The elimination takes place 30 to 60 % via the kidneys and 10 % via the intestine. The rest is reabsorbed in the enterohepatic circulation (Klinke and Silbernagel, 1996; Pschyrembel, 1990). This could be one possible approach for osteopathic treatment by influencing the mobility and function of the liver, kidney and intestine. This will be outlined in detail in chapter 5.

#### 2.4.2. Regulation of Steroids by Adrenocorticotrophic Hormone (ACTH)

As already mentioned and illustrated in Fig. 3, the neuroendocrine hormone systems are composed of several levels. Each hormonal axis regulates itself by mostly negative feedback mechanism. The secretion of androgens and glucocorticoids is controlled by ACTH, a hormone of the pituitary. The regulation happens at the hypothalamic-pituitary-adrenal (HPA) axis and is hierarchically organised (Klinke and Silbernagel, 1996). The secretion of ACTH depends on the corticotrophin releasing hormone (CRH) of the hypothalamus. The synthesis and secretion of CRH is inhibited through cortisol, responding to a long feedback loop. Because of its important role in the hypothalamic-pituitary-adrenal axis cortisol will be defined further in its connection with infertility in section 3.4. Furthermore the secretion of CRH underlies the endogen rhythm and limbic system (Klinke and Silbernagel, 1996).

Beside its stimulation of the adrenal cortex and the associated synthesis and secretion of corticoids, especially cortisol, ACTH has two other extra-adrenal effects. On the one hand it stimulates the adipolysis and on the other it intensifies the dermal pigment coating by stimulating the melanin synthesis. An intense browning of the skin and some mucous membranes due to a massive increased ACTH secretion is an important clinical sign to diagnose primary insufficiency of the adrenal cortex, which is called Morbus Addison.

Another adrenal defect, the adrenogenital syndrome, is caused by an enzyme defect and will be explained in the following chapter.

### 3. PATHOLOGIES OF HORMONEAL SYSTEMS

At all levels of hormonal circuit, from gene transcription to biosynthesis and degradation of the hormones, clinically relevant dysfunctions can occur. These dysfunctions mostly arise from defects in the regulation of hormonal systems and therefore lead either to hyperfunction or hypofunction of the disturbed hormonal system. A particular dysfunction of the endocrine system is the production of hormones by a tumour (paraneoplastic secretion of hormones) (Breckwoldt et al, 1994; Klinker and Silbernagel, 1996). In the following chapter different pathologies of the hormonal systems will be explained. Thus meaningful in- and exclusion criteria for any clinical study become obvious.

#### 3.1. Hyperandrogenaemia

Since this study is dedicated to hyperandrogenaemia, this main hormonal cause for infertility will be explained more precisely including its clinical symptoms. As already defined in the introduction hyperandrogenaemia is the general term used for an increased level of androgens in the serum because of an elevated production in the gonads or adrenal gland (Pschyrembel, 1990). Possible aetiological reasons can be ovarian causes (PCOS, tumours), adrenal causes (late onset, tumours), endocrinopathic causes (Cushing syndrome, hyperprolactinaemia) or drugs (dilatant, danazol, progestins, steroids). Most of these diseases are associated with hyperandrogenaemia, either being a cause or a consequence of it (Jagdish, 2001). For example, androgen producing tumours can lead to the rare extreme of virilisation, appearing in secondary sex characteristics as male physique, change of voice, clitoris hypertrophy, mamma hypoplasia, mostly alopecia and always amenorrhoea (Breckwoldt et al., 1996; Klinker and Silbernagel, 1994).

To diagnose hyperandrogenaemia the serum concentrations of testosterone, DHEA, LH, FSH have to be estimated. For exclusion reasons of other diseases like dysfunctions of the thyroid gland or hyperprolactinaemia further hormone levels are needed: TSH, T3 and T4 (Jagdish, 2001). An excess of androgens has local and systemic effects. It can cause premature follicle atresia and anovulation as observable in the so-called polycystic ovary syndrome (PCOS) (Hamilton-Fairley and Taylor, 2003; Utiger, 1996). As mentioned in the introduction about 25 % cases of infertility is due to hormonal causes (Breitach, 2007). Anovulation due to hyperandrogenaemia and resulting infertility is subsumed among these 25 %. The different possibilities of medical therapy in case of unfulfilled child wish are elucidated in chapter 4.

Beyond the problem of infertility women with hyperandrogenaemia are confronted first and foremost with the external changes in their appearance: hirsutism, acne, alopecia and android fat distribution (Freytag, 2003). The term hyperandrogenism is synonymous for hyperandrogenaemia

rather referring to the more android appearance of women. The effect hyperandrogenism takes on the concerned women was studied by Elsenbruch et al. (2003) with an evident result: female identification, sexual satisfaction and quality of life are strongly impaired.

### 3.1.1. Hirsutism

Hirsutism is the most unacceptable burden of how hyperandrogenaemia is noticed in public. Hirsutism is defined as the condition of abnormal or excessive hair growth of the male type concerning the facial, body and pubic hair growth of women (Pschyrembel, 1990). In healthy women the spread and density of androgen dependent hair follicles is restricted to the pubis and arm pit. Generally two hair types are distinguished: The vellum hair which is fine, inconspicuous, less pigmented and distributed over the whole body (except palmar and plantar), and the terminal hair which is stronger, more pigmented and characteristic for the hair of the head and the body. Especially the terminal hair is not only genetically determined but also hormonal since the dermal fibroblasts build dihydrotestosterone by an enzymatic reaction of  $5\alpha$ -reductase. Concerning the synthesis and metabolism of androgen see also section Fehler! Verweisquelle konnte nicht gefunden werden.. Concerning the vellum hair an excess of androgens leads to an extended proliferation time and hence longer, thicker and more pigmented vellum hair. Eventually vellum hair becomes terminal hair at the upper lip, chin, neck, breast (sternal and circum mamillar), abdomen (linea alba) and femoral inside as usually only observed in men (Breckwoldt et al., 1996). The so-called idiopathic hirsutism can be the consequence of an increased responsiveness of the hair follicles to androgen or an increased transformation of testosterone into the highly effective dihydrotestosterone in the area of the hair roots (Breckwoldt et al., 1996; Pschyrembel, 1990). Also the melanocytes and the sebaceous glands are sensitive to androgen which explains why hirsutism possibly occurs in combination with the disposition to seborrhoea and acne vulgaris.

Medical diagnosis is made by laboratory values of hormone concentrations. Changes of different hormonal parameters are detected in 50-75 % of women with hirsutism, such as an increased concentration of serum testosterone, increased metabolic clearance and reduced SHBG (Breckwoldt et al., 1996). Furthermore it is important to look for clinical signs of hyperprolactinaemia, e.g. galactorrhoea and dysfunction of the thyroid gland because of possible functional coherences to the onset of hirsutism (Kaiser and Leidenberger, 1996). These disease patterns will be explained in section 3.3.

One approach to evaluate and quantify hirsutism in women is the Ferriman-Gallwey score. The extent of hirsutism is measured with a score from 0 (no terminal hairs seen) to 4 (terminal hairs in a pattern similar to that of a very hirsute man) (Hines et al., 2001). The hirsutism scoring

system should be population specific as pointed out by Hassa (2005) in a study about Central Anatolian women. Another classification system to graduate the severity of hirsutism was suggested by Baron (1974) and is presented by Rabe (1992).

**Kriterien zur Einteilung von Patientinnen mit vermehrter Behaarung in drei Schweregrade  
(I = leicht, II = mittel, III = schwer)**

Schweregrad	Gesicht Oberlippe Kinn	ganze Bartregion	Brust	Schulter Hüfte Gesäß	Haarstraße Genitalbereich zum Nabel
I	dünnes, pigmentiertes Haar	nicht vollständig betroffen	einzelne Haare um die Mamille	keine Haare	keine oder nur einzelne Haare
II	pigmentiertes Haar	nicht vollständig betroffen	leichter Haarkranz um die Mamille	einzelne Haare	deutliche Haarstraße
III	dickes, pigmentiertes Haar	vollständig betroffen	deutlicher Haarkranz um die Mamille	mehrere pigmentierte Haare	stark ausgeprägte Haarstraße

Tab. 2 Classification criteria of hirsute women corresponding to three severity codes (Rabe et al., 1992, p. 20).

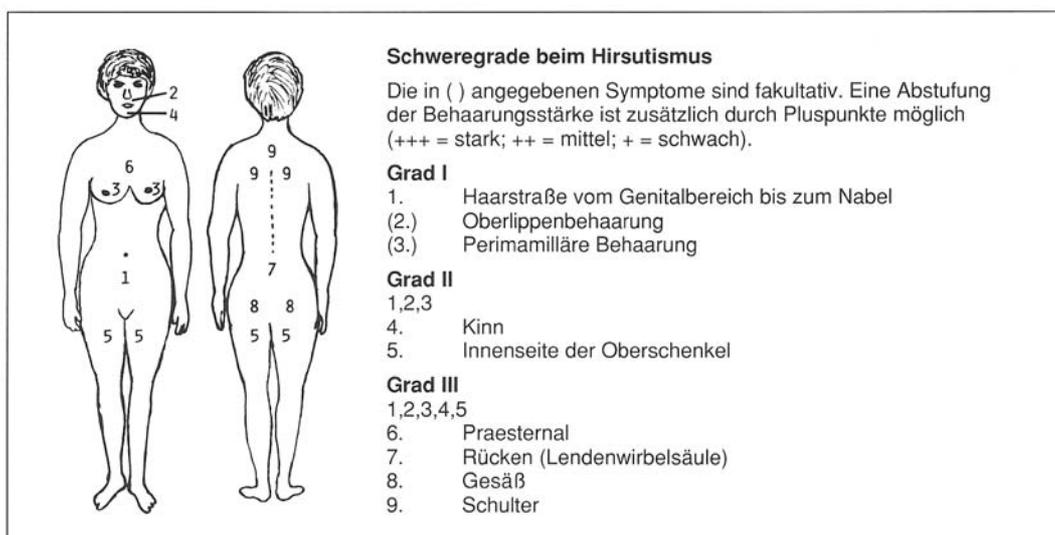


Fig. 9 Severity codes of hirsutism according to Baron, 1974 (Rabe et al., 1992, p. 20).

Baron subdivides hirsutism into three grades of severity referring to the location of terminal hair. Grade one is characterised by a hair route from the genital area to the umbilicus, by hair growth on the upper lip and perimamilar. Grade two includes these three zones and additionally chin and femoral inner side. Grade three moreover encompasses hair growth on the presternal, lumbar and gluteal region as well as on the shoulders. According to Rabe et al. (1992) both classification systems (Ferriman-Gallwey and Baron) seem to be obsolete and are almost not in use in the

practice since no correlation could be proven to the biochemical parameters. The estimation of the severity of hirsutism is based on the subjective impression of the observer and the psychological strain of the patient. A marginal hair growth in the face might be considered to be a bigger burden than a strong hair growth of the legs (Rabe et al., 1992).

Affected women can suffer from their masculine appearance, which does not conform to the society's opinion of an attractive woman with clean, hairless and tender skin. Not surprisingly hirsute women often attend cosmetic studios to have their moustache removed under painful procedures, e.g. laser methods or wax. The effectiveness of laser treatment to hair removal is confirmed in a controlled randomised study of Clayton et al. (2005) on 88 hirsute women with PCOS. They also report less anxiety and depression of the patients and all over more comfortable psychological state. Sonino et al. (1993) suggest an additional supporting psychotherapy to heal hirsute women from their significantly higher social fears, anxiety and psychotic symptoms. If medication is indicated hirsutism is treated with oral contraceptives among which drospirenone shows acceptable results after six cycles (Batukan and Muderris, 2006; Guido et al., 2004; Pehlivanov and Mitkov, 2007).

### 3.1.2. Acne

Those who suffered themselves of acne during their puberty - and that are 40-50 % of the population - may well remember the irritating pimples all over the face and the tremendous efforts to cover them with make-up. This type of acne is also called acne vulgaris and subsumed to the hormonal endogen type. Typically it affects the face, the décolleté and the region of the upper back and shoulders. A genetic disposition is known with mainly two components, namely the responsiveness of receptors of sebaceous glands to hormones and the sensitiveness of follicle epithelium to androgens (Breckwoldt et al., 1996; Rabe et al., 1992). The aetiology of acne starts with an increased production of sebum (seborrhoea) which correlates with the lipid content of the dermis and the severity of acne. On the basis of seborrhoea the following process can lead to acne: Sebaceous glands are occluded by hyperkeratosis that, in consequence, leads to a tailback of sebum and to a creation of a so-called comedone (keratinous plug). By bacterial decomposition of this sebum mass neutral lipid acids become free lipid acids. The latter diffuse in the circumjacent tissue where it comes to inflammation as secondary infection. For this fact acne cannot be considered as disease that is exclusively provoked by androgens (Breckwoldt et al., 1996; Rabe et al., 1992). The excessive keratosis with creation of comedones is an essential precondition. However, an increased activity of the sebaceous glands precedes the comedones (Breckwoldt et al., 1996). The involvement of various endocrine glands (pituitary, thyroid gland, adrenal cortex and ovaries) leads to a complex hormonal influence on the sebaceous glands. In

general, only the effect of androgens is analysed. The effect of progesterone on acne is assumed to be cumulative during the premenstrual phase. Oestrogens certainly inhibit the production of sebum and reduce the androgen level by suppression of gonadotropins. Apart from that, it is established that the adrenal hormones DHEAS and androstendion have less effect on the sebaceous glands than testosterone. Finally, the role of cortisol is not clarified yet with respect to the activity of the sebaceous glands. It probably acts as intermediary substance which means that the sebaceous glands should respond better to testosterone under the influence of cortisol (Rabe et al., 1992).

The principal medical treatment of acne is a therapy with oral contraceptives. They yield an increase of SHBG concentration and decrease of androgen level. A combination of gestagens (cyproteroneacetat also known as Diane-35®, chlormadinonacetat) and oestrogen is however preferable (Pschyrembel, 1990): "A double-blind study of Aydinlik (1992) shows an improved situation of acne in 72 % of women treated with Diane-35® compared to 35 % of those treated with a levornorgestrel containing micro-pill (Microgynon®)" (Aydinlik, 1992, cited by Rabe et al., 1992, p. 50). "After a treatment of three month with Diane-35® recrudescence was observed in 30 % of cases whereas 70 % stayed symptomless" (Török et al., 1991, cited by Rabe et al., 1992, p. 50).

### 3.1.3. Alopecia

Hair loss represents a further sign of androgenism which is considered in form of a bald head as a secondary male gender characteristic. In contrast to the terminal hair the growth of which is stimulated by androgens (c.f. hirsutism above) the scalp hair reacts to androgen stimulation contrariwise with hair loss (alopecia). Indeed not only men can suffer from the cosmetic problem and psychological strain resulting from hair loss but also women. In gynaecology there are mostly seen the endocrine forms, alopecia androgenetica and its special form alopecia climacteria. In the following the alopecia androgenetica is explained more precisely. It is defined as an increased loss of hair by genetic disposition. There is no obligation for the hormonal imbalance of hyperandrogenaemia. It is caused by an autonomous metabolism of hormones in the destined organ. This means that the effect depends not only on the hormone level in the serum but also a lot more on the number of androgen receptors in the concerned region. The destined organs show an amplified reaction to the circulating androgens (Breckwoldt et al, 1994; Pschyrembel, 1990; Rabe et al., 1992). A trichogram, for which a sample of 50 to 80 roots of hairs is retained, is important to assess the situation of hair growth in the case of alopecia (Rabe et al., 1992).

In women two different clinical symptoms can be observed:

- § Alopecia, male pattern: receding hairline and brow with a chaplet temporal and occipital,

§ alopecia, female pattern: hair is exceptionally lost at the central-parietal area. This pattern is more common at the reproductive age (Rabe et al., 1992).



*Fig. 10 Schematic depiction of the three severity codes of the female alopecia androgenetica (Rabe et al., 1992, p. 30)*

For men therapy is hardly effective until now; women can be treated with anti-androgens and oestrogen containing hair tonic (Pschyrembel, 1990). Of course, exogenic noxa (pesticides, heavy metals, hair chemicals), and deficiency of proteins, zinc, iron or vitamins in case of malabsorption or malnutrition has to be excluded as possible causes for hair loss. Other endocrine diseases (e.g. from the thyroid gland) have to be detected and treated respectively (Rabe et al., 1992).

#### 3.1.4. Android Fat Distribution

Freytag (2003) proved that hyperandrogenaemia possibly causes android fat distribution beyond hirsutism, acne and alopecia. Her research on hyperandrogenaemic women with PCOS confirmed the suggestion that obesity caused by hyperandrogenaemia is mostly adrenocortical obesity. Note that women with PCOS can be also lean. She also reports that both hyperandrogenaemia and obesity are related to the insulin metabolism. The pathologic mechanism of insulin influence on androgen production is elucidated in the next section about the PCOS.

According to Hamilton-Fairley and Taylor (2003), patients with a body mass index (BMI = kg / m<sup>2</sup>) more than 30 should first loose weight to normal limits before they could be treated for ovulation induction. Particularly in patients with PCOS obesity increases the likelihood to develop anovulation (Hamilton-Fairley and Taylor, 2003). Weight reduction may have a positive influence on hyperandrogenaemia. Due to weight loss the SHBG level increases and contributes thus to a reduction of free testosterone. In consequence, this enables complete follicle maturation (Freytag, 2003).

Concerning the satisfaction with their own attractiveness, weight seems not to be an important issue for hyperandrogenaemic women. This is one result of a survey of Elsenbruch et al. (2003) who interviewed 50 hyperandrogenaemic women with PCOS and 50 healthy controls about quality of life, psychosocial existential orientation and sexual satisfaction. Essentially the most disturbing factors concerning female identification are the other symptoms: First and foremost hirsutism, acne and alopecia.

### 3.2. Polycystic Ovary Syndrome (PCOS) and Insulin Resistance

As hyperandrogenaemia is often associated with PCOS, some more details are given on this complex disorder. The wide range of definitions of PCOS originates in its still unclear aetiology, the current state-of-art and the ever-changing classification. The database MeSH characterises the term PCOS since 1985 "by infertility, hirsutism, obesity, and various menstrual disturbances such as oligomenorrhoea, amenorrhoea and anovulation" (MeSH 4, download 12.08.2007). It is furthermore pointed out that the term polycystic may be misleading since the bilateral, usually enlarged ovaries are studded with atretic follicles, not with cysts (compare Fig. 11).



*Fig. 11 Transvaginal scan of polycystic ovary. Typically 10 or more follicles of < 10 mm in diameter ("string of pearls") are in a single transverse or longitudinal section through the ovary. Stromal density and ovarian volume increase (Hamilton-Fairley and Taylor, 2003, p. 546).*

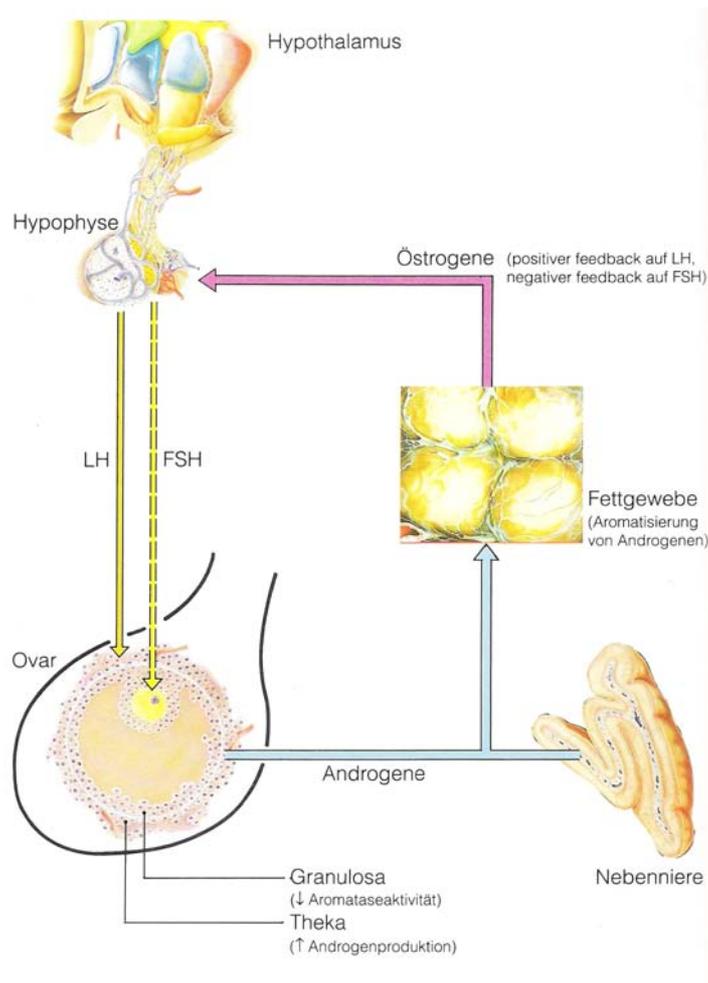
In 1990 on a conference sponsored by the National Institutes of Health (NIH) the disorder is discussed as a mixture of criteria comprising first hyperandrogenism and/or hyperandrogenaemia, secondly oligoovulation, and thirdly exclusion of known disorders such as Cushing's syndrome and hyperprolactinaemia. Polycystic ovaries on ultrasound as a fourth criterion were considered particularly controversial. In conclusion, the results of this expert conference essentially identified PCOS as a disorder of ovarian androgen excess (Broekman et al., 2006).

Alternatively, another conference held in Rotterdam in May 2003 defined PCOS, after the exclusion of related disorders, by two of the following three features: 1) oligo- or anovulation, 2) clinical and/or biochemical signs of hyperandrogenism, or 3) polycystic ovaries. In essence, the Rotterdam 2003 expanded the NIH 1990 definition creating two new phenotypes: 1) ovulatory women with polycystic ovaries and hyperandrogenism, and 2) oligo/anovulatory women with polycystic ovaries but without hyperandrogenism (Azziz, 2006).

Several study outcomes corroborate the latter classification of phenotypes because serum androgen concentrations may be normal in 30-50 % of women with oligomenorrhoea and PCOS (Pirwany et al., 1999, p.2963). This shows that hyperandrogenaemia does not have to be an obligatory sign of the PCOS. Concerning the Rotterdam consensus classification, Broekmans et al. (2006) noticed that by this definition the group of women with PCOS appears 1.5 times larger than by the old NIH classification of the syndrome. Especially "oligo/anovulatory women with less severe metabolic derangement will be added to the heterogenous group of women with PCOS" (Broekmans et al., 2006, p. 1210).

However, a task force of the Androgen Excess Society (AES) in August 2006 agrees to consider the PCOS first as a disorder of androgen excess or hyperandrogenism, although a minority considered the possibility that there may be forms of PCOS without evidence of hyperandrogenism. Clearly, more data are required to validate this assumption (Azziz et al., 2006). More evident than the association of PCOS and hyperandrogenaemia is the connection of PCOS to infertility. The PCOS, formerly known as Stein-Leventhal-Syndrome, affects 6-10 % of women in the reproductive age (Nestler, 2002; Palomba et al., 2005; Pirwany et al., 1999; Sukcharoen, 2004). The syndrome occurs about 20 % in the infertile population (Stadtmauer, 2002).

The aetiology of PCOS is not clarified until today. Hypothalamic activity, ovarian or adrenal disorders of the steroid hormone biosynthesis and failure in the insulin metabolism are discussed as probably causes. An increased production of androgens in the adrenal cortex may likely cause PCOS. Also obesity represents a probable pathogenetic factor since the FSH secretion of the pituitary is inhibited by the increased synthesis of oestrogens in the adipose tissue. Those additional acyclic oestrogens lead to an increased secretion of LH of the pituitary. In consequence the relative overbalance of LH-stimuli gives rise to an increased synthesis of androgens in the ovary which maintains the vicious circle (Breckwoldt et al., 1994). The vicious circle is depicted in the following picture according to Breckwoldt (1994).



*Fig. 12 The aetiology of the PCOS.* The vicious circle begins with an excessive androgen production of the adrenal cortex. These androgens are aromatised to oestrogens mainly in the subcutaneous fatty tissue. Oestrogen has a positive effect on the LH release but a negative on FSH. In consequence the high LH level leads to an overproduction of androgens of the theca cells. Due to the low FSH level the aromatase activity of the granulosa cells cannot be maintained and androgens cannot be transformed to oestrogens. Hence, excessive amounts of androgen of ovarian origin get into the circulation so that the vicious circle continues (Breckwoldt et al., 1996, p. 58).

Women with PCOS are in 50 % obese (Freytag, 2003) and show an android type of fat distribution (Evans et al., 1983), but they could also be lean (Kirchengast and Huber, 2001). Hyperinsulinaemic insulin resistance is a common finding in lean and obese women with PCOS (Pirwany et al., 1999) and is discussed in detail. Freytag (2003) summarised a prevalence of insulin resistance of 30-60 % among the women with PCOS. This insulin resistance is not symptomatic due to hyperandrogenaemia, but represents an increasing factor for hyperandrogenaemia and is therefore considered as causative factor (Freytag, 2003; Utiger, 1996). This results from a direct influence of insulin on the ovary and, simultaneously, from an indirect influence of insulin on the pituitary leading to increased secretion of LH. Hence, the ovary is stimulated twice and produces significantly more male hormones (Pirwany et al., 1999; Utiger, 1996).

The elevated LH level at normal FSH level leads to a pathologically increased LH-FSH ratio ( $>2$ ). Furthermore hyperinsulinism may increase the androgen secretion of the adrenal gland (Freytag,

2003). As insulin has also an effect on the metabolism of the liver, smaller amounts of sexual hormone binding globulin (SHBG) are produced. This protein binds especially testosterone in order to render it transportable. In the time of being bound to SHBG, these hormone molecules are temporarily ineffective. If there is less SHBG available, the free testosterone given by the percentage of total testosterone to the amount of SHBG will augment and consequently affects the PCOS negatively (Breitach, 2007; Homburg, 2002; Utiger, 1996).

Increased levels of insulin mostly arise from insulin resistance, i.e. the diminished response of cells to insulin. The elevated blood glucose level provokes the body to secrete even more insulin into the bloodstream. The insulin resistance places these women to higher risk of other disorders linked to insulin resistance, namely type 2 diabetes, hypertension, dyslipidaemia and heart disease (Nestler, 2002). From Nestler's point of view the PCOS is "...a systemic malady whose heart lies in insulin resistance." (Nestler, 2002, p. 1953). Utiger (1996) reports that the larger amount of insulin resistance in women with PCOS remains unexplained. Further literature which presents a solution for this problem has not been published until today. A study of Eisenbruch et al. (2006) about the quality of life of PCOS patients noticed a remarkable impairment of female identity. The medical care goes beyond the cosmetic problematic of the hyperandrogenism (hirsutism, acne and alopecia) and the unfilled child wish. Due to the disadvantageous prognosis of the metabolic syndrome in women with PCOS, the prevention of long term risks of these patients is highly important.

To summarize, insulin is an amplifying factor for hyperandrogenaemia (Freytag, 2003; Stadtmauer et al., 2002).

### 3.3. Hyperprolactinaemia and Hyperthyreosis

Other reasons for anovulation and hyperandrogenaemia and in consequence infertility can be disorders in the hormone synthesis of prolactin and of the hormones of the thyroid gland (T3, T4). Prolactin is typically increasingly released of the pituitary during lactation. Its secretion is stimulated by oestrogens and glucocorticoid as well as through afferent nerves from the acromastium during lactation. Apart from this the hypothalamic thyroid releasing hormone (TRH) stimulates the pituitary to release thyroid stimulating hormone (TSH) and stimulates the prolactin secretion as a concomitant effect. This influence will be described in more detail below. Prolactin inhibits the hypothalamic secretion of GnRH which leads to reduced LH and FSH secretion of the pituitary. Hence, in the case of increased prolactin, maturation of the oocytes is disturbed in most cases and ovulation impeded (Klinke and Silbernagel, 1996). Effects range from anovulation, hypophyseal amenorrhoea to weakness of the corpus luteum and naturally to galactorrhoea (Breitach, 2007; Kaiser and Leidenberger, 1996). Further prolactin stimulates the

adrenal synthesis of cortisol and androgens which in case of hyperprolactinaemia leads to a secondary overproduction of androgens of the adrenal cortex. This androgen excess is associated with the onset of hirsutism as stated above (Kaiser and Leidenberger, 1996; Rabe et al., 1992).

Dopamine of hypothalamic neurones controls prolactin secretion within a short feedback loop. The prolactin inhibiting hormone (PIH) is also involved. As endogen PIH derives chemically from GnRH, PIH and prolactin participate in the menstrual cycle and, in consequence, influence fertility (Klinke and Silbernagel, 1996).

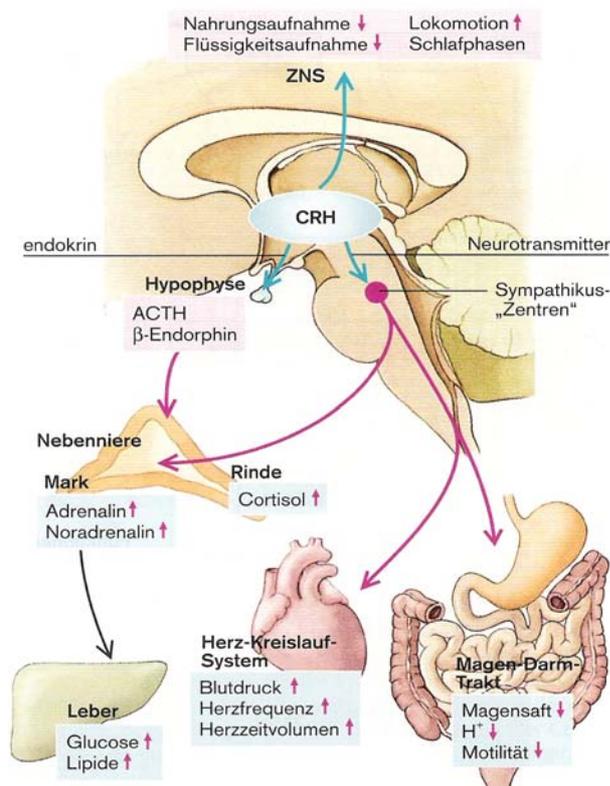
Hyperprolactinaemia results from a tumour (adenoma, prolactinoma) in one third of the patients. The most frequent tumour that generates prolactin is the micro adenoma (diameter < 1cm). In dependence on the dosage also medicaments can cause an increased production of prolactin, namely various neuroleptic drugs, antidepressants, histamine antagonists, sympatholytics, anti-emetic drugs and oestrogens (Kaiser and Leidenberger, 1996). In addition hypothyreosis is often a cause for hyperprolactinaemia. The thyroid releasing hormone (TRH) of the hypothalamus activates the pituitary to produce thyroid stimulating hormone (TSH). TSH stimulates the thyroid to produce T3 and T4. Thus the function of the thyroid is also regulated by the hypothalamus-pituitary-gland-axis (look also Fig. 3). Thyroxin (T3, T4) stimulates the SHBG production of the liver. By this way it influences the level of free, metabolic effective testosterone on the basis of which hyperandrogenaemia is diagnosed (Rabe et al., 1992).

In the case of hypothyreosis the hypothalamus augments the TRH-secretion to increase the TSH-secretion and likewise the activity of the thyroid gland. As concomitant effect the pituitary reacts to TRH not only with an increased production of TSH but also of prolactin (Breitach, 2007; Rabe et al., 1992). Prolactin can cause hyperandrogenaemia as explained.

### 3.4. The Influence of Stress and Cortisol

Negro-Vilar (1993) reports that stress influences the hypothalamic-pituitary-adrenal (HPA) axis and possibly affects the reproductive function. As described in section 2.4.2, the main elements in this axis are corticotrophin-releasing hormone (CRH), adrenocorticotrophic hormone (ACTH) and cortisol. In response to the secretion of CRH into the pituitary portal vasculature the secretion of corticotrophins are highly activated in the anterior pituitary and ACTH is released. The elevated levels of ACTH increase cortisol secretion from the adrenal gland, which leads to a number of adaptive changes in the metabolic activity.

Chronic anovulation is associated with hypothalamic (or psychogenic) amenorrhoea due to elevated cortisol levels and abnormal response to CRH. Enhanced CRH activity leads to suppression of gonadotropin secretion (luteinising hormone-releasing hormone LHRH) and, thereby, to decreased gonadal function (Negro-Vilar, 1993).



*Fig. 13 Multiple Effects of CRH.* The neurotransmitter CRH is effective at the regulation of centres of the vegetative nervous system. In addition to its effects as releasing hormone of ACTH CRH is an important factor of the regulation of multiple reactions of the body to stress (Klinke and Silbernagel, 1996, p. 461).

In addition to cortisol the endogenous opiate  $\beta$ -endorphin seems to influence the female cycle. In patients with anorexia nervosa it was observed that augmented  $\beta$ -endorphin resulting from psychic stress can suppress the hypothalamic neurones producing GnRH. The pituitary is less stimulated and therefore FSH and LH is less secreted or not at all. Consequently maturation of the oocyte, ovulation, synthesis of oestrogen and progesterone, normal composition of the endometrium and eventually menstruation do not occur. Competitive athletes may develop the same cycle distortions when the psychological stress adds to the physical stress. In both, anorexia nervosa and competitive sports, anovulation is primarily due to the reduced total fat mass, that reduces the aromatisation of androgens into oestrogens, and due to the increased secretion of  $\beta$ -endorphin and cortisol (Breckwoldt et al, 1994). Hence, amenorrhoea if related to weight loss (anorexia nervosa) or intense exercising (competitive sports) should represent an exclusion criterion for any clinical study on hyperandrogenaemia.

Note that Morbus Cushing and the Cushing-Syndrome are also considered as exclusion criteria. These severe diseases arise from permanent overproduction of cortisol either through increased ACTH secretion (e.g. of the pituitary or an external tumour as bronchial carcinoma) or through an increased cortisol production of the adrenal cortex itself (e.g. adrenal adenoma). Clinical symptoms are characterised by the multiple effects of the overproduced glucocorticoid: amyosthenia, osteoporosis, striae rubrae due to rupture of collagen dermal fibres, diabetes and pre-diabetes. Adrenal-cortical obesity and moon-shaped face are the typical fat distribution

resulting from a change in the lipid metabolism. The increased cortisol synthesis also affects the metabolism of mineral corticoids which is apparent as hypertension and hyperkalaemia and alkalosis. In addition hyperplasia of the adrenal cortex increases the androgen production so that typical symptoms of virilism such as hypertrophy of clitoris, deep voice, hair loss and amenorrhoea and infertility are often associated to the Cushing-Syndrome. In women these androgenic effects are often the first signs of hormonal imbalance (Breckwoldt et al., 1994; Klinke and Silbernagel, 1996).

The adrenogenital syndrome is an autosomal recessive genetic disorder that occurs at a rate of 1:5000 and represents – like the hypercortisolism – a severe dysfunction of the adrenal cortex. This congenital hyperplasia of the adrenal cortex is already present at birth and characterised by a deficiency of the hormones aldosterone and cortisol. The reduced synthesis of these adrenal hormones yields a reactive overproduction of ACTH. The body is flooded with adrenal androgens which may manifest in an enlarged penis, small testis and early development of masculine characteristics in males. In females features comprise ambiguous genitalia, failure to menstruate, deep voice and excessive hair (Breckwoldt et al., 1994; Kaiser and Leidenberger, 1996). The late onset adrenogenital syndrome is a benign form of the congenital adrenogenital syndrome. Amenorrhoea and postpubertal hirsutism are the main characteristics. Early diagnosis is important in every form of congenital hyperplasia of the adrenal cortex since these patients need a lifelong suppressive glucocorticoid therapy (Kaiser and Leidenberger, 1996).

Being a genetic disorder the adrenogenital syndrome cannot be healed completely. In particular, osteopathy does not claim to be able to directly change genetic factors. Osteopathic treatment in the context of genetic disorders aims to reduce the concomitant impairment of the quality of life. The clinical study that is intended to be conducted within the framework of this master thesis is conceptualised with measurable outcome. Hence, adrenogenital syndrome and its benign late-onset form represent exclusion criteria.

## 4. CONVENTIONAL TREATMENT

Because of the coherences between hyperandrogenaemia and PCOS, as demonstrated in the second chapter, most of the clinical studies of hyperandrogenaemia investigated the medical influence on women with PCOS, anovulation, infertility and endocrinopathic symptoms such as insulin resistance and hyperandrogenaemia.

Subsequently I summarise the studies with the main aim to improve the hormone cycle so that regular ovulation takes place and pregnancy becomes possible. If medicamentous treatment fails, surgical interventions like ovarian drilling and in-vitro fertilisation remain as last options to fulfil the wish of children.

The treatment of the external characteristics of hyperandrogenaemia as hirsutism, acne and alopecia is mentioned in the corresponding sections 3.1.1, 3.1.2, 3.1.3 and 3.1.4.

### 4.1. Medical Ovulation Induction

#### 4.1.1. Clomiphene Citrate

Clomiphene citrate (CC) was the first medicament to treat anovulatory infertility. Its action can be explained as mainly antioestrogenic - by blocking oestrogen receptors in the pituitary - thereby increasing the FSH and LH pulse frequency and concentration so that an increased number of follicles reach ovulation (Hamilton-Fairley and Taylor , 2003; Palomba et al., 2005). The effectiveness of CC in anovulatory women with PCOS is 60-85 % concerning ovulation rate, whereas it is only 30-40 % concerning pregnancy rate (Palomba et al., 2005; Sukcharoen, 2004). This could be due to "the antioestrogenic effect on the endometrium, cervical mucus, uterus blood flow, the influence on tubal transport and oocyte quality and maturity, and the increased risk in subclinical pregnancy loss" (Palomba et al., 2005, p.4072). Hamilton-Fairley and Taylor (2003) refer to similar results concerning ovulation and pregnancy rate.

"CC is routinely used [...] to treat infertile anovulatory PCOS patients due to the low costs, the limited dose-dependent side effects and the simplicity of administration and management (no need for ongoing monitoring)" (Palomba et al., 2005, p. 4069). In contrast Hamilton-Fairley and Taylor (2003) advise "ovarian ultrasound monitoring because of the risk of multiple follicle development and the small but prevailing risk of ovarian hyperstimulation syndrome" (Hamilton-Fairley and Taylor, 2003, p. 548). They report of an incidence of twins in about 10 % and triplets in 1 %.

Women who do not ovulate with increased dose of CC are called "cc-resistant". The reason is poorly understood. Although there is currently no data available about this phenomenon it appears that the efficacy of CC therapy is decreased in the presence of obesity, hyperandrogenaemia, elevated testosterone concentrations and severe insulin resistance

(Sukcharoen, 2004). For these women metformin should be the first choice of the medical practitioner and preferable to CC in hyperandrogenaemic women. Studies named in the following section support this theory.

The correlations between hyperandrogenaemia and PCOS and insulin resistance are explained in the second chapter on pathologies.

#### 4.1.2. Metformin

Metformin is an insulin sensitizing drug for the treatment of hyperglycaemia. It is recently used to treat infertile women with PCOS and hyperandrogenaemia (Palomba et al., 2005). Hamilton-Fairley and Taylor (2003) advise caution because metformin is not licensed for this indication and the results of convincing trials are still awaited. It decreases insulin levels and, as a consequence, lowers circulating total and free androgen levels with a resulting improvement of the clinical sequelae of hyperandrogenism (Homburg, 2002).

In most of the studies metformin was given in a dose of 1500-2000 mg daily, e.g. 850 mg twice a day (Hamilton-Fairley and Taylor, 2003; Homburg, 2002).

The reviews of Homburg (2002) and Nestler (2002) summarise the evidence for the use of metformin alone or in combination with clomiphene citrate to treat the infertility of PCOS (see section 3.1.2.). The results are an increased incidence of ovulation induction and regular menstrual cycle (Stadtmauer, 2002).

Pirwany et al. (1999) found in their study about the effects of metformin on ovarian function, follicular growth and ovulation rate in obese women with oligomenorrhoea that "metformin has a rapid effect upon the abnormal ovarian function of hyperandrogenic women with PCOS, correcting the disordered steroid metabolism and ovulation rate; however, there appeared to be no effect in cases where the circulating androgen concentration were normal." (Pirwany et al., 1999, p.2963)

"The results reported by Nestler and Jakubowicz indicate that drugs like metformin that increase insulin sensitivity and decrease hyperinsulinemia can reduce androgen secretion and, by raising sexual hormone-binding globulin concentrations in the serum, also limit the action of androgen" (Utiger, 1996, p.658).

In contrast, Ehrmann et al. (1997) did not find a direct effect of metformin on gonadotropin or ovarian steroid production that is independent of weight loss. They "have shown that metformin does not reduce significantly the hyperinsulinemia or excess androgen secretion in obese non-diabetic women." (Ehrmann et al., 1997, p.529) This study has a sample size of 14 women and the dose of metformin of 850mg was given three times daily for 12 weeks. "However, since then some 20 studies have demonstrated a beneficial effect on insulin metabolism and/or hormonal parameters." (Homburg, 2002, p.854)

Concerning the treatment of anovulatory infertility caused by PCOS, metformin plus clomiphene is more effective than clomiphene alone in inducing ovulation. For the treatment of irregular menses caused by PCOS in women not attempting conception, metformin therapy for 4-6 months may restore ovulatory menses in the majority of women (Barbieri R.L., 2003).

In a prospective randomized, double-blind, placebo-controlled trial Eisenhardt et al. (2006) had an outcome concerning ovulation of 67 % of metformin-treated women compared with only 45 % in the placebo group, shown by biphasic body temperature curves. Lord reports of an overall ovulation rate up to 57 % achieved by using metformin or metformin and clomiphene (Lord JM et al., 2003).

#### 4.1.3. Dexamethason

Dexamethason is a glucocorticoid and mainly used to diagnose a functional or an autonomic adrenal disorder within the so-called dexamethason-blocking test. Thereby the synthesis and secretion of some adrenal steroids (glucocorticoids and androgens) is reduced because of the inhibition of ACTH-secretion by glucocorticoids as dexamethason. Normally the steroid production of an autonomic adrenal tumour cannot be reduced by this way. Apart of this it helps to decide about further long-term application of dexamethason at women with ovarian dysfunction due to hyperandrogenaemia. In this case androgen levels in the plasma will decline if dexamethason is taken (Kaiser and Leidenberger, 1996). Dexamethason is given as an adjunct to CC. It suppresses the adrenal androgen secretion and may induce responsiveness to CC in previous non-responders, mostly hyperandrogenaemic women with PCOS and elevated concentrations of DHEAS.

Although this method obtains some success, it often induces side-effects as increased appetite and weight gain which is counterproductive in women with PCOS (Sukcharoen, 2004).

#### 4.1.4. Gonadotropins

Treatment with gonadotropins injections as follicle stimulating hormone is indicated in women with mainly hypothalamic-pituitary causes of anovulation or with PCOS and no response to clomiphene (Hamiton-Fairley and Taylor, 2003). The high success rate of gonadotropins in treatment of ovulation induction is shown in a lot of studies. But especially in PCOS women there a higher risk of ovarian hyperstimulation and multiple pregnancies due to frequent multi-follicular growth is persistent. To avoid these negative outcomes an experienced operator and careful sonographic and biochemical monitoring are needed during gonadotropin administration (Hamiton-Fairley and Taylor, 2003; Palomba et al., 2005; Sukcharoen, 2004).

Furthermore there is a relevant investment of time and money (Palomba et al., 2005).

## 4.2. Surgical Ovulation Induction

### 4.2.1. Laparoscopic Ovarian Drilling

CC-resistant patients will be treated with metformin or with laparoscopic ovarian diathermy as a second step for disease management (Palomba et al., 2005). At laparoscopy, 5-6 diathermy or laser punctures are made in the ovary.



*Fig. 14 Ovarian diathermy. Ovary showing small holes made in the cortex at laparoscopy using a diathermy point to encourage ovulation in a patient with polycystic ovary syndrome (Hamilton-Fairley and Taylor, 2003, 549).*

This ovarian diathermy, also called “drilling”, has a comparable success rate to administration of follicle stimulating hormones but less risk of multiple pregnancy or ovarian hyperstimulation syndrome. Complications can arise from surgery and adhesion formation. (Hamilton-Fairley and Taylor, 2003).

The ovulation rate is about 82 % after laparoscopic ovarian diathermy. 63 % conceived either spontaneously or after medication to which the patient had previously been resistant. Pregnancy rates are similar to gonadotropin therapy. The main advantage of laparoscopic ovarian diathermy is a significant reduction in multiple pregnancy rates compared with gonadotropin therapy (Sukcharoen, 2004).

### 4.2.2. In-Vitro Fertilisation and Embryo Transfer

The in-vitro fertilisation (IVF) remains the last option to provide for pregnancy.

In Austria there are 5000 to 6000 IVF yearly in the meantime, but only about one third is effective (Feichtinger, W., cited in “Neue Vorarlberger Tageszeitung”, 05.08.2007).

Certainly, women treated in such way are under psychological stress, not forgetting the long way and the unsuccessfully former treatments until it comes to an in-vitro fertilisation.

The results at women with PCOS are similar to matched controls treated for other indications.

Polycystic ovaries may confer an advantage regarding the number of oocytes retrieved and the number of embryos available for transfer and cryopreservation. But the risk of ovarian hyperstimulation is especially high in these women which makes ovarian stimulation difficult

(Sukcharoen, 2004). Pre-term deliveries represent another risk of IVF (Urđl, W., cited in "Neue Vorarlberger Tageszeitung", 05.08.2007).

In 2006 1568 babies were born which is a success rate of 31.3 % after IVF (Schafferhofer, 2007). For further information about IVF and ART (assisted reproductive technologies) look also at the "fertility guide" of the National Collaborating Centre for Women's and Children's Health (2004).

#### 4.3. Success Rate and Side-Effects of the Standard Medical Treatment

Beyond the success rate of the standard therapy women are interested in its possible side-effects. First, the possible success has to be summarized. The standard medication (e.g. metformin) leads in 4-6 month to ovulatory menses (Barbieri, 2003). The ovulation rate is about 57 % with metformin (Lord JM et al., 2003) and about 60-85 % with clomiphene citrate (CC), whereas it is only 30-40 % concerning the pregnancy rate (Palomba et al., 2005; Sukcharoen, 2004). The margin of side-effects of ovulation and infertility treatment ranges from weight gain, nausea and vomiting to ovarian hyperstimulation and even to an increased risk of cancer (Hamilton-Fairley and Taylor, 2003; Palomba et al., 2005; Pirwany, 1999; Sukcharoen, 2004).

„Metformin was associated with side effects in the form of nausea, vomiting, and gastrointestinal disturbance [...]. Metformin is contraindicated in the presence of even mild renal impairment because of a danger of lactic acidosis, and it is associated with decreased absorption of vitamin B12.“ (Lord JM et al., 2003, p.955). In order to avoid gastric irritation that can occur at the start of treatment with metformin a special approach to the dose is recommended. E.g. treatment starts with a dose of 850mg once a day for the first week and increases to 850mg twice daily for the following weeks (Pirwany, 1999). In this study to the effects of metformin of Pirwany et al. (1999) diarrhoea and vomiting caused 3 of 18 persons to withdraw from the study.

Ovarian hyperstimulation is a common risk especially at the treatment with further drugs such as gonadotropins at women with polycystic ovarian syndrome (PCOS) which is associated with hyperandrogenaemia (Hamilton-Fairley and Taylor, 2003; Palomba et al., 2005; Sukcharoen, 2004). Other complications can be multiple pregnancies with a frequency of 10 % (Hamilton-Fairley and Taylor, 2003).

Another problem can be adhesions resulting of scars of laparoscopy ovarian diathermy. In the osteopathic view scars affect the tension of tissue and the function of visceral organs. They are the main cause of mechanical and physiological dysfunctions. In case of laparoscopy the umbilical ligaments can be affected and can cause a restricted mobility to the bladder, the uterus and, indirectly, of the ovaries (Barral, 2005; Paoletti, 2001; Riepler-Reisecker, 2006).

Finally Hamilton-Fairley and Taylor (2003) report on a study which shows an increased risk of ovarian cancer in women using clomiphene longer than 12 months. Therefore the Committee on

Safety of Medicines in the United Kingdom advises the intake of clomiphene not longer than six month (Hamilton-Fairley and Taylor, 2003).

## 5. POSSIBLE MODELS EXPLAINING THE OSTEOPATHIC APPROACH OF TREATMENT

The following chapter will elucidate the osteopathic approach on disorders of the hormonal system as infertility caused by hyperandrogenaemia. Therefore some general words to osteopathy have to be said.

The founder of osteopathy Andrew Taylor Still envisaged a science including knowledge of philosophy, anatomy and physiology for the whole body together with their clinical application in both diagnosis and treatment (foreword by Becker in "Teachings in the Science of Osteopathy" by Sutherland, edited by Wales, 1990, p. ix). A. T. Still began his studies of the body with bones - where the name "osteopathy" originates from. He appreciated the human being in a trinity of body, mind and spirit which functions in perfect health when all interrelated components work in harmony, and each part is in perfect place and free to do its work (Sutherland, 1990). Therefore A. T. Still regarded not only the interrelationship of structure and function of bones and soft tissues but also humours, fasciae, nerves, vessels and viscera (Stark, 2007; Sutherland, 1990). Later Sutherland added the craniosacral concept concentrating on the cranial bones, membranes and fluids of the body.

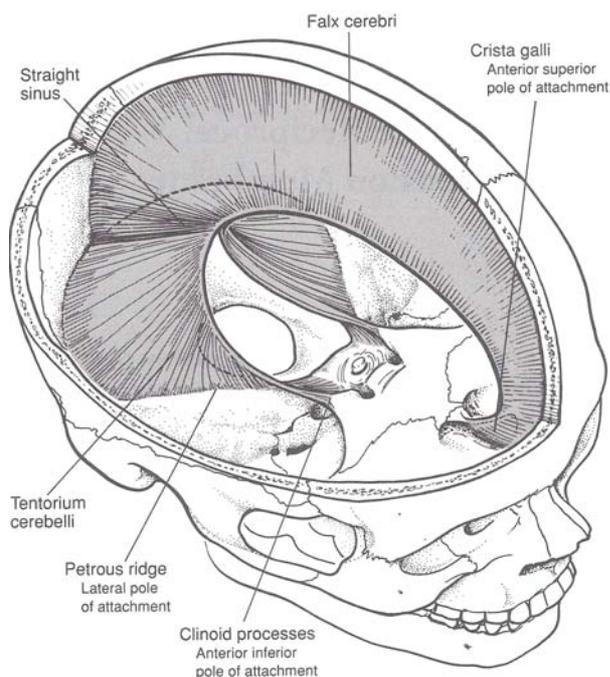
The aim of osteopathic treatment is to mobilise the organism's self healing properties and to allow the fluids to circulate freely in the body (Riepler-Reisecker, 2006). To investigate how osteopathy can work on the body to improve hormonal balance I begin with the explanation of cranial, fluidal and fascial models. I continue with structural, muscular work and then finish with visceral treatment and its connection to the nervous system. Particular attention is given to the three levels of hypothalamus, pituitary and endocrine glands which regulate the neural-endocrine systems as described in detail in section 2.3. Of course, I also consider the possibility to improve the elimination of the hormones via the liver, gall bladder and the intestines.

### 5.1. The Cranial Concept

In 1899 Sutherland began its studies of the skull and its articulations whereupon he developed the cranial concept in the following years (Sutherland, 1990). In this concept he sees the entire body as a unit of physiological function under the name of the primary respiratory mechanism, including the following principles: the fluctuation of cerebrospinal fluid, mobility of intercranial and interspinal membranes, the inherent motility of brain and chord (neural tube), articular mobility of cranial bones and involuntary mobility of the sacrum between the ilea (Magoun, 1976; Sutherland, 1990). These features, the production and resorption of the cerebrospinal fluid and the inherent motility of the neural tube, generate a palpable rhythm. This rhythm is received by

the interspinal and intercranial membranes and passed on the cranial bones as well as on the sacrum. In the following some features will be illuminated more exactly.

Amongst dysfunction in the vascular or nervous system or interosseous strains the craniosacral therapy focuses on the dura mater, commonly known as the reciprocal tension membrane (Sutherland, 1990). "It is a tough, nonextensible, fibrous membrane that has an outer and an inner wall." (Sutherland, 1990, p.39)

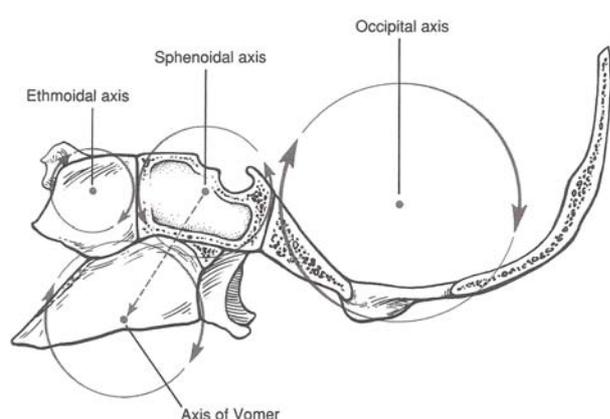


*Fig. 15 The cranial component of the reciprocal tension membrane, showing the schematic representation of the poles of attachment, (Sutherland, 1990, p. 40).*

The inner wall builds three folds dropped down between parts of the brain as you can see on Fig. 15. The whole membrane attached to all bones of the neurocranium holds with its three sickles on the inside of the cranium all these bones together (Sutherland, 1990). The inner layer is also attached on the anterior and posterior clinoid processes of the sella turcica. There, the pituitary is located and covered by the diaphragma sellae, part of the dura mater. "The infundibulum from the hypothalamus passes through to the posterior part of the pituitary" (Sutherland, 1990, p.39). The communication between hypothalamus and pituitary happens via this infundibulum and the surrounding vessels (Liem, 2001; Magoun, 1976; Paoletti, 2001). In Sutherland's opinion the mobility of the pituitary body within the sella turcica is essential to its function which can be negatively affected by a different tension of the diaphragma sellae (Liem, 2001; Magoun, 1976; Paoletti, 2001; Sutherland, 1990). In the so-called inhalation phase of the sphenobasilar synchondrosis (SBS) the opening for the pituitary stalk is wider whereas in the exhalation phase the opposite happens (Liem, 2001). The term inhalation and exhalation phase does not

correspond to normal breathing but means the motion phases of the bones according to the primary respiratory mechanism.

According to his principles named above, Sutherland (1990) teaches that the sphenoid bone circumrotates to and fro on its transverse axis as illustrated in Fig. 16. In addition he determined movement (flexion, extension, internal and external rotation, inhalation and exhalation phase) and axis for each bone which can be studied in further literature of him (1990), Magoun (1976) or Liem (2001).



*Fig. 16 The cranial base in flexion, showing the rotation that takes place about parallel transverse axes. Note that the ethmoid and the occiput rotate in the same direction while the sphenoid rotates in the opposite arc, as would be the case with three intermeshed cog wheels. The dotted line represents the vector of force transmitted from the movement of the sphenoid through the vomer (Sutherland, 1990, p. 43).*

Via its attachments on the sphenoid and the occiput the reciprocal tension membrane can provoke dysfunctions on the sphenobasilar synchondrosis (SBS), the so-called SBS-pattern. In a study about diabetes Kiegerl (2006) found such SBS-dysfunctions in each patient which could correlate to a disturbed function of the endocrinal system. SBS-dysfunctions as relevant lesions in all patients were likewise stated by Riepler-Reisecker (2006) in her study about congestive menstrual disorders and premenstrual syndrome. Although these studies were conducted each with ten controls only, in conclusion restrictions of the SBS seem to have an important influence on the function of the hormonal system. Disturbances of the SBS can be caused also by visceral or muscular skeletal restrictions which are transferred to the SBS by fascial chains as explained in following sections.

Furthermore the pituitary can indirectly be affected by the vomer. Regarding Fig. 16, this bone is responsible for the drainage of the sinus sphenoidalis on which the pituitary lies and it can be compared to a plunger-like actor (Liem, 2001; Magoun 1976; Nusselein, 2007). The vomer itself is influenced by the maxilla and hence by the teeth.

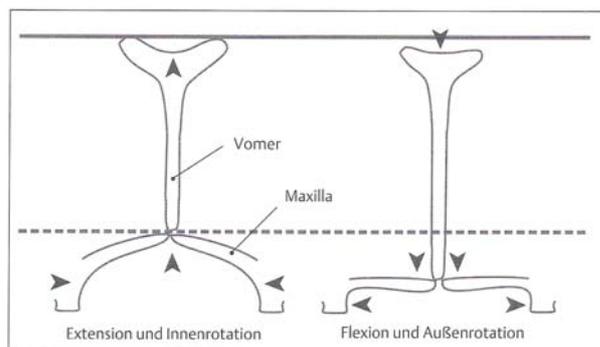


Fig. 17 Maxilla and vomer in inspiration and expiration phase, (Liem, 2001, p. 270).

The question which bone is the main transmitter of the movement of the sphenoid is differently discussed by the osteopaths. In Magoun's opinion the main transmitter are the palatines, whereas Busquet considers the temporalia and the vomer (Liem, 2001).

This means, a problem of infection or position of a tooth of the maxilla can irritate the pituitary's function via the maxilla to the vomer or via the palatines further to the sphenoid (Nusselein, 2007). In addition, in a personal interview (2007), Nusselein mentioned that a tongue which is too big or is often pressed against the hard palate inhibits the pumping mechanism of the vomer onto the sinus sphenoidalis and affects the sphenoidal movement via the palatines respectively.

To complete the reciprocal tension membrane the sacrum has to be mentioned. It is connected by the interspinal membrane to the intercranial membrane and cranial bones. Precisely, the dura mater is fixed on the inside of the skull (as in Fig. 15) and strongly on the first and second cervical vertebrae and the second sacral vertebra, and finally with its filum terminale on the coccyx (Barral and Mercier, Band 1, 2005). In the sense of a reciprocal tension membrane tension can be forwarded from one end or fixing point to another, meaning lesions from the sacrum (or even the foot or any other part of the lower extremities) can be transferred to the cranium and vice versa. This connection explains why Sutherland's concept is named craniosacral therapy. The sacrum in turn can be affected of the lower extremities so that dysfunctions from even the feet can disturb the primary respiratory mechanism as well as the function of the pituitary gland and in such way the endocrinal hormonal system (Monnier, 2004).

## 5.2. Fluids: Blood, Cerebrospinal Fluid and Lymphatic Fluid

A.T. Still attached great importance to the fluids (blood, cerebrospinal and lymphatic fluid), because they supply the skin, the fasciae, the muscles and the nervous system. He understood the fluids as nourishing element. In addition, he assigned a certain power to them which could liberate the system of anything that we call disease. Therefore, to promote life, the fluids should be able to circulate freely (Stark, 2007).

There are only two osteopathic studies of pilot character that report of the interrelation of fluidal systems and the hormonal metabolic system. The study about diabetes of Kiegerl (2006) has shown that the level of blood sugar decreases with osteopathic treatment but without long term effect. One possible explanation is the change of chemical and hormonal parameters due to increased mobility and stimulation of the "body fluids" (Kiegerl, 2006). That is why I assume that osteopathy can also have a positive effect on the hormonal status of hyperandrogenaemic women. Moreover the findings from Riepler-Reisecker (2006) show a reduced fluctuation of the cerebrospinal fluid between cranium and sacrum in patients with congestive menstrual syndrome or premenstrual disorder.

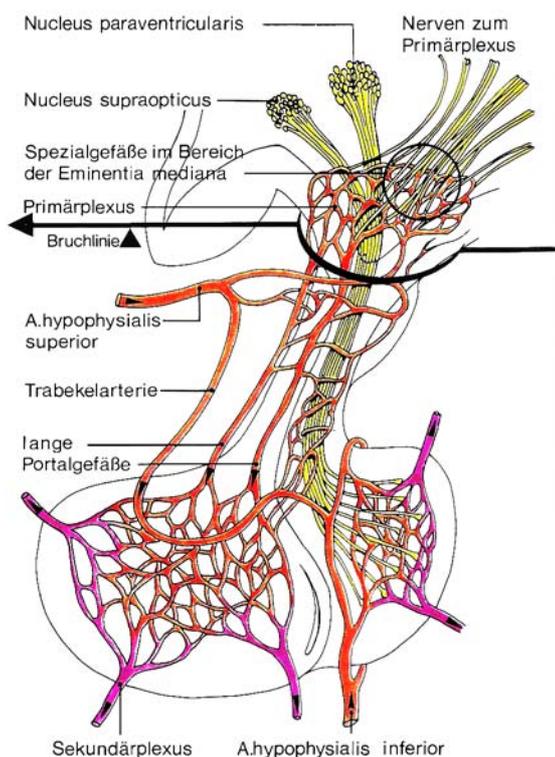
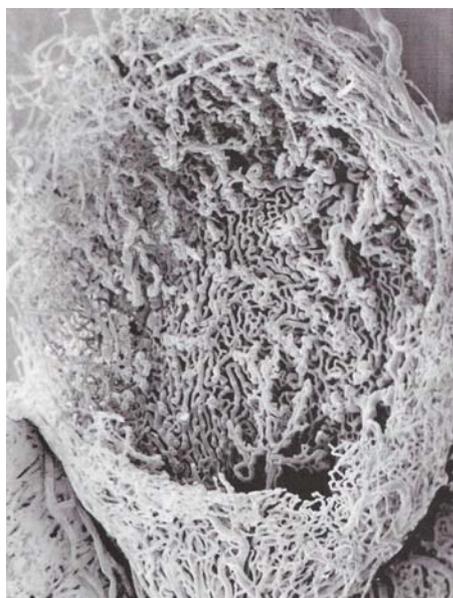
Below the different fluids and their functions are explained in detail from an osteopathic point of view.

### 5.2.1. The Blood

„The rule of the artery is supreme“, A.T. Still once stated. According to the interpretation of Liem and Dobler (2002) and Magoun Jr. (2007), blood is distributed in the entire body through arteries and veins, furthermore the unity of the body is organised around this substance (blood), and blood takes care of our health as part of the immunology system. Further, pure and healthy blood allows the body to work properly and to convalesce in case of disease. Therefore A.T. Still asked his students to look for and to activate the present amount of health in the body; disease, he said, can be found by everyone (Magoun Jr, 2007). The osteopathic philosophy implies that the circulation and activity of blood depends on the functionality of the fasciae, and is under control of the nervous system. An impaired blood circulation leads to stagnation and fermentation. Decongestive osteopathic treatment aims to improve not only the supply of the tissues and the removal of metabolic waste, but also to impede fixation and fibrosis (Liem and Dobler, 2001).

With regard to the hormonal system the rich vascularisation of the pituitary has to be mentioned, depicted in Fig. 18. This amazing capillary plexus indicates the importance of the vascularisation and of the secretion of hormones into the blood stream.

*Fig. 18 Vascularisation of the pituitary and primary capillary plexus of the upper pituitary stalk 300-fold magnified, (Breckwoldt et al., 1994, p. 44).*



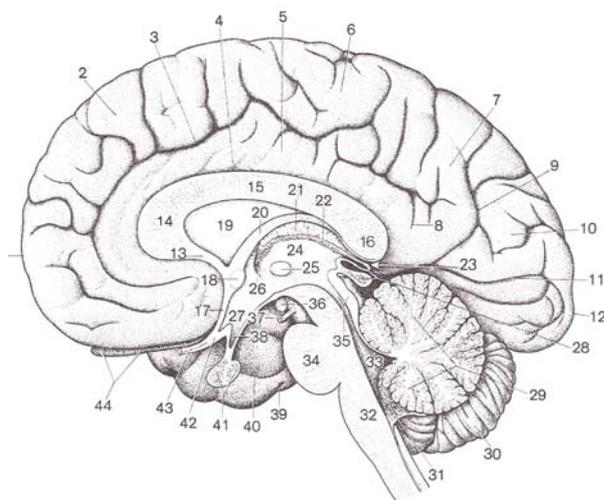
Additionally the pituitary is embedded in the venous plexus, namely the cavernous sinus. From here the drainage of the pituitary continues via the sinus petrosus and sigmoideus to the jugular vein. These venous sinuses run between the two layers of the dural membranes. The blood flow is supported by the mobility of the bones e.g. of the temporalia which moves the blood forward within the sinus petrosus (Sutherland, 1990). A change in mobility of the sutures of the vault or in the tension of the dura mater as well as restrictions of the jugular foramen impair the drainage of the venous sinuses and thus of the brain including the hypothalamus and the pituitary. As a consequence of the worsening of the venous sinus drainage the resorption and fluctuation of the cerebrospinal fluid is also affected (Sutherland, 1990).

To resume, the sphenobasilar synchondrosis (SBS) and the reciprocal tension membrane influence the haemodynamic of the pituitary. This could be verified by Andrianov and Bespala who conducted a study with children having cranial dysfunctions. On the basis of duplex sonography they could prove a normalisation of the haemodynamic in 75 % after cranial and cervical treatment (Liem, 2001).

### 5.3. The Cerebrospinal Fluid

The cerebrospinal fluid (CSF) transports numerous hormones and other substances and is one further component of the primary respiratory mechanism according to Sutherland (Paoletti, 2001). It is mainly produced of the choroid plexus of the lateral ventricles and partly of the plexus on the top of the third and fourth ventricle. The epithelia of the choroid plexus exhibit tight junctions to

the arterial blood from which the CSF is extracted. These tight junctions are organised such that ingredients of the blood cannot easily reach the CSF and thus the brain, but ingredients of the CSF can easily permeate into the bloodstream (Frick et al., 1987; Liem, 2001). Here, I like to point out the role of the third ventricle for the transmitter function of the CSF between the central nervous system and the humoral system. The connections are depicted in Fig. 19.



*Fig. 19 A cross-section of the brain, showing the third ventricle (24) with its choroid plexus (21+22), hypothalamus (27), infundibulum (38), pituitary with adeno- and neurohypophysis (41), N.opticus (43), Lamina terminalis (17), fourth ventricle (33), (Frick et al., 1987, p. 310).*

The CSF circulates from the ventricle system in the cranial and spinal subarachnoid space. From there it permeates into the extracellular fluid along the dural sheath of the central nervous system and finally reaches the microtubules of the fasciae. By this way the CSF comes in contact with the whole body (Liem, 2001; Paoletti, 2001). The largest part of the CSF is reabsorbed by the arachnoid villi of the venous sinus (the venous system of the crane) and redirected to the blood circuit via the jugular vein. A smaller part returns to the blood circuit via the lymphatic fluid from the above mentioned extracellular fluid and the microtubules (see Fig. 20).

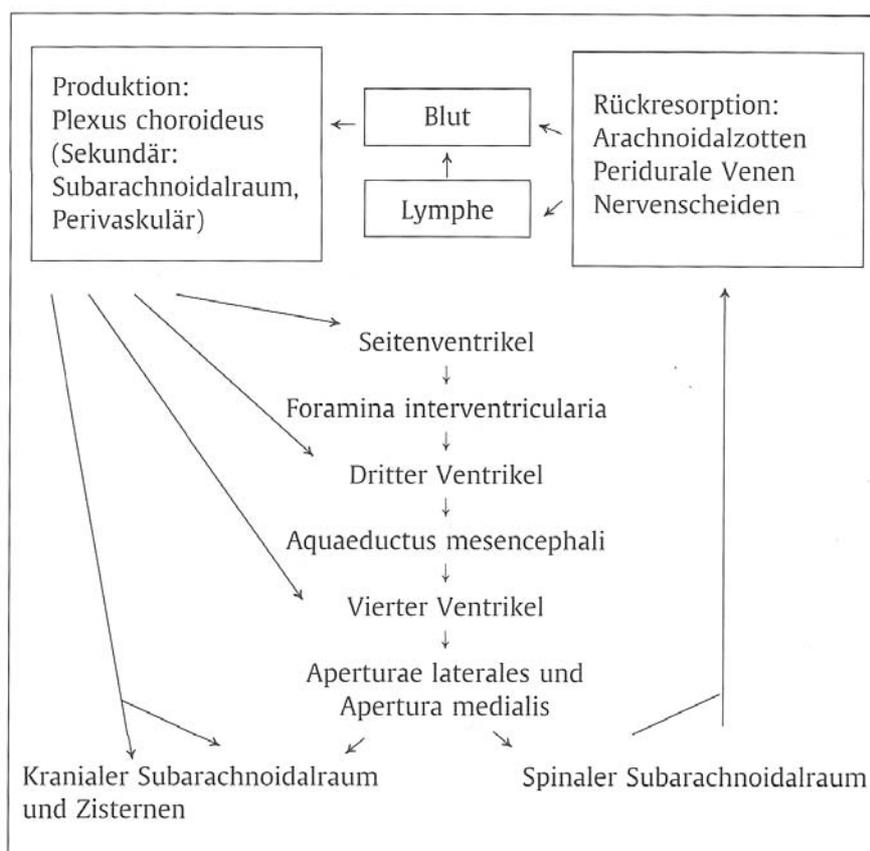


Fig. 20 Schematic view of the pathways the CSF is taking, (Liem, 2001, p. 221).

Liem (2001) reports the following hormonal influences: Corticosteroids enhance the resorption of CSF, oestrogens increase the volume of CSF and glucocorticoids reduce its production. Liem (2001) also describes a vegetative influence since the CSF production is reduced up to 30 % in case of an increased tone of the sympathetic nervous system. The parasympathetic nervous system brings the CSF production back to 100 %.

The interchange between the chemicals of the CSF and the blood occurs at all choroid plexuses. To ensure the chemical interchange and the physiologic function the primary respiratory mechanism has to be free in its action (Sutherland, 1990). The compression of the fourth ventricle (CV4) is one of the recommended techniques to bring the body in homeostasis. It is indicated for endocrine disorders and also used to reduce the activity of the sympathetic nervous system. CV4 increases the intracranial pressure so that the CSF spreads into the smallest pathways encompassing the microtubules of the fasciae and the extra- and intracellular fluid spaces. This leads in general to an enhanced supply of the body cells and improved lymphatic circulation. The biodynamic, bioelectric and biochemical features of the CSF stimulate the entire activity of interchange. In order to treat dysfunctions of the hypothalamic-pituitary system, there is an additional osteopathic technique that compresses the 3<sup>rd</sup> ventricle (CV3) and that may be preferred over the CV4 due to the anatomic conditions (Liem, 2001).

### 5.3.1. The Lymphatic Fluid

Beyond the arachnoidal villi the lymphatic system partly reabsorbs CSF in form of the interstitial fluid. From the peripheral blind endings of the lymphatic system the fluid is transported via the collector vessels to the thoracic duct and the right lymphatic duct which discharge into the subclavian veins. The thoracic duct is the main lymphatic vessel absorbing lymphatic fluid of three quarters of the body, among others of the abdominal viscera, the liver, small intestine, ovaries and adrenal gland. Only the right superior quarter of the body drains via the right lymphatic duct. The thoracic duct runs together with the aorta through the thoracolumbar diaphragm. During respiration the diaphragm exerts a pumping mechanism. In consequence the lymphatic fluid is sucked from the thoracic duct and the right lymphatic duct into the venous angles (Földi and Kubik, 1999). This is an important factor for the lymphatic transport.

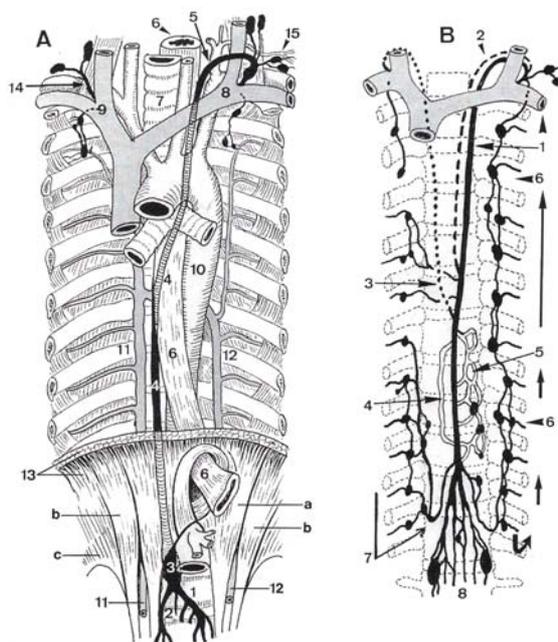


Fig. 21 Topography of the thoracic duct, (Földi and Kubik, 1999, p. 15)

Another transport mechanism of the lymphatic fluid is the arterial pulsation especially effective on the thoracic duct and the deep lymphatic system (Földi and Kubik, 1999). Some authors present techniques to promote the venous and lymphatic drainage such as lymphatic pump and myofascial techniques (Degenhardt and Kuchera, 1996; Lesho, 1999; Liem, 2001). Lesho (1999) criticises that there is no such controlled trial that confirms the effectiveness of lymphatic pump techniques. However, it is widely assumed that this technique improves cellular activity by mobilising fluids and supports removal of metabolic waste. More promising are myofascial techniques since Paoletti (2001) reports that the lymphatic transport happens exactly with the

same frequency as fascial motility, i.e. with a pulse of 10-12 contractions per minute. The lymphatic fluid uses the fasciae as transport medium which is a general way of communication for the different body fluids. Földi and Kubik (1999) underline the importance of the lymphatic system for the functions of the central nervous system, the drainage of which is supported by perineuro-lymphatic and haemangio-lymphatic connections.

Chapman made a completely different observation and detected neurolymphatic reflex points.

These reflex points are located in the lymphatic superficial tissue which has nervous connections to all organs and the ductless glands. Based on these so-called Chapman-reflex points he developed a method of diagnosis and treatment of visceral disease (Magoun Jr, 2007; Monnier, 2004).

#### 5.4. Fascia

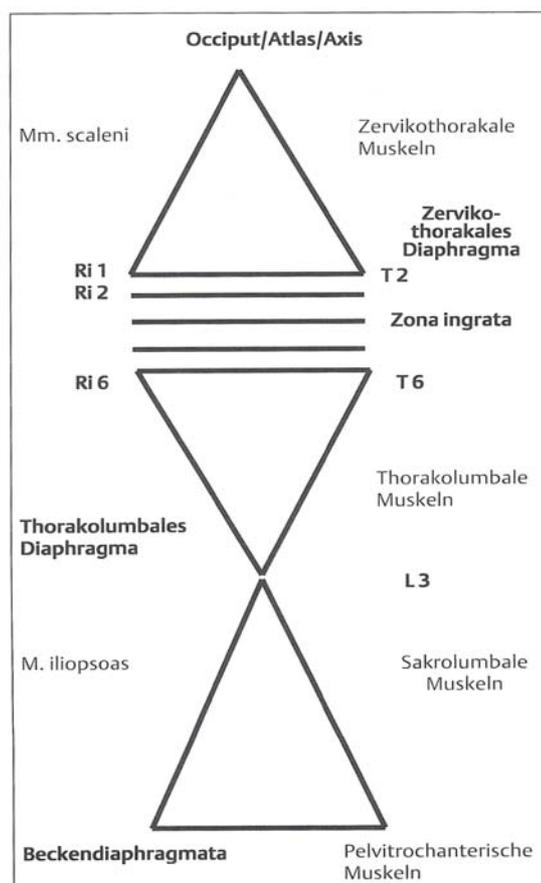
The "fascia gives nourishment to all parts of the body" (Still, 1902e, p. 64, cited by Stark, 2007, p. 280). "By its action we live, by its failure we shrink or swell and die" (Still, 1899g, p. 164, cited by Stark, 2007, p. 280). Both statements of Still reflect his perception of the important role of the fasciae. Still saw a relationship between fasciae and vitality. The pathologies occurring in this scheme are to be solved with the help of fluid flow. This shows how closely the fluidal and fascial concepts are related. In this regard, Still's goal in treatment was to "restore harmony and balanced fluid flow" (Stark, 2007, p. 283).

Fascial dysfunction in the sense of less mobility of the fasciae leads to a reduced cellular metabolism such as diminished cell inspiration, nutrition and elimination. The free flow of intercellular and lymphatic fluids will be hindered, too, in case of fascial dysfunction (Liem, 2001). The fasciae are considered as communication structure between the cerebrospinal fluid, the lymphatic fluid and the plasma of the blood. In the osteopathic point of view, the communication is governed by the primary respiratory rhythm because of its influence on the drainage of the fascial tissue and cells (Liem, 2001). This conjoining property of the fascia is important for the humoral communication of the hormone axis of hypothalamus, pituitary and adrenal cortex, and ovary, respectively.

Neuromuscular imbalance or somatic dysfunction can inhibit fascial motion. The imposed functional restrictions are typically located in the so-called transitional zones (Pope, 2003). The fascial system is mainly built of longitudinal tractions and separated by transversal fascial layers that are the tentorium cerebelli (part of the above mentioned intercranial membranes), the craniocervical (atlanto-occipital), the cervicothoracic, the thoracolumbar diaphragm and the diaphragm pelvis. These transversal diaphragms divide the body in sections, the so-called triangles in Little's model (Liem, 2001). The upper triangle contains lungs and heart, the middle

one the intestinal tract and the lower one the urogenital system. The zona ingrata between the 2<sup>nd</sup> and 6<sup>th</sup> thoracic vertebrae is a relatively rigid zone and absorbs strains from above and below in order to protect the cardiac nervous plexus. The 3<sup>rd</sup> lumbar vertebra has a key position because it is the body's gravity point and connects the middle and lower functional triangles. Furthermore it is connected to the upper triangle by the midriff and to the lower extremities by the iliopsoas muscle. Note that the cisterna chyli is often on a level with the 3<sup>rd</sup> lumbar vertebra so that it presumably effects the lymphatic circulation. The function of the triangles depends on the condition of the diaphragms which in turn are interconnected.

*Fig. 22 The model of the functional triangles is an approach to classify the whole organism according to physiological and structural perspectives. All structures of every triangle are interrelated in a functional, physiological and pathophysiological manner. The diaphragms separate these triangles (Liem, 2001, p. 381).*



In the following the craniocervical, the thoracolumbar and pelvic diaphragm are explained in detail. Liem (2001) describes the atlanto-occipital joint and the atlanto-axial joint as craniocervical diaphragm. "All muscles and fascia which insert on the occiput could constrict and block more or less the cranosacral system if they are in hypertension" (Liem, 2001, p.408). He writes of an indirect endocrinal conjunction of this craniocervical diaphragm to the hypophysis via the sphenobasilar synchondrosis (SBS).

The thoracolumbar diaphragm (midriff) plays an important role for circulation. "Already Still mentioned in 1899 that the midriff could cause more different diseases than every other part of the body in case this

tendomuscular structure has an abnormal tension [...]” (cited Liem, 2001, p. 386). Since aorta, vena cava and ductus thoracicus pass through the midriff, hypertension of the midriff could affect the circulation of blood and lymphatic fluids in detrimental way. This means that the communication of the viscera as ovaries and adrenal cortex with the hypothalamus and the pituitary would be disturbed.

Because of the complexity of the craniosacral system disorders of the hypothalamic-hypophyseal unity could be ascendant lesions of the facial bones, the sacrum and the fascial system. Visceral restriction could be transferred to the SBS via the fascia buccopharyngea and visceral lodge as well as the fascia praevertebralis which have their insertion underside the corpus sphenoidalis, on the tuberculum pharyngeum. These connections are illustrated in the following figure (Fig. 23) of Paoletti (2001).

These manifold structures present large possibilities to interfere with the craniosacral system, the freely moving fasciae and fluids (Liem, 2001).

In consequence, the myofascial techniques support the venous and lymphatic drainage (Lesho, 1999).

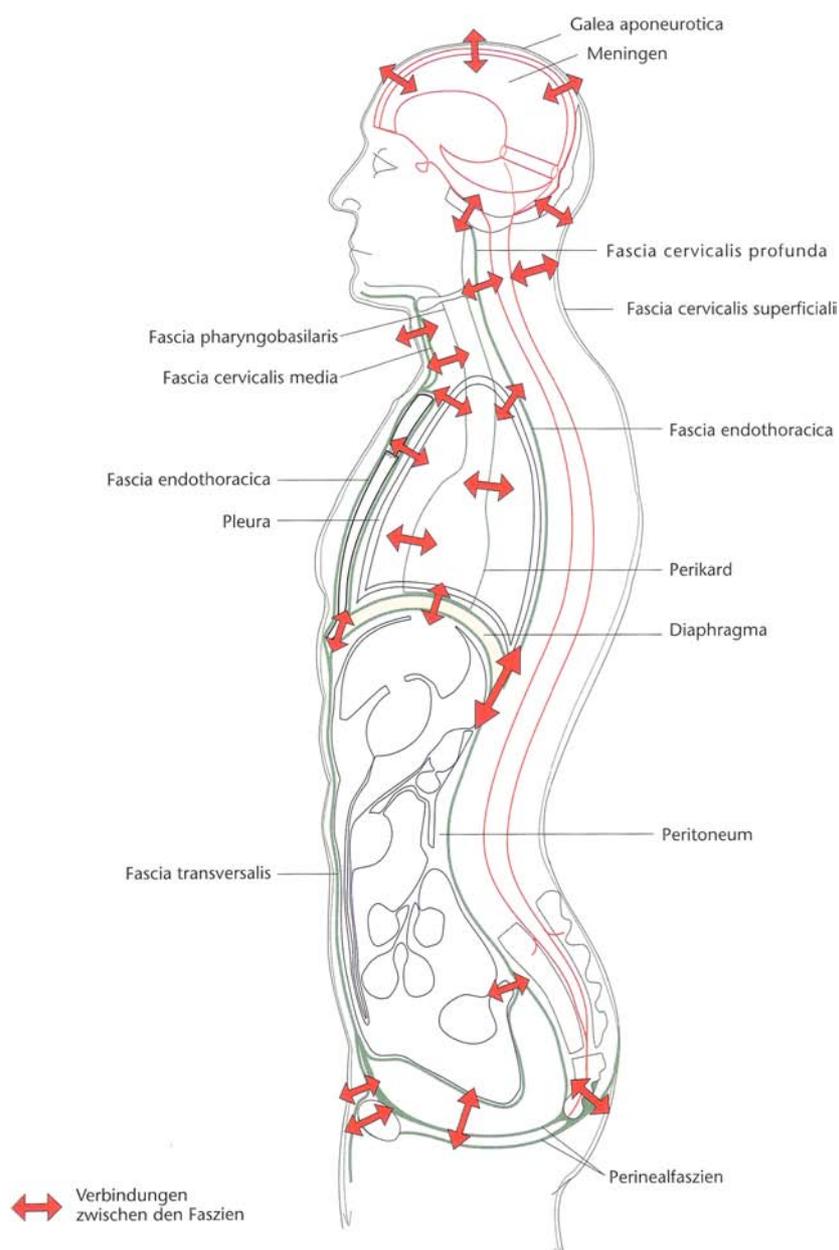


Fig. 23 The fasciae in general and her connections between them (Paoletti, 2001, p. 111)

Finally the pelvic diaphragm and the perineum are of particular importance for the urogenital system and its vasomotor function. Different tensions of the perineum can evoke congestion and a functional change in the pelvic organs (Barral and Mercier, 2005). A hypertension of the pelvic floor can for example limit the mobility of the sacro-coccyx joint. This dysfunction may prolongate to the duramater with the filum terminale as the end that is fixed at the coccyx. Thus, mechanical disturbance of the pelvic floor may directly influence the primary respiratory mechanism, explained in section 5.1 (Barral and Mercier, 2005; Liem, 2001).

### 5.5. Neurophysiologic Mechanisms, Somatic and Visceral Dysfunctions

In order to achieve the goal of balanced fluid flow, A.T. Still used the regulation of bones and viscera (Stark, 2007). The term somatic dysfunction that is defined as palpable pathological change of the tissue texture caused by neuromuscular and visceral pathological processes (Denslow, 2001; Liem and Dobler, 2002). Of note, the visceral dysfunction is equally characterised, as the somatic dysfunction, by a diminished functionality of certain structures (visceral, skeletal, arthrodiagonal and myofascial) and a reduced activity of the connected lymphatic, vascular and neural systems. Because of the close neighbourhood of the spinal vertebrae and the autonomous system via the sympathetic trunk and ganglia, the neuromuscular system is considered as an attributing factor of organic disease that contributes to the imbalance of the homeostatic mechanism of the body. To understand this theory the neurophysiologic mechanisms have to be explained. Periodic pressure or stimulus of afferent somatic and visceral nerves can lead to a spinal segmental facilitation according to Irvin Korr. This is to be understood as an exaggerated excitable state of the spinal cord due to a summation of afferent impulses. In consequence abnormal efferent impulses arrive at muscles via the anterior horn and the peripheral nerves and at blood vessels, perspiratory glands and viscera via the lateral horn and the autonomous nerves (sympathetic and parasympathetic nervous systems). Hence, a visceral dysfunction or pathology is reflected by an aberration in the musculoskeletal tissue texture and the intervertebral joint motion (viscerosomatic reflex). Analogously, a somatic dysfunction can affect organs in general (somatovisceral reflex) (Lesho, 1999; Liem and Dobler, 2002).

In the following the spinal connections of the viscera which are involved in hormone production and elimination are shortly listed according to Schünke et al. (2005).

#### Adrenal gland

- Sympathetic innervation:

Nervi splanchnici major (T5-9) et minor (T10-11)

- Parasympathetic innervation:

Truncus vagalis posterior (mainly built of the nervus vagus dexter)

Both sympathetic and parasympathetic nerves reach the adrenal gland via the renal and suprarenal plexus.

The parasympathetic innervation of the adrenal gland has not been confirmed yet. Functionally it can be seen as a sympathetic ganglion which releases adrenalin and glucocorticoid (cortisol) through neurovascular contacts in stress situations. Therefore, the adrenal gland shows a rich vascularisation.

#### Ovary

- Sympathetic innervation:

Nervi splanchnici minor and imus (T10-12) reach the ovary via ganglia renalia and ganglion mesentericus superius to the plexus ovaricus.

- Parasympathetic innervation:

Nervi splanchnici pelvici (S2-4) and plexus hypogastricus inferior

Liver and gall bladder

- Sympathetic innervation:

Mainly nervus splanchnicus major (T5-9) and celiac ganglia

- Parasympathetic innervation:

Truncus vagalis posterior

Both built together the plexus hepaticus and innervate liver, gall bladder and intra- and extrahepatic biliary tract. The contraction of the gall bladder and so its emptying takes place under the parasympathetic control of the vagus nerve (Barral, 2005).

Intestines

- Sympathetic innervation:

The superior mesenteric plexus consisting of the nervi splanchnici major, minor, imus and lumbales (T5-L2) innervates the entire small intestine and the right part of the colon until the half transverse colon.

The inferior mesenteric plexus built of the nervi splanchnici lumbales (L1-2) innervates the left half of transverse colon, left part of the colon, the sigmoid and upper part of the rectum.

The hypogastric plexus built of the nervi splanchnici lumbales and sacrales (L3-S3) innervates the remaining rectum.

- Parasympathetic innervation:

Analogously, the sympathetic innervation the intestine is also section-wise innervated of the parasympathetic nervous system. The first part of the colon and the entire small intestine is innervated of the truncus vagalis. The remaining intestine is innervated of the nervi splanchnici pelvici (S2-4).

In summary, the truncus vagalis is the main parasympathetic nerve to the viscera. Due to its anatomic run through the foramen jugulare, cervical fasciae and the midriff - all being locations vulnerable to possible entrapment neuropathy - it connects the cranial, fascial and visceral system (Liem and Dobler, 2005; Sutherland, 1990).

## 5.6. Neuroendocrine Mechanism and Emotional Influence

Somatic and visceral as also emotional stimuli can influence the activity of the autonomous, the endocrine and the immune system through the hypothalamus, pituitary and spinal chord (Liem

and Dobler, 2005). Emotions are generated mainly in the limbic system which is directly linked to the hypothalamus. It has been well established by anatomical research, that visceral and somatic fibres are closely connected with brain regions that are involved in emotional behaviour. One of these brain regions is the locus coeruleus that is both connected to the limbic system and the afferent neural fibres coming from the spinal cord. Especially for nociception, the spinal segments play an important role. By chronic stimulation neuroplastic changes take place that may enhance pain perception and lead to further chronification. As also somatosensory stimuli are processed in the spinal cord, both systems (the somatosensory and the nociceptive system) may influence each other. By this interaction clinical phenomena such as hyperalgesia or hyperaesthesia can be explained. The aforementioned limbic structures including the hypothalamus can react differently to the incoming stimuli (somatic, visceral, emotional). Depending on the amount and type of information the limbic and endocrine system can lead to an increased activity of the sympathetic nervous system and to increased activity of the hypothalamus-pituitary-adrenal axis (Liem and Dobler, 2005).

It is notable that nociceptors and proprioceptors are activated by an irritation of articulation, muscles or viscera which leads consequently to facilitation and reduced stimulus threshold (Liem and Dobler, 2005). Changes in the adjacent and segmental tissues are oedema (vascular), pain (neural) and muscles contraction or fibrosis (myofascial). Oedema arise from reduced lymphatic flow which itself depends on myofascial compression (Degenhardt and Kuchera, 1996). This points out the complexity of the body's function mechanisms and confirms A.T. Still's principle of interdependency of structure and function. As soon as only one single structure is impaired or even knocked out, its proper function is also affected and vice versa. Precise examination and particularly evaluation of soft tissue changes determine which specific osteopathic treatment is indicated and to which extent in order to mitigate the patient's suffering and at the best to cure him completely and with lasting effect. We have however to keep in mind that lesions occur without causing clinical abnormality. Denslow could show a decrease of soft tissues abnormalities and increased ease of joint function by manipulative treatment (Denslow, 2001).

### 5.7. Osteopathic Manipulative Treatment and Visceral Manipulations

Osteopathic manipulative therapy (OMT) is not defined as a single technique. It comprises rather 100 techniques and procedures which are distinguished into six major groups: High-velocity techniques with low amplitude (which resemble chiropractic adjustment), muscle energy, counterstrain, myofascial release, craniosacral and lymphatic pump techniques (Lesho, 1999). OMT seems to be a promising approach to influence the somatic dysfunction and its interfering impulses on the hormonal system by changing  $\beta$ -endorphin level. The endogenous opiate  $\beta$ -

endorphin is elevated as cortisol in stress situations and both have an analgetic effect. Because of this fact Breckwoldt presumes stress as causative factor in those women who have both amenorrhoea and increased  $\beta$ -endorphin level. Compare section 2.4. Some studies on the effect of OMT report a significant change in  $\beta$ -endorphin concentration; others do not (McPartland, 2005). In studies of Christian et al. (1988) and of Sandler et al. (1990) no significant change of  $\beta$ -endorphin level could be detected due to OMT. Furthermore Christian et al. (1988) doubt an interrelation of OMT and the hypothalamic-pituitary-adrenal axis. Yet the most recent study seeking for pain markers showed an increased serum level of  $\beta$ -endorphin 24 hours post OMT (Degenhardt et al., 2007). This result confirms the findings of Lesho (1999) who discovered not only an effect of OMT on the nociceptors but also an enhanced release of  $\beta$ -endorphin. Indeed, more studies are needed to clarify the biochemical effect of OMT (Degenhardt et al., 2007; McPartland, 2005). To conclude, the effect of OMT on the  $\beta$ -endorphin level is discussed differently, but, if there is an effect, then it is the increased release of  $\beta$ -endorphins under OMT. It remains questionable if OMT can have a throttling effect on the release of  $\beta$ -endorphins in case of elevated  $\beta$ -endorphin level, i.e. if OMT may influence the hormone level in case of hormonal infertility.

There are no controlled trials available which evaluate the different effect of various osteopathic manipulative techniques (high velocity thrust, counterstrain, myofascial release, general osteopathic treatment, craniosacral treatment) on the autonomous nerves system. Sutherland (1990) refers to the response of the sympathetic nervous system, through the lateral chain ganglia, to correction of strains between vertebrae and ribs. I personally presume a high velocity thrust e.g. on a costovertebral joint to stimulate the sympathetic nervous system and, in contrast, a cranial technique e.g. a compression of the fourth ventricle to calm the sympathetic nervous system. Liem (2001) reports that the compression of the fourth ventricle is originally a technique to reduce the craniosacral rhythm, but that nowadays a more regulating homeostatic effect is assumed.

Furthermore, in case of hormonal fertility dysfunctions, Barral states a restriction of the cervical spine and assigns this to the hypothalamic-pituitary axis (Barral and Mercier, 2005). This implies that an OMT of the cervical spine could influence the hypothalamic-pituitary hormone system. Yet a proof remains to be given.

In addition to the OMT visceral manipulations are available to the osteopath to influence the physiology or with A.T. Still's words: "to restore harmony and balanced fluid flow" (Stark, 2007, p. 283). Treatment of the viscera is indicated in case of restrictions of organs and connected structures, scars and insufficient vascularisation. For a physiologic balance and harmonic function all organs

and, of course, the surrounding structures have to be free in motion (Barral and Mercier, 2005). Due to the presumably vascular effect of visceral manipulations I suppose a similar effect on the hormone circulation and thus a better communication in the axis of hypothalamus-pituitary-ovary respectively -adrenal axis. Even Barral, who is the most known visceral researcher and an expert on this field, could not prove an effect of visceral urogenital manipulation on the hypothalamus-pituitary axis.

The relevant anatomical connections of the viscera are highlighted in the ensuing section according to Barral and Mercier (2005) and Schünke et al. (2005). Possible treatment of the respective organs will also be reflected.

The ovaries can move relatively freely because they are not hold by the visceral peritoneum. Their mobility is only limited by the suspending ligaments: ligamentum suspensorium and ligamentum ovarium proprium. The former connects the ovary to the lumbar fascia, the latter to the uterus. It is worth mentioning the anatomic run of the ovarian artery, which reaches the ovary along the ligamentum suspensorium, and the different drainage of right and left ovarian vein. The right ovarian drains directly in the inferior vena cava whereas the left one goes the way around the left renal vein. The drainage of the left kidney and the left ovary can be impaired by a constriction of the left renal vein through the superior mesenteric artery. This fact is associated with the fact that more cysts are found on the left than on the right ovary. Concerning the possible techniques to improve the mobility of the ovaries Barral and Mercier recommended an indirect mobilisation via the mobilisation of the uterus.

The uterus is horizontally suspended in the pelvic area through the ligamenta lata to the ilea, in the vertical direction through the ligamenta teres uteri to the labia majores and in the sagittal direction through the sacro-recto-utero-vesico-pubical ligaments. The latter do not only connect the uterus but also the peritoneum to the urinary bladder which does not allow an independent treatment of either organ. Between the two layers of the ligamenta lata is the parametrium that contains adipose and connecting tissues, the ureter and the uterine artery and vein. Due to its dependence on the different filling states of the bladder and rectum the uterus is a rather mobile organ. Its free motion upward, rotation and side bending should be confirmed through osteopathic testing. Of advantage here, the female urogenital suspension system contains fibromuscular ligaments which are contractile as the pelvic floor. Thus treatment is effective in case of restriction because a muscle relaxes more easily than a ligament. If necessary the adjacent organs (sigmoid, caecum, bladder) and other structures such as the pelvic floor and coccyx have to be mobilised.

The adrenal gland which, placed in a fascial lodge above the kidneys and under the diaphragm, have to follow the diaphragmatic movement. The amplitude of normal breathing ranges between

3 and 4 cm. The posterior renal fascia adheres to the ventral side of the spine. The anterior renal fascia is closely connected with the Toldt-fascia, the fascia of the ascendant and descendent colon. The inferior end of the renal fascia is loose which allows the kidney a relative mobility. A pathological downward glide of the kidney is denoted nephroptosis. "Typically the capsule of the adrenal gland stays unchanged on the same place" (Barral, 2005, p.169). This fact can be explained by the existence of a horizontal separating fascial layer between kidney and adrenal gland. It has not been proven yet if a nephroptosis can influence the adrenal gland's function. Barral (2005) employed pyelography to investigate whether an ectopic kidney is not only in an unusual position but also restricted in its mobility. He could influence the mobility of the kidney by osteopathic manipulation of the ectopic kidney but not the position. That leads to the concept that the mobility of an organ is much more important than its position. However, no information is published on sample size and the way how mobility is quantified. It can be concluded that visceral osteopathic treatment has an apparently hypothetic influence on the function of an organ such as the elimination of hormones within the kidney (compare also sections 2.1.1 and 2.4.1).

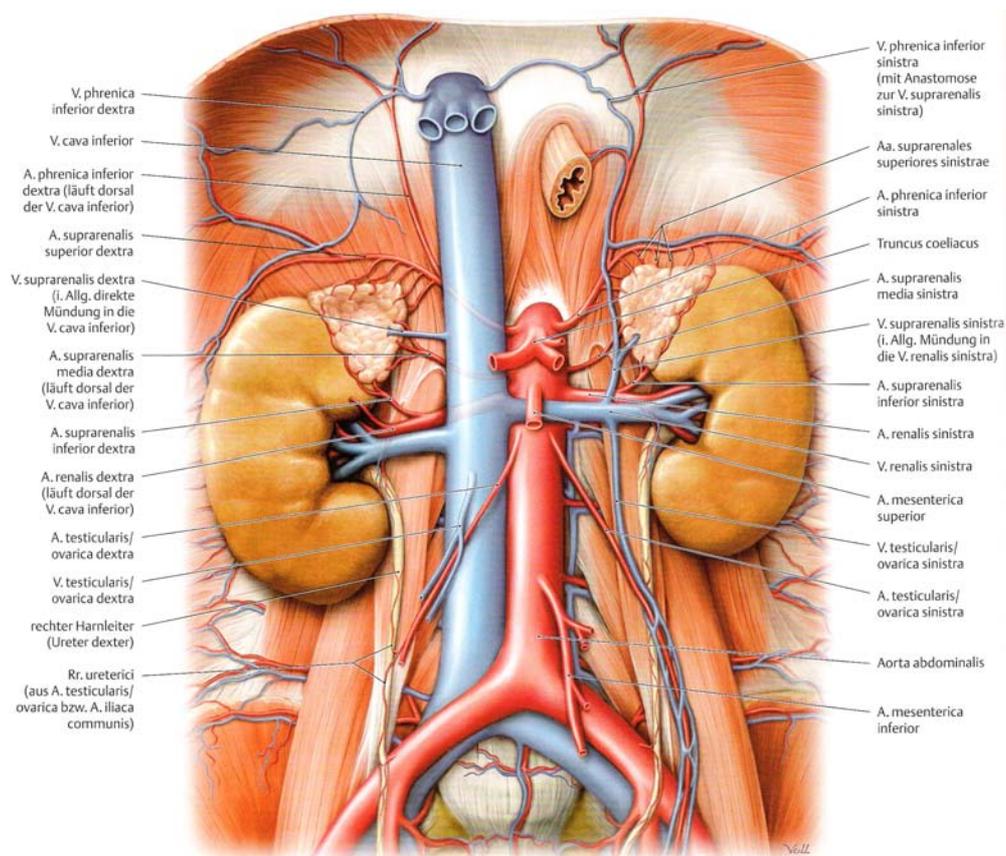


Fig. 24 Adrenal gland (Prometheus, 2005, p. 280). Beyond the vascularisation of the kidneys and the adrenal gland, the disadvantageous anatomical situation for the venous drainage of the left ovary is illustrated.

Coming back to the adrenal gland I suggest to achieve a possible change in its mobility and vascularisation and thus a modified neuroendocrine function through the following osteopathic

techniques: myofascial treatment of the renal and Toldt fascia, visceral manipulation of the caecum and the ascending colon on the right side as well as sigmoid and descending colon on left side, visceral manipulation of the kidney's slide face onto the psoas muscle, counterstrain technique of the surrounding muscles psoas, quadratus lumborum and midriff, and finally mobilisation of restricted intervertebral joints to exploit the somatovisceral and somatosomatic reflex. The motility of the kidney could be affected by the neuroreflective mechanism which is related to the 6<sup>th</sup> and 7<sup>th</sup> thoracic vertebrae and the 1<sup>st</sup> and 2<sup>nd</sup> lumbar vertebrae according to Barral (2005).

The liver inactivates the hormones through reduction and conjugation to sulphates and glucuronic acid so that its activity is increased after ovulation in the second half of the female cycle. Due to its anatomical integration the liver is connected to almost every other organ and the musculoskeletal system: The hepatorenal ligament leads to the right kidney, the tight hepatoduodenal ligament leads to the upper duodenum, the right colon flexure and the omentum majus, and the thin hepatogastric ligament leads to the stomach. The latter ones are part of the omentum minus. Via the falciform ligament, which runs to the umbilicus and continues as vesicoumbilical ligament, the liver is indirectly connected to the bladder and the uterus. The coronary ligament on the backside of the liver cranially adheres on the midriff and via its lateral ends, the so-called triangular ligaments on the left and on the right side of the midriff. The coronary and triangular ligaments as well as the capsule of the liver are innervated by the phrenic nerve which is linked to the cervical spine and the shoulder.

Restrictions of the 4<sup>th</sup> and 5<sup>th</sup> cervical and the 9<sup>th</sup> thoracic vertebra have therefore been associated with liver problems (Barral and Mercier, 2005). Later on, the association can be extended to the 7<sup>th</sup> with 10<sup>th</sup> thoracic vertebra (compare 2<sup>nd</sup> volume on visceral osteopathy of Barral, 2005). The viscerosomatic projection of the liver onto the right shoulder is given by a branch of the phrenic nerve.

The gall bladder, the biliary tract and the sphincter oddi should be tested on their mobility and tension because these structures are responsible for the further removal of the metabolised hormones out of the liver. The aim of osteopathic treatment is to mobilise this region in order to improve possibly the circulation of blood, lymphatic fluid and bile, thus the elimination of steroids could be stimulated and the level of testosterone would decrease. This means to achieve satisfactory mobility of the liver-gall bladder-duodenum-complex and the normal tension on the sphincter oddi where the hepatocystic duct enters the duodenum. By means of contrast enhanced X-ray, Barral and Mercier (2005) could prove an increase of bile flow subsequent to visceral manipulation of the gall bladder and the biliary tract. Yet they could not prove objectively an increased metabolism of the liver.

The small intestine is parted into the following sections: Duodenum, jejunum and ileum. Relevant anatomical connections are the omentum minus, i.e. a part of the peritoneum which interconnects the upper part of the duodenum, the liver, the gall bladder, the pylorus and the stomach. It additionally attaches the duodenum to the posterior abdominal wall where the peritoneum itself is relatively strongly attached to the spine. In this part of the body restrictions of the spine could possibly impair the mobility of the duodenum.

Another structure that belongs to the small intestine and is called the muscle or ligament of Treitz prolongates from the duodenojejunal flexure to the left dome of the midriff. The function of this muscle is unclear, but the muscle seems to be a relict of the ancient times when man moved on all fours. Probably it kept the duodenojejunal flexure in position. According to Barral and Mercier (2005) strains and sphincter-like rotations of the Treitz's muscle are often found by palpation.

In the context of the small intestine, also the mesentery represents a structure relevant for osteopathic treatment. On the one hand it attaches the entire small intestine on the posterior abdominal wall from the caecum to the second lumbar vertebra. On the other hand the blood vessels for the arterial and the venous supply of the entire small intestine run between both layers of the mesentery. This underlines the importance of visceral manipulations which could improve the fluidal circulation and reduce spasm of sphincters or intestinal wall (Barral and Mercier, 2005). A visceral technique to free the mesentery might have at least an effect on the functionality of the small intestine. This is enabled by the neural fibres of the plexus mesenteric superior which are not only associated with the artery mesenteric superior but also with the functionality of the small intestine (Liem and Dobler, 2002). Moreover, pathological fixations of the duodenum can affect the skeletal system, mostly the 7<sup>th</sup> and 12<sup>th</sup> thoracic vertebrae, and the 1<sup>st</sup> lumbar vertebra (Barral and Mercier, 2005). However, according to Barral and Mercier (2005), fixations of the jejunum and ileum are reflected by limited mobility and/or pain of the 10<sup>th</sup> thoracic to the 2<sup>nd</sup> lumbar vertebra.

## 6. METHODS

In order to be able to approach the topics hyperandrogenaemia and infertility from an osteopathic point of view I gave first an overview of the physiology with respect to the hormonal system, its interaction and regulation (chapter 1). Therefore I studied common textbooks such as Klinker and Silbernagel (1996), Frick et al. (1987), Schünke et al. (2005), Breckwoldt et al. (1994). Chapter 2 lists all pathologies that are related to hyperandrogenaemia and infertility. The information given is gathered from the mentioned literature as well as from the textbooks of Raabe (1994), Kaiser and Leidenberger (1996) and published studies. For the literature search in the database pubmed the keywords used were: Hyperandrogenaemia, hirsutism, acne, polycystic ovary syndrome, infertility. Chapter 3 resumes the actual conventional treatment of hyperandrogenaemia and infertility. Further keywords used for the literature research in pubmed were treatment, medicamentous. On this basis I sought for literature on how osteopathy approaches to hyperandrogenaemia and infertility (chapter 4). Under the keywords osteopathy, hyperandrogenaemia and infertility there were no studies available in pubmed. In the osteopathic research database I found two studies to unexplained infertility (Kapper, 2006; Kirchmayr, 2006) but none to hormonal caused infertility. Yet, in the internal database of the European School of Osteopathy (ESO) I could find two studies approaching to infertility within the framework of a bachelor thesis. Mouterde aimed to "to discuss various causes of female infertility amenable to osteopathy and provide a rationale for infertility treatment" (Mouterde, 2001, p. 3). Due to a lack of published studies she was forced to limit her project to empirical findings of experienced osteopaths. Data were collected by interview; no documentation was added. Her work gives a general summary of possible anatomical structures related to the reproductive system and an idea of some osteopathic techniques to treat infertility. The statements and conclusions given are rarely corroborated by literature. The second study of an ESO student represents a paramedical approach to infertility (Monnier, 2004). This work provides a good review on paramedical treatments comprising osteopathy and further approaches such as acupuncture. Monnier concentrates on an osteopathic approach of unexplained infertility with regard to possible mechanical causes.

Moreover, the osteopathic research database contains a gynaecological study of Riepler-Reisecker (2007) on dysmenorrhoea and menstrual disorders. Also, one osteopathic study deals with the metabolic system on the example of diabetes (Kiegerl, 2006).

There are no osteopathic studies to other topics concerning the hormonal system, e.g. hyperthyroidism, In addition to these specific publications a variety of general osteopathic textbooks were consulted (Barral and Mercier, 2005; Paoletti, 2001; Liem, 2001; Sutherland, 1990; Magoun, 1976; Stark, 1990; Földi, 1999). Of note, the literature basis PubMed that above all

provides articles originating from classical medicine contains also a few publications on osteopathic treatments applied to other pathological phenomena than hyperandrogenaemia, e.g. on the effectiveness of OMT on nociception.

The literature research was thought to be complemented by an additional clinical trial of within-subject design. This allows for control of the dependent variables on the individual itself by repeated measurements. Also a control group is not compulsory which anyway would be hard to justify from an ethical point of view in the case of infertility. However, the acquisition of patients with hyperandrogenaemia and/or infertility turned out to be more difficult than anticipated. First of all, the resulting sample does only consist of hyperandrogenaemic women. Furthermore, due to the limited time of conducting this study and due to the marginal number of acquirable subjects the intended inclusion criteria had to be relaxed (see below). For example, no reference value is available for one of the subjects, resulting in a total of three subjects with hyperandrogenaemia. I am very well aware that any results gained from this small sample cannot be generalised and that I am rather elucidating a series of individual cases.

In detail, the patients are characterised by the following inclusion and exclusion criteria:

Inclusion criteria:

- sane women of reproductive age between 18 and 45
- hyperandrogenaemia

Exclusion criteria:

- mental disorders
- hypo- or hyperthyroidism
- hyperprolactinaemia
- pituitary adenoma
- chromosomal syndromes: turner 45X, androgen insensitivity 46XY
- weight (BMI < 19) or exercises related amenorrhoea (physiologically reduced GnRH)

It should be pointed out that the frequently made diagnosis of combined PCOS and hyperandrogenaemia does not represent an exclusion criterion. Furthermore, amenorrhoea and oligomenorrhoea that can be caused by a disturbed feedback-control of the hypothalamic-hypophyseal-ovary system (Kaiser and Leidenberger, 1996) are not considered as exclusion criterion either. A pathologically increased prolactin level does certainly represent an exclusion criterion, but was not assessed due to its rare prevalence and because of avoiding additional costs. Besides, hyperprolactinaemia is partly excluded in the case of simultaneous hyperthyroidism.

The study design is as follows: An observation period, free of any treatment, guarantees the lasting of the hormonal levels. The observation period was followed by six treatments in intervals of two weeks. Due to the summer holidays that overlapped with the study period the treatment distance of two week could not always be maintained. Two of the patients were one time treated after three instead of two weeks.

Osteopathic treatment was practised by myself. It included all osteopathic techniques I am familiar with and which were taught of different osteopaths at the international Vienna School of Osteopathy: Structural, parietal, muscle energy, visceral and cranial techniques.

For objective control blood samples are taken to measure the hormonal levels (LH, FSH and testosterone) before and after the observation period as well as after the third and the last treatment. The LH-FSH-ratio is relevant to diagnose hyperandrogenaemia as LH should not be more than twice as high as FSH in a healthy woman. This ratio is considered to be cycle independent and, hence, proves also suitable as diagnosis tool if cycles are irregular and/or without ovulation. Yet the concentration of testosterone is still the most important and robust parameter to diagnose hyperandrogenaemia.

On a separated documentation sheet the cooperating doctor was asked to report hormone values, in- and exclusion criteria as well as the medical history of every patient.

Subjective perception of the own present complaints and the history of present complaints was assessed by a survey together with questions on the general past medical history and inclusion/exclusion criteria. Based on the questionnaire of Astrid Kapper and the questionnaires of the emergency hospital Heidelberg modified by Leidenberger (Rabe et al., 1992), I created an extended questionnaire (see appendix) in order to assess the homogeneity of the sample.

The first questionnaire was collected at the beginning of the study. It comprises 33 questions about in- and exclusion criteria (9,10), health in general (1,22-24,30,31), stress level (11,12), hirsutism and acne (18-21), and general past medical history with a particular focus on gynaecology (2-8,13-17,25-29,32,33). The influence of stress on the reproduction is shown in section 2.3 (Negro-Vilar, 1993). The questions concerning lifestyle are of particular interest since Barbieri (2001) reviewed its potential impact on fertility. He reports that a consumption of more than four alcoholic drinks weekly, more than 250 mg caffeine daily and smoking cigarettes are associated with decreased fertility (Barbieri, 2001). Balanced and healthy nourishment supports the self healing mechanisms of the body. This was already one of the main statements of early osteopaths concerning their treatment (Magoun Jr, 2007).

The second questionnaire comprises 14 questions that were posed to the participants at the end of the study. Different aspects of the state of health (1,4,9,10,11,12), stress level (2,3), hirsutism and acne (6-8), gynaecological changes (5) and own profits of the therapy (13) were covered.

## 7. OUTCOME

### 7.1. Summary of the Questionnaires according to Tabelle 3

Included subjects were women aged 30, 32, and 44 years that reported to be generally healthy. None of them was infertile according to the WHO's definition. Two were already mother of two children (S2, S3). Their BMI ranged between 19 and 25. Endocrinological and obstetrics history revealed that two women suffered from acne like skin changes, one of them showed hirsutism in addition. S1 had been treated with hormonal medication for her skin problems until two years before. None of the three subjects showed signs of alopecia. None of them showed sign of galactorrhoea or others signs of hyperprolactinaemia. One woman (S3) had been treated for hypopituitarism that had clinically appeared as primary amenorrhoea 28 years before. S1 and S2 complaint about menstrual abdominal pain and urogenital inflammation of the vagina (S1 and S2) and of the kidneys (S1) in the past. All of them had no physical trauma or relevant surgery. All subjects complained about pain in various skeletal regions of the spine or pelvic area.

All of them were non-smokers, consumed alcohol and caffeine in a reasonable amount and reported balanced nourishment. None of them suffered from allergies or food incompatibilities. S3 reported an extraordinary healthy way of living with no alcohol or caffeine consumption and optimal nourishment. All included subjects were medication free. With regard to sportive activity, only S2 reported to do cycling on a regular basis.

Two of the subjects reported of high stress levels in professional life (S1) and private life (S3).

With respect to the cranial concept (section 4.1) and the idea that the pituitary can be possibly influenced by the facial bones maxilla and vomer, subjects were asked for relevant problems of teeth or the temporomandibular joint. All subjects reported having none of these problems. The wisdom teeth of S1 were extracted in March and April 2007. The left upper wisdom tooth of S3 was extracted in January 2007; the other wisdom teeth were extracted in 1996, 2002 and 2006. S2 has not any tooth extraction.

After the osteopathic treatment, all subjects reported that they had a benefit from it and that they would generally recommend this type of treatment to others.

Question 1-31	Content	Subject 1 (S1)	Subject 2 (S2)	Subject 3 (S3)
	reason for consultation	child wish since 4 month, acne	amenorrhoea since 4 month	acne, hirsutism
	age	30	44	32
	BMI	25	19	22
	profession	nurse	medical secretary	office clerk
1	general state of health	average / <i>good</i>	good / <i>good</i>	good / <i>good</i>
2	nicotin	former smoker	no	no
3	alcohol	1-3x/week	1-3x/week	no
4	coffee	2 cups/day	2 cups/day	no
5	food stuffs	all	all	all
6	balanced nourishment	average	average	perfectly balanced
7	allergies/ incompatibilities	no	no	no
8	relevant weight changes	no	yes (3 kg in 2 month)	no
9	regular sport	no	yes (cycling 3-4x/week)	no
10	stress in profession	average / <i>high</i>	low / <i>low</i>	average / <i>average</i>
11	stress in privat life	low / <i>low</i>	high / <i>high</i>	average / <i>average</i>
12	medicaments at present	no / <i>no</i>	no / <i>no</i>	no / <i>no</i>
13	medicaments in the last 5 years	homoeopathy, pill till 2 years ago	no	no
14	contraceptive hitherto	mechanical since 2 years	hormonal until 01/2007	mechanical
15	menarche at the age of	14	16 ½. (hormonally induced due to hypopituitarism)	11
16	regular cycle	yes, 28 days / <i>unchanged</i>	no, since 01/2007 / <i>yes, 28 days</i>	yes, 26-28 days / <i>unchanged</i>
17	hormonal treatment due to irregular cycle	no	yes (induction of menarche)	no
18	skin problems	yes, acne, unctuous / <i>unchanged</i>	no / <i>no</i>	yes, unctuous / <i>unchanged</i>

19	hormonal treatment for skin	yes	no	no
20	hirsutism	abdomen / <i>unchanged</i>	no / <i>no</i>	chin, upper lip, breast, abdomen / <i>unchanged</i>
21	alopecia	no / <i>no</i>	no / <i>no</i>	no / <i>no</i>
22	problems of breathing of circulation of assimilation of elimination	no / <i>no</i> cold feet / <i>unchanged</i> pyrosis, flatulence / <i>no</i> obstipation / <i>unchanged</i>	no / <i>no</i> no / <i>no</i> flatulence / <i>no</i> no / <i>no</i>	no / <i>no</i> no / <i>no</i> no / <i>no</i> no / <i>no</i>
23	headache depression other diseases	yes / <i>no</i> no / <i>no</i> no / <i>no</i>	no / <i>no</i> no / <i>no</i> no / <i>no</i>	no / <i>yes, at times</i> no / <i>no</i> yes, kidney / <i>no</i>
24	serious diseases	no	no	yes, meningitis at age 6 months
25	inflammation urogenital	vagina, kidney	no	vagina
26	operations urogenital	no	no	no
27	operations elsewhere	no	yes, tonsillectomy	no
28	trauma	no	psychic (son was struck by a lorry)	no
29	abdominal pain	menstrual pain / <i>unchanged</i>	menstrual pain / <i>unchanged</i>	no / <i>no</i>
30	vertebral pain	thoracic spine, coccyx / <i>no</i>	cervical, thoracic, lumbar / <i>thoracic, lumbar, sacrum,</i> <i>coccyx</i>	cervical spine, sacrum / <i>cervical spine</i>
31	osteopathic treatment in the last 2 years	yes	no	no

*Tab. 3* This table summarises both questionnaires given at the beginning and the end of the study. It contains questions and answers of the three subjects to their past and present history in general and in obstetrics as well as to their life style. Not all questions were demanded twice. Answers to those, which were asked a second time at the end of the study, are pointed out italic and bold.

## 7.2. Results of Medical Documentation and Hormonal Measurements

According to the obstetric none of the patients had hypo/hyperthyroidism, hyperprolactinaemia, pituitary adenoma or chromosomal syndromes.

Importantly, none of the subjects showed polycystic ovaries in the sonography which are commonly related to hyperandrogenaemia.

Two of the women had born each two children (S2 and S3) and one woman had not been pregnant before (S1).

Hormonal levels (LH, FSH, testosterone) before, during and after osteopathic treatments are detailed in Tab. 4.

In brief, all women showed an increased testosterone levels ( $> 0.78$ ) shortly before osteopathic intervention. In two of them, according to file review, testosterone levels had already been elevated one year (S3) and two years (S1) earlier, suggesting longstanding hyperandrogenaemia. In one subject no information on previous testosterone levels could be obtained. After three treatment sessions two of three patients showed nominally lower testosterone levels, one subject had a slightly increased level (S1). After further three sessions of osteopathic treatment one woman showed a stable normal value (S2), one woman showed a re-increased abnormal level (S3), and one woman showed a highly increased level but has become pregnant.

The LH-FSH-ratio was normal ( $<2$ ) thru out all measurements in two patients. Only in subject 3 the LH-FSH-ratio was abnormally high (3.4), and normalised after three treatment and remained normal after further three treatments. It should be noted that the same patient had shown normal LH-FSH-ratio two years before.

TSH values were normal in all subjects at the beginning of the study, suggesting normal thyroid function.

subject	S1	S2	S3
date of 1st measurement	24.05.2006	-	06.04.2005
LH	2.92	-	5.29
FSH	4.2	-	4.3
LH-FSH-ratio	0.7	-	1.23
testosterone	1.18	-	1.34
→ no treatment	→ no treatment	→ no treatment	→ no treatment
date of 2nd measurement	20.03.2007	10.04.2007	28.03.2007
LH	1.78	18.33	7.45
FSH	4.9	11.8	2.2
LH-FSH-ratio	0.4	1.5	3.4
testosterone	0.93	1.17	1.09
TSH	1.17	2.44	2.37
→ 3 treatments every 2 weeks	→ 3 treatments every 2 weeks	→ 3 treatments every 2 weeks	→ 3 treatments every 2 weeks
date of 3 <sup>rd</sup> measurement	06.06.2007	06.06.2007	20.06.2007
LH	2.66	9.62	2.73
FSH	3.9	11.2	2.9
LH-FSH-ratio	0.7	0.9	0.9
testosterone	0.97	0.4	0.82
→ 3 treatments every 2-3 weeks	→ 3 treatments every 2-3 weeks	→ 3 treatments every 2-3 weeks	→ 3 treatments every 2-3 weeks
date of 4 <sup>th</sup> measurement	31.07.2007	18.08.2007	09.08.2007
LH	0.22	6.57	4.07
FSH	21.0	6.1	2.8
LH-FSH-ratio	0.01	1.1	1.4
testosterone	1.97	0.29	1.20

*Tab. 4* This table lists dates and values (LH, FSH, testosterone and TSH) of measurement according to Dr. Stagg's documentation. The LH-FSH-ratio is calculated. Increased values are pointed out bold.

## 8. DISCUSSION

### 8.1. Problems in Patient Recruitment

A larger study group would have been desirable for sufficient power of statistical analysis. The recruitment of patients proved to be an unexpected difficulty in the practice of the cooperating gynaecologist Dr. Staggl. First, the open-mindedness to possible alternative treatments and the willingness of the concerned women to cooperate was unexpectedly low. Further local gynaecologists could not be convinced to participate on the study by either selecting women or controlling and analysing their blood values.

For this reason, Dr. Staggl browsed his data bank for women formerly suffering from hyperandrogenaemia and undergoing classical hormonal therapy. These 72 women represented potential patients, but only 10 were willing to participate on the study in case that their values (testosterone, LH, FSH) were still pathologic. Yet, the blood values of the willing women have declined to the norm until the beginning of the study. Regrettable, effectiveness of the medical to osteopathic treatment cannot be compared due to the obvious difference of number and date of the measurements. In brief, 5 of these 10 women, aged between 23 and 44 years, had acne; one suffered additionally alopecia. The other 5 women had problems to conceive. One of these women showed increased testosterone value after 1½ years under metformin treatment, but normal value 8 month later when she terminated her child wish. Another woman refused medicamentous therapy. Interestingly, she showed normal testosterone value after 3 years when she had terminated the child wish. According to Dr. Staggl this fact can presumably be explained by a stress relaxation because of fulfilled desire for children and therefore by the self-regulation of the hormonal level. A similar high impact of various psychic factors is recognised by Sonino et al. (2007) who propose to change from a solely biomedical treatment to a more psychosomatic approach in order to achieve more effectiveness in endocrinology.

A general issue in conducting clinical studies is the financing.

### 8.2. Quality of Osteopathic Treatment

Concerning the quality of osteopathic treatment, experience is a substantial factor. As a relative novice, I am still not trained sufficiently in all suitable techniques for treating hormonal disturbances, e.g. compression of the fourth ventricle. Even worse, I am not at all familiar with some of the possible relevant techniques, e.g. compression of the third ventricle. An immediate consequence is a reduced comparability to other scientific studies as, for instance, the work of Riepler-Reisecker (2007). An option would have been to employ an experienced osteopath. Yet, in general, examination and palpation of a patient, evaluation of the findings and performance of

the techniques depend on the daily condition of the practitioner. All these factors form the individual way of treating and determine, of course, the perfection and effectiveness of a treatment.

### 8.3. Methodology of the Series of Case Studies

To control for or even to reduce possible confounders, it is desirable that a single practitioner is employed and that this person is not the study conductor. This intention follows the concept of "blinding" and aims at increased objectivity. Also, it is important to constrain the number of treating persons because treating approach and strategy differs from osteopath to osteopath.

One subjective factor that is immanent to osteopathy and cannot be negated is the individual assessment of how and whether the treatment worked (Liem and Dobler, 2002). This is reported to the study conductor.

Standardisation of treatment and schematic therapy are contrary to the osteopathic philosophy that each person should be treated individually. However, it is paramount to guarantee a certain amount of standardisation in testing and mobilising possibly affected structures of the hormonal system. In this sense the osteopathic approach to hyperandrogenaemia, as described in chapter 5, should involve the examination and treatment of SSB, membranes and fluids that are responsible for the vascularisation of the brain. Examination and/or treatment of the diaphragms should be performed to guarantee a free fluctuation of all fluids and thus a free communication between brain, endocrine glands and elimination organs. Of particular importance is the mobility of those viscera (kidney, liver, gall bladder and intestine) that are related to the metabolism of hormones. A visceral technique to free the mesentery would have at least an effect on the functionality of the small intestine. This is enabled by the neural fibres of the plexus mesenteric superior which are not only associated with the artery mesenteric superior but also with the functionality of the small intestine (Liem and Dobler, 2002). Furthermore, the free mobility of the spine should be examined due to the possible influence of viscerosomatic and somatic-visceral reflexes, respectively. Finally a CV3 or CV4 treating part can be recommended to balance the hormonal system in general, e.g. to finalise the treatment session as in Riepler-Reisecker (2007). A treatment with a similar and predetermined design may improve the quality of the study. Sympathy between patient and osteopath plays a minor but not neglectable role for the overall success of the treatment.

### 8.4. Blood Samples and Confounding Effects of Hormones

Furthermore it would have been desirable if a larger number of hormones were tested. To specify which organ causes the elevated testosterone level, it would have been necessary to analyse the

concentration of the pre-stages of testosterone: dehydroepiandrosterone (DHEA) and androstenedione (adrenal) and oestradiol (ovary follicle). The sex hormone binding globulin (SHBG) and the free testosterone are other specific parameters. SHBG is regarded as the best marker of a person's androgen status. It is considered more sensitive than total testosterone since only the unbound free testosterone can exert its effects. A measuring of the free testosterone level would go beyond the scope of this study due to the associated high laboratory costs. However, the measuring of the SHBG level would have represented a reasonable, additional measurement since "SHBG is thought to be an indirect measure of androgenicity" (Haffner, S.M., 2000, p.56). This way the ratio of total testosterone to SHBG can be determined and thus the free testosterone level can be estimated. The empirical equation to assess free testosterone (Ly and Handelsman, 2005) yields results that are as satisfying as the ones gained with the laboratory reference method. Therefore it represents a valid and reliable alternative to the golden standard. In comparison to other calculation methods such as the so-called free androgen index (FAI) deviate systematically from the laboratory free testosterone level (Ly and Handelsman, 2005). Furthermore the concentration of GnRH would give information about a possible dysfunction of the hypothalamic-hypophyseal system. Yet, to keep the costs low, these parameters were not measured.

The significance of the blood values of the hormones have to be seen critical since hormones undergo a certain dynamic of secretion as explained in section 2.1.1. A single hormone value in the plasma will therefore be only significant if the conditions of the blood collection such as the time of the day are known. That is why in clinical practice analysis of hormone values are mostly gained from multiple blood collections. Also, free and bound hormones are to be recorded simultaneously for the purpose of valid conclusions.

Moreover, it is questionable whether the minimum of one month suffices to determine a reliable reference value of the initial hormone level and whether this period suffices to detect significant autonomous changes of the hormone concentrations. A measurement of the hormones for an observation period of 3 months before treatment would sincerely be the best way to evaluate if the osteopathic treatment led to an apparent change in the hormonal level. However, such a design is beyond the scope of this study's time limit and, in addition, would tax the women's patience unnecessarily.

To investigate the existence of ovulations LH-strips or basal body temperature charts are available. They are however insufficiently reliable for detection of ovulation and, moreover, their application represent an enormous effort for the patients (National Collaborating Centre for Women's and Children's Health, 2004). Ovulation can be confirmed retrospectively by measuring

the serum progesterone in the midluteal phase (National Collaborating Centre for Women's and Children's Health, 2004). For this purpose, knowledge on the occurrence of the midluteal phase is required as well as an additional blood sample. Therefore, this method is not feasible. The determination of ovulation has not been of interest anymore as soon as the target group of this study was redefined due to the problems in patient recruitment. The LH-FSH-ratio suffices to investigate hyperandrogenaemia in this respect.

Because weight can influence the concentrations of hormones (Kirchengast and Huber, 2001), I assessed the size and the weight of each patient to calculate the corresponding BMI (body mass index =  $\text{kg}/\text{m}^2$ ). Although I know about its questionable validity to assess obesity (Freytag, 2003) – for instance, a body builder is judged to be obese simply because of his muscle weight – I used this well-known BMI to exclude women with weight related amenorrhoea according to the WHO's classification (Hamilton-Fairley and Taylor, 2003). I criticise myself because I missed to remeasure the weight after the last treatment. This would prove that hormonal changes were not weight related.

Yet one could think of determining the waist-hip-ratio in the hope that this measure reflects the type of fat distribution (gynoid are android). Attention has to be paid in interpreting the resulting value of the waist-hip-ratio since it only provides an idea of the body silhouette and not a distinction between a strong skeleton and an android type of fat distribution (Kirchengast and Huber, 2001). Alternatively, the fat distribution can be quantified by specific instruments such as the so-called lipometer (Freytag, 2003). A lipometer was not available to me.

## 9. SUMMARY AND CONCLUSION

The present work addresses the question whether the hormonal system of women with hyperandrogenaemia can be influenced by osteopathic treatment. More precisely I investigated the effect of mobilisations and manipulations of the spine, pelvic, hips and other affected parts of the skeleton on the hormonal system. Muscles energy techniques, counterstrain, visceral and cranial treatment were equally applied.

Currently, there is still a lack of objective clinical trials on osteopathic treatment effectiveness. To best of my knowledge this work is the first one that approaches hyperandrogenaemia from an osteopathic perspective. The poor amount of publications tackling this topic is not surprising if one takes into account the variety of problems encountered during the present study and osteopathic trials in general. This includes the acquisition of patients, the costs, and the availability of measuring instruments. Therefore the intended clinical trial was impossible to perform in order to support the literature research on hyperandrogenaemia and infertility. The remaining case series did not allow for proper statistical analysis and inference. Concerning the three individuals the concentrations of testosterone could be lowered in one of the cases to normal value while results were inconsistent in the other two cases. Interestingly, in the one case pregnancy occurred within 7 month but without any change of the pathological hormone concentrations. However, from the theoretical point of view, osteopathy represents a good treatment method. Systematic literature review showed that in fact there are osteopathic theories included to improve hormonal systems. Osteopathic treatment was well accepted by the patients and supported general well-being in all cases.

From the above it is clear that the effectiveness of osteopathic treatment on the hormonal system has to be investigated in further studies. To ensure the validity of any results, a large number of female patients and a homogenous sample are necessary. A more differentiated blood test to control the hormones, e.g. the different states of testosterone (DHEA, DHEAS) and SHGB, would be useful for reliable conclusions.

In addition to these aspects, the study content and aim needs to be reformulated. The question is if it would be preferable to investigate the effect of osteopathic treatment on the androgen level independent of any child wishing as e.g. in case of PCOS with accompanying hyperandrogenaemia. If an intended reduction of free testosterone is achieved, a further study could be appended about the infertility problem caused by hyperandrogenaemia. If such successes could be provided, affected women would be convinced more easily to participate in the proposed subsequent study.

Finally, the cost-effectiveness of osteopathy should be compared to standard therapy such as medical treatment and ART (Assisted Reproductive Technologies), and also the duration until the treatment proved successful should be looked at between the various approaches. The "guideline fertility" of the National Collaborating Centre for Women's and Children's Health (2004) comprises a comprehensive overview on cost-effectiveness of ART in dependence of the women's age.

The choice of treatment depends, of course, on which treatment is the most promising and still represents a compromise between possible risk factors and the chance to succeed (Habbema et al., 2004). If these questions were clarified and osteopathy turned out to be a serious treatment variant, we could offer an alternative to the classical therapy of hyperandrogenaemia and infertility.

## 10.ACKNOWLEDGEMENT

First of all I would like to express my gratitude to the gynaecologist Dr. Werner Staggl for his cooperation and his unremitting efforts to acquire subjects out of his clinical clientele. He made the gynaecologic investigation and the blood collection to control the hormone levels. With professional competence, Dr. Staggl revised additionally the chapter about medical and surgical treatment of hyperandrogenaemic women. Therefore I cordially thank him.

Special thanks go to my sister Susanne Heim who helped with the translation into English and proof-read the most chapters of the present thesis. Due to her productive concerns regarding my formulations and her advice how to work precisely in academic writing the thesis has gained clearly on quality. Furthermore a sincere thanks to Philipp Sämann for his professional support on the interpretation of the results.

Thanks go to Lisa Cichocki for technical assistance and layout and to Christopher Pritchard for his occasional help with translation of the chapter about physiology.

I also thank Sonja and Elisabeth Bilgeri for providing their practice premises.

Finally many thanks go to my lecturer, my colleagues, my family and my friends for giving encouragement, helpful suggestions and technical support. Without this help I would not have completed this project.

This master thesis was conducted in cooperation of the Donau-Universität Krems and the Vienna School of Osteopathy. I would like to thank Peter Sommerfeld for methodological advice and Katharina Musil for the excellent mentoring throughout the entire master thesis.

## 11. LIST OF ABBREVIATIONS

ACTH: adrenocorticotrophic hormone

BMI: body mass index = weight (kg) / body height (m<sup>2</sup>)

CRF: corticotrophin releasing factor (or hormone)

DHEA: dehydroepiandrosterone

DHEAS: dehydroepiandrosterone sulphate

DNA: deoxyribonucleic acid

FSH: follicle stimulating hormone

GnRH: gonadotropin releasing hormone

HPA: hypothalamus-pituitary-adrenal (axis)

LH: luteinising hormone

MeSH: medical heading subjects

PCOS: polycystic ovary syndrome / polycystic ovaries syndrome

OMT: osteopathic manipulative treatment

TRH: thyrotrophin releasing hormone

TSH: thyroid stimulating hormone

SHBG: sex hormone binding globulin

WHO: world health organisation

## 12. TABLE OF FIGURES

- Fig. 1 Frequencies of different causes of infertility in Europe 2006 published by Dr.med. E. Breitach, see also <http://www.wunschKinder.net/theorie/ursachen-der-unfruchtbarkeit/>.
- Fig. 2 Biosynthesis, transport and mechanism of effectiveness of peptides (proteo) hormones on one hand and steroid hormones and hormones of the thyroid gland on the other hand (Klinke and Silbernagel, 1996, p. 442).
- Fig. 3 Regulation in neural-endocrine systems (Klinke and Silbernagel, 1996, p. 444).
- Fig. 4 The menstrual Cycle. Concentrations of the hormones in the plasma are illustrated simultaneous with the ovarian function, the change of the uterus and the basal temperature (1, 2, 3 and 4 mark the points in time 1-4 of Fig. 5) (Klinke and Silbernagel, 1996, p. 486).
- Fig. 5 The hormonal interaction between hypothalamus, pituitary and ovary. During the follicle phase (1) the gonadotropins cause the growth of the follicle and the release of oestrogens. In the middle of the cycle (2) LH is increasingly released by the pituitary and effects the ovulation. In the luteal phase (3) the corpus luteum releases oestrogen and progesterone which cause now a recurrent inhibition of the hypothalamus and the pituitary increasingly. Hence, the corpus luteum is less activated and stops finally its function. The negative feedback of oestrogen and progesterone disappears, the end of the cycle (4) is reached and a new one can begin. (Klinke and Silbernagel, 1996, p. 489)
- Fig. 6 Structure and function of the adrenal gland. The three layers of the adrenal cortex synthesise each its characteristic final product: mineral corticoid, glucocorticoid and androgens. Adrenocorticotrophic hormone (ACTH) of the pituitary stimulates all three zones, but the mineral corticoids are mainly under control of angiotensin II. The adrenal mark is controlled by the sympathetic nervous system (Klinke and Silbernagel, 1996, p. 463).
- Fig. 7 Synthesis of corticoids. Based on cholesterin, the final products of each adrenal zone underlie several enzymatic reactions. Therefore the enzymes 5 and 6 are characteristic for the aldosterone synthesis and contained in the zona glomerulosa, enzyme 7 in the zona fasciculata (cortisol synthesis) and enzyme 8 for the zona reticularis (Klinke and Silbernagel, 1996, p. 464).
- Fig. 8 The grading of effectiveness of the different androgen molecules (Breckwoldt et al., 1994, p. 59).
- Fig. 9 Severity codes of hirsutism according to Baron, 1974 (Rabe et al., 1992, p. 20)
- Fig. 10 Schematic depiction of the three severity codes of the female alopecia androgenetica (Rabe et al., 1992, p. 30)
- Fig. 11 Transvaginal scan of polycystic ovary. Typically 10 or more follicles of < 10 mm in diameter ("string of pearls") are in a single transverse or longitudinal section through the ovary. Stromal density and ovarian volume increase (Hamilton-Fairley and Taylor, 2003, p. 546).
- Fig. 12 The aetiology of the PCOS. The vicious circle begins with an excessive androgen production of the adrenal cortex. These androgens are aromatised to oestrogens mainly in the subcutaneous fatty tissue. Oestrogen has a positive effect on the LH release but a negative on FSH. In consequence the high LH level leads to an overproduction of androgens of the theca cells. Due to the low FSH level the aromatase activity of the granulosa cells cannot be maintained and androgens cannot be transformed to oestrogens. Hence, excessive amounts of androgen of ovarian origin get into the circulation so that the vicious circle continues (Breckwoldt et al., 1996, p. 58).
- Fig. 13 Multiple Effects of CRH. The neurotransmitter CRH is effective at the regulation of centres of the vegetative nervous system. In addition to its effects as releasing hormone of ACTH CRH is an important factor of the regulation of multiple reactions of the body to stress (Klinke and Silbernagel, 1996, p. 461).
- Fig. 14 Ovarian diathermy. Ovary showing small holes made in the cortex at laparoscopy using a diathermy point to encourage ovulation in a patient with polycystic ovary syndrome (Hamilton-Fairley and Taylor, 2003, 549).
- Fig. 15 The cranial component of the reciprocal tension membrane, showing the schematic representation of the poles of attachment, (Sutherland, 1990, p. 40).
- Fig. 16 The cranial base in flexion, showing the rotation that takes place about parallel transverse axes. Note that the ethmoid and the occiput rotate in the same direction while the sphenoid rotates in the opposite arc, as would be the case with three intermeshed cog wheels. The dotted line represents the vector of force transmitted from the movement of the sphenoid through the vomer (Sutherland, 1990, p. 43).

- Fig. 17 Maxilla and vomer in inspiration and expiration phase, (Liem, 2001, p. 270).
- Fig. 18 Vascularisation of the pituitary and primary capillary plexus of the upper pituitary stalk 300-fold magnified, (Breckwoldt et al., 1994, p. 44).
- Fig. 19 A cross-section of the brain, showing the third ventricle (24) with its choroid plexus (21+22), hypothalamus (27), infundibulum (38), pituitary with adeno- and neurohypophysis (41), N.opticus (43), Lamina terminalis (17), fourth ventricle (33), (Frick et al., 1987, p. 310).
- Fig. 20 Schematic view of the pathways the CSF is taking, (Liem, 2001, p. 221).
- Fig. 21 Topography of the thoracic duct, (Földi and Kubik, 1999, p. 15)
- Fig. 22 The model of the functional triangles is an approach to classify the whole organism according to physiological and structural perspectives. All structures of every triangle are interrelated in a functional, physiological and pathophysiological manner. The diaphragms separate these triangles (Liem, 2001, p. 381).
- Fig. 23 The fasciae in general and her connections between them (Paoletti, 2001, p. 111)
- Fig. 24 Adrenal gland (Prometheus, 2005, p. 280). Beyond the vascularisation of the kidneys and the adrenal gland, the disadvantageous anatomical situation for the venous drainage of the left ovary is illustrated.
- Fig. 25 Severity codes of hirsutism according to Baron, 1974 (Rabe et al., 1992)
- Tab.1 Phases of the female cycle, extracted from Bischof (2007).
- Tab. 2 Classification criteria of hirsute women corresponding to three severity codes (Rabe et al., 1992, p. 20)
- Tab. 3 This table summarises both questionnaires given at the beginning and the end of the study. It contains questions and answers of the three subjects to their past and present history in general and in obstetrics as well as to their life style. Not all questions were demanded twice. Answers to those, which were asked a second time at the end of the study, are pointed out italic and bold.
- Tab. 4 This table lists dates and values (LH, FSH, testosterone and TSH) of measurement according to Dr. Stagg's documentation. The LH-FSH-ratio is calculated. Increased values are pointed out bold.

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# 14.APPENDIX

## 14.1. Documentation by the Doctor

Datum:

Name:

Alter:

Größe:

Gewicht:

Gravidität/Geburt/Abort:

War für das Zustandekommen bisheriger Schwangerschaften eine Behandlung nötig?

ja           nein           womit? \_\_\_\_\_

Sind Ovarialzysten vorhanden (PCOS)?    rechts           links           beidseits

Zusätzl. Diagnosen:

Liegt oder lag eines der folgenden Krankheitsbilder vor?

Hypothyreose            ja  (aktuell , vergangen )          nein           unbekannt

Hyperthyreose            ja  (aktuell , vergangen )          nein           unbekannt

Hyperprolaktinämie      ja  (aktuell , vergangen )          nein           unbekannt

Hypophysenadenom      ja  (aktuell , vergangen )          nein           unbekannt

Chromosomale Syndrome (Turner...)    ja           nein           unbekannt

Hormonmessung	1.	2.	3.	4.
Datum				
LH				
FSH				
Testosteron				
Östrogen				
Prolaktin				
TSH				

Abschlussbefund: (zusammen mit der 4. Hormonmessung)

Datum:

Gewicht:

## 14.2. First Questionnaire

Datum:

Name:

Alter:

Beruf:

1. Wie würden Sie Ihren allgemeinen Gesundheitsstatus beschreiben?

sehr gut  gut  durchschnittlich  schlecht  sehr schlecht

2. Rauchen Sie?

- Raucherin
- Nichtraucherin
- Ex-Raucherin

3. Wieviel Alkohol trinken Sie in der Woche?

keinen  1-3x/Woche  4-6x/Woche  täglich

4. Trinken Sie regelmäßig koffeinhaltigen Kaffee?

ja  nein

Wieviel Tassen Kaffee trinken Sie am Tag?\_\_\_\_\_

5. Essen Sie eine der nachfolgenden Speisen nie?

Fleisch  Fisch  Gemüse  Obst  Milch  Zucker  Getreide

6. Wie würden Sie die Ausgewogenheit Ihrer Ernährung beschreiben?

sehr gut  gut  durchschnittlich  schlecht  sehr schlecht

7. Wurden bei Ihnen Allergien oder Nahrungsmittelunverträglichkeiten festgestellt?

ja  nein

Welche?\_\_\_\_\_

8. Haben Sie in den letzten 5 Jahren sehr schnell Gewicht ab- oder zugenommen?

ja  nein

9. Betreiben Sie regelmäßig Sport?

ja  nein

Welchen?\_\_\_\_\_

Wie oft in der Woche?\_\_\_\_\_

10. Wie schätzen Sie den Stresslevel in Ihrem Berufsleben ein?

kein Stress       gering       durchschnittlich       hoch       sehr hoch

11. Wie schätzen Sie den Stresslevel in Ihrem Privatleben ein?

kein Stress       gering       durchschnittlich       hoch       sehr hoch

12. Nehmen Sie Medikamente?

- Medikamente, die den Blutdruck senken
- Medikamente, die die Schilddrüsenfunktion beeinflussen
- Medikamente, die den Blutzuckerspiegel beeinflussen
- Medikamente, die den Blutfettspiegel senken
- Medikament gegen Schmerzen
- Entzündungshemmer
- Hormonpräparate; welche? \_\_\_\_\_
- andere; welche? \_\_\_\_\_
- keine

13. Haben Sie innerhalb der letzten 5 Jahre über längeren Zeitraum Medikamente genommen?

ja       nein

Welche? \_\_\_\_\_

14. Welches Verhütungsmittel wurde in der Regel bisher verwendet? Wie lange?

- hormonell (z.B. Pille, Hormonspirale, -pflaster, -spritze, -ring) \_\_\_\_\_
- mechanisch (z.B. Kupferspirale, Pesar, Kondom) \_\_\_\_\_

15. Wie alt waren Sie zum Eintritt der 1. Regelblutung? \_\_\_\_\_

16. Haben Sie einen regelmäßigen Zyklus zwischen 26 - 32 Tagen?

ja       nein

Wie viele Tage? \_\_\_\_\_

17. Haben Sie bisher aufgrund von Zyklusunregelmäßigkeiten eine Hormonbehandlung gehabt?

ja       nein

Womit? \_\_\_\_\_

18. Haben Sie Hautprobleme?

- Akne
- fettige Haut
- keine

19. Hatten Sie wegen Hautproblemen eine Hormonbehandlung?

ja       nein

20. Haben Sie dem männlichen Typus entsprechende Behaarung?

- Kinn
- Wangen
- Oberlippe
- Brust
- Bauch
- Lendenwirbelsäule/Kreuzbein
- Oberschenkel
- nein

21. Leiden Sie unter vermehrtem Haarausfall?

- beginnende oder bestehende Bildung von Geheimratsecken
- lichtetes Haar im Scheitelbereich
- nein

22. Haben Sie Probleme in folgenden Systemen?

- Atmung (z.B. Kurzatmigkeit, Asthma) \_\_\_\_\_
- Durchblutung (z.B. kalte Hände oder Füße) \_\_\_\_\_
- Verdauung (z.B. Sodbrennen, Magenverstimmung, Blähungen) \_\_\_\_\_
- Ausscheidung (z.B. Durchfall, Verstopfung) \_\_\_\_\_
- nein, in keinem der genannten

23. Haben Sie Probleme wie:

- Kopfschmerzen
- Depressionen
- andere
- nein

24. Hatten Sie jemals eine ernsthafte Erkrankung?(z.B. Hepatitis, Tuberkulose, Anämie, Anorexia...)

ja       nein

Welche? Wann? \_\_\_\_\_

25. Hatten oder haben Sie Entzündungen folgender Systeme?

- Gebärmutter
- Eileiter
- Eierstöcke
- Vagina
- Blase
- Nieren
- keine

26. Hatten Sie Operationen des Unterleibs/Urogenitaltraktes?

- Gebärmutter      (Datum: \_\_\_\_\_)
- Eileiter            (Datum: \_\_\_\_\_)
- Eierstöcke        (Datum: \_\_\_\_\_)
- Blase                (Datum: \_\_\_\_\_)
- Blindarm          (Datum: \_\_\_\_\_)

- andere \_\_\_\_\_
- keine

27. Hatten Sie andere Operationen?

- ja       nein

Welche? Wann? \_\_\_\_\_  
(z.B. Schilddrüse, Hypophyse, Gallenblase, Skelettsystem)

28. Haben Sie eines oder mehrere folgender Traumen erlitten?

- Autounfall
- Schleudertrauma
- Sturz auf Steiß
- andere schwere Unfälle o. Stürze
- keine

29. Haben Sie Schmerzen im Bauchraum?

- Regelschmerzen
- vom Zyklus unabhängige Schmerzen im Bauchraum
- keine

30. Haben Sie Schmerzen der Wirbelsäule?

- Halswirbelsäule
- Brustwirbelsäule
- Lendenwirbelsäule
- Kreuzbein
- Steißbein
- nein

31. Wurden Sie innerhalb der letzten 2 Jahre osteopathisch behandelt?

- ja       nein

## 14.3. Second Questionnaire

Datum:

Name:

1. Wie würden Sie Ihren allgemeinen Gesundheitsstatus beschreiben?  
sehr gut  gut  durchschnittlich  schlecht  sehr schlecht
2. Wie schätzen Sie den Stresslevel in Ihrem Berufsleben ein?  
kein Stress  gering  durchschnittlich  hoch  sehr hoch
3. Wie schätzen Sie den Stresslevel in Ihrem Privatleben ein?  
kein Stress  gering  durchschnittlich  hoch  sehr hoch
4. Hat sich etwas an der Einnahme (Dosierung, abgesetzte oder zusätzliche Medikamente) Ihrer Medikamente verändert?  
ja  nein   
 wenn ja, was? \_\_\_\_\_
5. Haben Sie einen regelmäßigen Zyklus zwischen 26 - 32 Tagen?  
ja  nein   
Wie viele Tage? \_\_\_\_\_
6. Haben sich Ihre Hautprobleme verändert?  
 Akne  
 fettige Haut  
 nein  
 Ich hatte zu Beginn der Studie bereits keine Hautprobleme.
7. Hat sich etwas an Ihrer Behaarung verändert?  
 Kinn  
 Wangen  
 Oberlippe  
 Brust  
 Bauch  
 Lendenwirbelsäule/Kreuzbein  
 Oberschenkel  
 nein  
 Ich hatte bereits zu Beginn der Studie keine dem männlichen Typus entsprechende Behaarung.

8. Hat sich etwas an Ihrem Haarausfall verändert?

- ja
- nein
- Ich hatte bereits zu Beginn der Studie keinen übermäßigen Haarausfall.

9. Haben Sie Probleme in folgenden Systemen?

- Atmung (z.B. Kurzatmigkeit, Asthma) \_\_\_\_\_
- Durchblutung (z.B. kalte Hände oder Füße) \_\_\_\_\_
- Verdauung (z.B. Sodbrennen, Magenverstimmung, Blähungen) \_\_\_\_\_
- Ausscheidung (z.B. Durchfall, Verstopfung) \_\_\_\_\_
- nein, in keinem der genannten

10. Haben Sie Probleme wie:

- Kopfschmerzen
- Depressionen
- andere
- nein

11. Haben Sie Schmerzen im Bauchraum?

- Regelschmerzen
- vom Zyklus unabhängige Schmerzen im Bauchraum
- keine

12. Haben Sie Schmerzen der Wirbelsäule?

- Halswirbelsäule
- Brustwirbelsäule
- Lendenwirbelsäule
- Kreuzbein
- Steißbein
- nein

13. Hatten Sie einen Nutzen aus der osteopathischen Behandlung?

- ja       nein

14. Würden Sie Osteopathie weiter empfehlen?

- ja       nein