1. **Introduction**

Reproduction can be defined as a process by which new individuals of the same kind are generated (e.g. Mascarenhas, Cheung, Mathers, & Stevens, 2012). As a part of general health and development, reproductive processes, functions and behaviors are assumed to affect one's well-being and seem to be essential throughout the entire lifespan (Ehlert & Fischbacher, 2012).

For women, the basis of successful reproduction is a healthy reproductive system, including an active hypothalamus-pituitary gonadal (HPG) axis and a working menstrual cycle (e.g. Chrousos, Torpy, & Gold, 1998; Kalantaridou, Makrigiannakis, Zoumakis, & Chrousos, 2004; Wingfield & Sapolsky, 2003). However, women's reproduction includes not only the functioning of the reproductive system, but also reproductive behavior. Mating behavior is assumed to be a central aspect of reproductive behavior (Buss, 2006; Buss & Schmitt, 1993; Wingfield & Sapolsky, 2003). Furthermore, there is evidence that the key hormones necessary for reproduction and the reproductive system also interact with neuroendocrine systems associated with reproductive behavior, such as sexual and mating behavior (e.g. Bullivant et al., 2004; Diamond & Wallen, 2011; Roney, 2009; Roney & Simmons, 2013; Roney, Simmons, & Gray, 2011; Schultheiss, Dargel, & Rohde, 2003; Wallen, 1995; Welling et al., 2007).

Nevertheless, the function of the reproductive system and the overt reproductive behavior can be influenced by a number of factors, such as stress. The concept of stress can be defined as a challenging and/or threatening situation that exceeds an individual's capacity to cope (Lazarus & Folkman, 1984). Stress is assumed to elicit a multidimensional psychobiological stress

response, such as negative affect, the activation of the sympatho-adrenomedullary (SAM) system, and the hypothalamic-pituitary-adrenal (HPA) axis. Activation of these systems leads to changes within an organism in order to supply the body with energy (e.g. Chrousos & Gold, 1992; Habib, Gold, & Chrousos, 2001; Kaltsas & Chrousos, 2007; Tsigos & Chrousos, 2002). These processes include the mobilizing of adaptive behaviors and the inhibition of costly behavior, such as reproduction (Chrousos et al., 1998; Dobson, Ghuman, Prabhakar, & Smith, 2003; Kalantaridou et al., 2004). In female mammals, it is assumed that the inhibitory effect of stress on reproduction consists of three components: impairment of the uterine maturation, disruption of ovulation, and inhibition of proceptive and receptive sexual behavior (Wingfield & Sapolsky, 2003).

To date, a large amount of studies have suggested that in women too, stress exerts an inhibitory effect on the HPG axis, and as a consequence on the menstrual cycle (for a review, see Chrousos et al., 1998; Dobson et al., 2003; Kalantaridou et al., 2004), such as irregular menstrual cycles (e.g. Allsworth et al., 2007; Gordley, Lemasters, Simpson, & Yiin, 2000; Hannoun, Nassar, Usta, Zreik, & Abu Musa, 2007; Jarvelaid, 2005; Li et al., 2011; Nohara, Momoeda, Kubota, & Nakabayashi, 2011; Yamamoto, Okazaki, Sakamoto, & Funatsu, 2009; Zhou et al., 2010). However, little is known about potential protective factors, which might have a beneficial effect on the reproductive system and the menstrual cycle or might attenuate the effect of stress on the menstrual cycle. A recent concept that has been linked to individuals' psychobiological health and is assumed to modulate the effect of stress on individuals' health is resilience (e.g. Humphreys, 2003; Leppert, Gunzelmann, Schumacher, Strauss, & Brahler, 2005; Pinquart, 2009; Wagnild, 2009). However, the question of whether

resilience is associated with healthy menstrual functioning and/or may attenuate the inhibitory effect of stress on the menstrual cycle has likewise never been addressed.

In numerous female species, stress decreases reproductive behaviors (Wingfield & Sapolsky, 2003). In the animal model, for example, it has been shown that stress affects female mating behavior (Kavaliers & Ossenkopp, 2001; Lopez, 1999; Vitousek & Romero, 2013). Research on the effect of stress on women's reproductive behavior remains insufficient. Recent studies have demonstrated that stress seems to exert an inhibitory effect on women's reproductive behavior, such as sexual desire and arousal (e.g. Bodenmann, Ledermann, Blattner, & Galluzzo, 2006; Dunn, Croft, & Hackett, 1999; Maserejian et al., 2010; Morokoff & Gillilland, 1993; Ter Kuile, Vigeveno, & Laan, 2007). However, to date, the effect of stress on women's mating behavior is unknown.

The objective of this thesis was therefore to gain a better understanding of how stress can affect women's reproductive functioning, with an emphasis on the regularity of the menstrual cycle, and whether there are potential protective factors such as resilience that are associated with healthy menstrual functioning. Furthermore, women's mate-choice behavior, with a particular emphasis on hormonal dynamics throughout the menstrual cycle in interaction with stress induction, was assessed.

The theoretical background (Part I) of the empirical studies (Part II) is presented in Chapters 2-5. In Chapter 2, a general overview of women's reproductive system and reproductive disorders is described. In Chapter 3, an attempt is made to elucidate women's reproductive behavior. Chapter 4 is devoted to the psychobiological aspects of stress. In Chapter 5, the association between stress and the psychobiology of women's reproduction is focused upon.

Finally, Chapter 6 briefly summarizes the research findings and a conceptualization of the studies is undertaken. Subsequently, in Part II of this thesis, the data from the two conducted studies are presented. In Part III, the thesis concludes with a general discussion of the obtained results.

PART I: THEORETICAL BACKGROUND

2. Women's Reproductive System and Reproductive Disorders

Female successful reproduction depends on healthy reproductive organs and an ovulatory menstrual cycle. Nevertheless, women's reproductive system can be influenced by a number of psychobiological factors, leading to deviations from the normal secretion of gonadal hormones associated with several reproductive disorders. Therefore, this first chapter discusses the endocrinology of the menstrual cycle and women's menstrual cycle disorders, with a focus on disorders associated with the menstrual cycle rhythm. Moreover, different variables that are assumed to influence the menstrual cycle are outlined.

## 2.1 Endocrinology of Women's Reproduction

The endocrine basis of women's reproduction is a healthy menstrual cycle resulting from a normal secretion of the HPG axis hormones. There is evidence that the key hormones of the HPG axis are not only essential for healthy reproduction, but also seem to interact with behavioral neuroendocrine systems. Therefore, the menstrual cycle and the HPG axis, regulating ovarian physiology, are described in the first section, and the HPG axis and its key hormones are described in the second section.

2.1.1 The Menstrual Cycle

The menstrual cycle usually includes two successive stages: the follicular and the luteal phase. However, some authors argue that the menstrual cycle should be divided into three distinct phases: the follicular phase, the ovulatory phase, and the luteal phase (Hawkins &

Matzuk, 2008). The menstrual cycle of healthy women lasts, on average, for 28 days. Nevertheless, it varies considerably from woman to woman, from about 25 to 31 days (Tschudin & Bitzer, 2005). Whereas the follicular phase can vary in length (12-16) days, the luteal phase lasts for approximately 14 days, correlating with the life span of the corpus luteum (Baird, Baker, McNatty, & Neal, 1975; Lenton, Landgren, Sexton, & Harper, 1984). Normal menstrual bleeding lasts for around 3-5 days and about 2-5 sanitary towels are required per day (Tschudin & Bitzer, 2005). The first menstruation is called the menarche and usually occurs between the ages of 12-13 years (Anderson, Dallal, & Must, 2003). The end of women's reproductive phase is referred to as the menopause, with the median age at menopause in Europe ranging from 50-53 years of age (Palacios, Henderson, Siseles, Tan, & Villaseca, 2010).
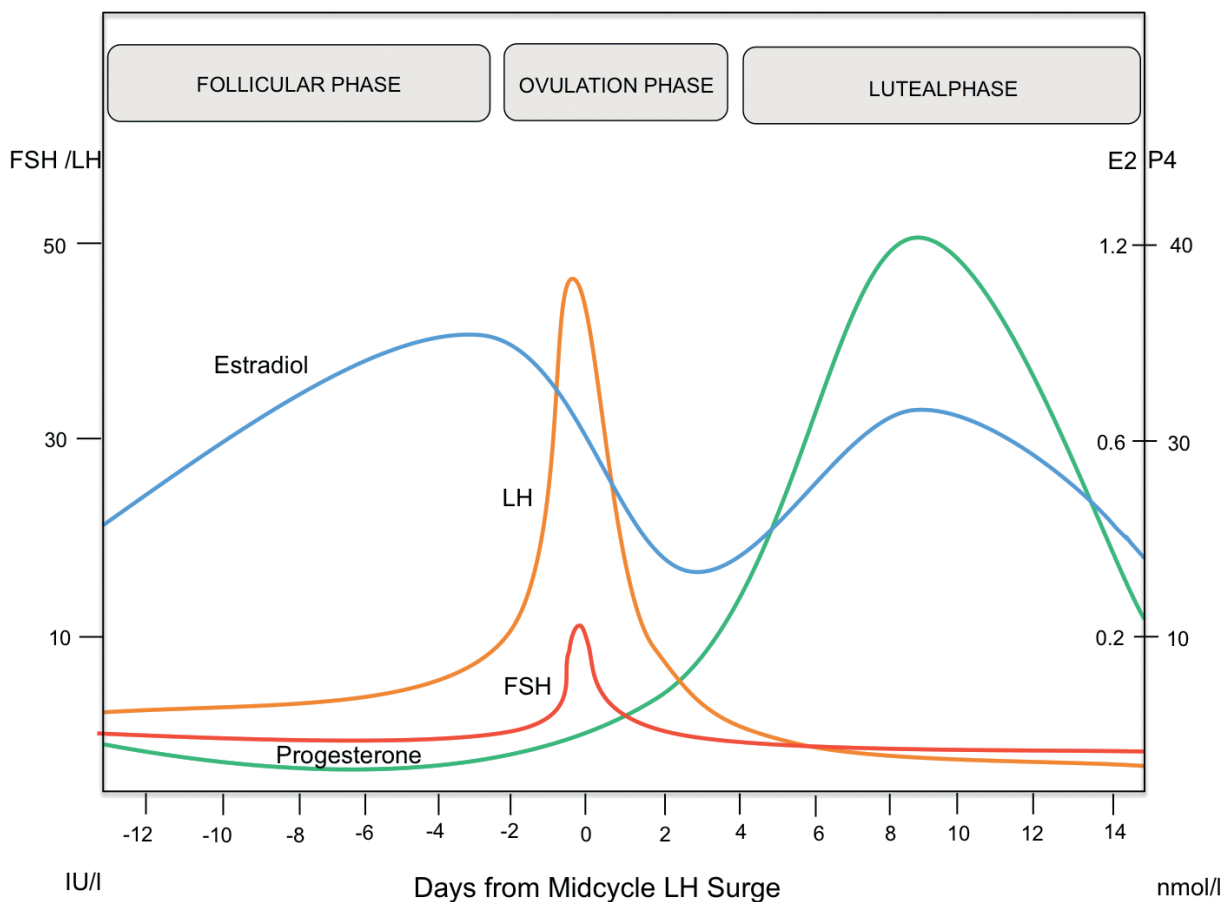
Figure 1. Changes in gonadal hormones across the menstrual cycle (adapted from: Interpretation: Endokrinologie – Sexualität, by Matter, L., Burki, D. and Keller, A., 2013, retrieved from www.vivomecum.ch. Reference ranges adapted from: "Establishment of detailed reference values for luteinizing hormone, follicle stimulating hormone, estradiol, and progesterone during different phases of the menstrual cycle on the Abbott ARCHITECT ® analyzer", by Stricker et al., 2006, Clinical Chemistry and Laboratory Medicine, 44, p.883-887).

Menstrual bleeding, meaning the bleeding and the loss of the tissue lining of the uterus, marks the first day of the menstrual cycle (Birbaumer & Schmidt, 2010; Ehlert, 2011). During menses, the levels of estrogens and progesterone (P4) drop to their lowest levels and small episodic pulses of gonadotropin-releasing hormone, referred to as GnRH, originate from the hypothalamus functions to stimulate the anterior pituitary, leading to small pulses of luteinizing and follicle-stimulating hormones (LH and FSH) (Dicken, Menke, & Neal-Perry, 2010; Leung, Cheng, & Zhu, 2003). The presence of FSH then stimulates the development of several follicles (Hawkins & Matzuk, 2008). The theca, a layer of cells surrounding the follicle, produces androgens, which are converted to estradiol (E2) due to aromatase (Czajka-Oraniec & Simpson, 2010). This increase in E2 and the down-regulation of FSH due to negative feedback leads to the development of a single dominant follicle (Birbaumer & Schmidt, 2010; Speroff & Fritz, 2005). The dominant follicle, which develops outer layers of cells (granulose cells) and a fluid-filled space (antrum), secretes further estrogens (Hawkins & Matzuk, 2008). The elevated estrogen levels stimulate growth in the tissue and blood vessels in the uterus, resulting in the thickening of the uterus lining (Birbaumer & Schmidt, 2010). At a very high level, E2 reaches a threshold above which the negative feedback of E2 on LH is reversed, and E2 stimulates the release of LH, generating a pre-ovulatory LH surge (Ehlert,

2011). The mid-cycle LH/FSH peak stimulates enzymes in the follicle, which causes the follicle to swell and rupture, resulting in ovulation (Speroff & Fritz, 2005). The oocyte travels into the Fallopian tubes, where fertilization can take place, and the remaining follicular cells in the ovary become a part of the corpus luteum (Hawkins & Matzuk, 2008). The following luteal phase is characterized by the formation of the corpus luteum and its production of P4 and estrogens, which help to prepare the endometrium for implantation and maintenance of pregnancy (Birbaumer & Schmidt, 2010). The corpus luteum also produces inhibin, which suppresses FSH and inhibits the growth of other ovarian follicles (Hawkins & Matzuk, 2008). After ovulation, the LH/FSH levels fall to their normal and low levels, whereas estrogens levels fall somewhat after ovulation and rebound due to the secretion by the corpus luteum (Birbaumer & Schmidt, 2010). The corpus luteum regresses after approximately 14 days. The decline in inhibin, estrogens and P4 levels remove the negative feedback control on FSH, and its level increases again to initiate the next menstrual cycle (Hawkins & Matzuk, 2008).

2.1.2 The Hypothalamus-Pituitary-Gonadal (HPG) Axis

The HPG axis and its key hormones synchronize neuroendocrine physiology essential for reproduction and are known to modulate neurotransmitter systems associated with behavior (see also section 3.1.2 Endocrinology of Women's Reproductive Behavior and section 3.2.4 Endocrinology of Women's Mating Preferences).
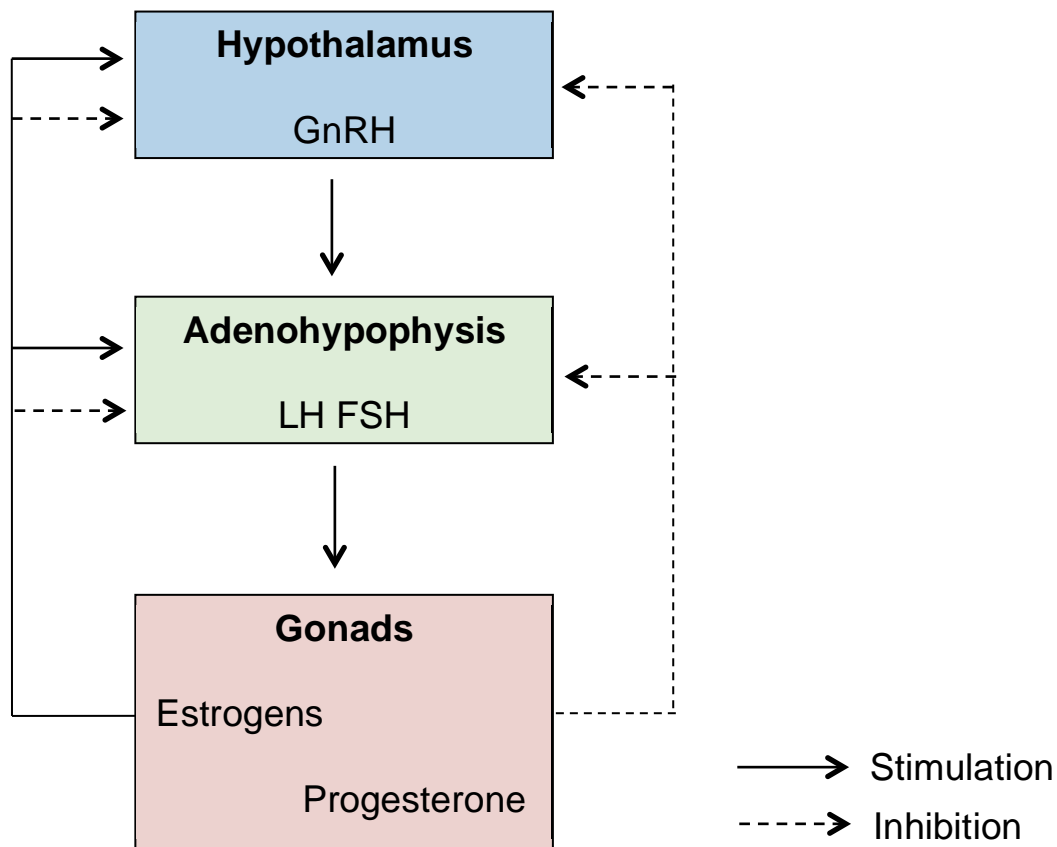
Figure 2. Schematic representation of the hypothalamus-pituitary-gonadal (HPG) axis (adapted from: Psychoendokrinologie und Psychoimmunologie (p.27), by U. Ehlert and R. von Känel, 2011, Berlin Heidelberg: Springer.)

2.1.2.1 Gonadotropin-Releasing Hormone (GnRH)

GnRH is an amino acid neuropeptide that is released in a pulsatile fashion. The pulsatile rhythm of GnRH is crucial to reproduction because it drives gonadotropin and subsequent gonadal steroid secretion (Leung et al., 2003). GnRH is synthesized and released from neurons within the hypothalamic structure and it is assumed that multiple neuroendocrine

modulators can affect GnRH pulse frequency. Most importantly, gonadal steroids feed back effects on GnRH pulse frequency (Dicken et al., 2010).

2.1.2.2 Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH)

FSH and LH are released from the anterior pituitary and are heterodimeric glycoprotein hormones (Dicken et al., 2010). In women, LH supports the theca cells, whereas FSH initiates follicular growth. The LH pulse amplitude increases throughout the menstrual cycle, whereby the mid-cycle LH surge lasts for about 24-48 hours and triggers ovulation (Dicken et al., 2010). The decrease of E2 and P4 in the late luteal phase leads to a lack of suppression of FSH. Consequently, it increases in the early follicular phase and stimulates the maturation of follicles and follicular growth (Hawkins & Matzuk, 2008).

2.1.2.3 Estrogens

Estrogens are endogenous sex steroid hormones. The most potent, naturally occurring estrogen is estradiol (E2), followed by estrone (E1) and estriol (E3). During the reproductive years, E2 is the most predominant estrogen in terms of serum level and activity (Bennink, 2008). During pregnancy, E3 is produced in larger quantities by the placenta and, after menopause, E1 becomes the most important estrogen since it is produced by adipose tissue (Bennink, 2008). While only about 1% of E2 circulates freely, the remainder is appended to a substance referred to as sex hormone-binding globulin (SHBG) or albumin (Dicken et al., 2010). Estradiol is mainly produced by the antral follicle during the follicular phase, but can also be released in smaller amounts by other tissues, such as the liver or the adrenal glands (Dicken et al., 2010). It has been suggested that in normally cyclic women, E2 exhibits an ultradian rhythm and a diurnal variation, with higher levels in the morning, whereby the E2 post-awakening period is influenced by the menstrual cycle phase, showing a more