Obesity and fertility : connecting metabolism and reproduction through neuropeptides

Courtney Moyer

Obesity and fertility: Connecting metabolism and reproduction through neuropeptides

Courtney Moyer

The University of Toledo

2016

Table of Contents

Introduction....1

Problem....2

Purpose....2

Research Question....3

Definitions....3

Methodology....4

Literature Review

- Fertility....5
- Infertility....11
- Nutrition Status....17
- Neuropeptides....25
- Connections between Energy Balance and the HPG Axis....31
- Application to Clinical Practice....39

Conclusion....52

Discussion....53

Key Points....54

References....56

Abstract....61

Introduction

Reproduction has a significant role within many people's lifestyles, culture, and ambitions. Unfortunately, about 11% of American women struggle with fecundity or infertility (Chandra, Copen &Stephen, 2013). The inability to conceive can be due to a number of causes ranging from anatomical to biochemical origins. In addition to the challenge of conception, fertility treatment methods can be strenuous and enduring. According to the National Survey of Family Growth, between 2006-2010, 12% of American women or their partners had used fertility treatment methods (Chandra, Copen, & Stephen, 2014). In 2012, about 38% of assisted reproductive technology procedures resulted in live-birth deliveries (Sunderam et al., 2015). Fertility assistance service expenses vary, ranging from hundreds to thousands of dollars. For the majority of states, these services are not covered under health insurance plans. In addition to the expense of treatments, the assistance can have undesirable side effects. Despite the obstacles people face when seeking fertility assistance, there is promise for fertility advancement as research continues to uncover etiologies behind infertility and develop specific treatments for the underlying cause.

While a number of endocrine and anatomical causes of infertility are inevitable, there are some factors couples have the ability to control themselves. As many conception-seeking individuals pursue methods to improve their chances of pregnancy, it is worthwhile to investigate modifiable factors that individually increase conception odds prior to undergoing reproduction treatments. A holistic approach to pregnancy improves both the parents' wellbeing and the safety of the conception platform.

Obesity and energy balance are among the multiple sources of infertility influencing additional research and interventions. More than one third of adults in the United States were

obese according to the 2011-2012 National Health and Nutrition Examination Survey data (Ogden, Carroll, Kit, & Flegel, 2014). Coronary heart disease, diabetes, dyslipidemia, and hypertension are merely a few of the potential consequences of obesity. As nutritional status weighs on the minds of countless Americans, its effect on one's health has gained attention. Precisely, the role of energy balance on fertility has raised question. If obesity is able to increase one's risk of a multitude of conditions, its role on fertility may be just as significant. There may also be a way to measure this impact and create focused treatment plans designed to monitor and conquer this issue.

Problem

Infertility affects a large number of Americans interested in conception. Women struggling with weight may be able to simplify fertility treatment if they can recognize how nutrition is impacting their chances of fertility. With a large number of Americans struggling with weight and appropriate eating behaviors, understanding the correlation between these issues and potential complications is important. Revealing markers of fertility status influenced by nutrition can serve as tools to both analyze and monitor one's reproductive abilities. Implementing enhanced lifestyle modifications to obtain a healthy energy balance may serve as a more efficient treatment strategy towards regaining fertility than once conceived.

Purpose

The purpose of this literature review is to reveal the potential effect that energy status, specifically obesity, has on fertility status and to emphasize markers that may serve as a measurement of one's reproduction capabilities.

Research Question

Is there a significant energy balance impact on fertility status? If so, are there reliable markers capable of capturing this relationship?

Definitions

Gonadotropin releasing hormone (GnRH) is defined by Merriam-Webster Medical Dictionary Online (2015c) as a hormone secreted by the hypothalamus that stimulates the anterior lobe of the pituitary gland to release gonadotropins (as luteinizing hormone and follicle-stimulating hormone)

Luteinizing hormone (LH) is defined by Merriam-Webster Medical Dictionary Online (2015e) as a hormone secreted by the anterior lobe of the pituitary gland that in the female stimulates ovulation and the development of corpora lutea and in the male the development of interstitial tissue in the testis

Follicle stimulating hormone (FSH) is defined by Merriam-Webster Medical Dictionary Online (2015a) as a hormone produced by the anterior lobe of the pituitary gland that stimulates the growth of the ovum-containing follicles in the ovary and activates sperm-forming cells

Obesity is defined by Merriam-Webster Medical Dictionary Online (2015f) as a condition that is characterized by excessive accumulation and storage of fat in the body and that in an adult is typically indicated by a body mass index of 30 or greater

Leptin is defined by Merriam-Webster Medical Dictionary Online (2015d) as a peptide hormone that is produced by fat cells and plays a role in body weight regulation by acting on the hypothalamus to suppress appetite and burn fat stored in adipose tissue

Ghrelin is defined by Merriam-Webster Medical Dictionary Online (2015b) as a 28-amino-acid peptide hormone that is secreted primarily by stomach cells with lesser amounts secreted by other cells (as of the hypothalamus), that is a growth hormone secretagogue, and that has been implicated in the stimulation of fat storage and food intake

Methodology

Using PubMed and EndNote, articles discussing reproduction and/or energy balance were chosen. Review and research articles within the last ten years have been chosen. There have been older articles chosen to thoroughly explain the physiology of the reproductive and nutrition networks for definitional purpose. The majority of information regarding the connection between the networks and impact on humans has been published within the last five years. The keywords included in searches include “fertility”, “infertility”, “reproduction”, “HPG axis”, “GnRH”, “LH”, “energy balance”, “nutrition”, “kisspeptin”, “leptin”, “obesity”, and “neuropeptides”. When available, these terms were specified to be included in the title or abstract of the article. First-tier search designs include literature reviews focused on neuropeptides connecting energy balance to the effects on fertility status in humans. Second-tier research designs would include literature reviews of the same neuropeptides in animals. Inclusion criteria included women of reproductive age, with a variety of BMIs, and a goal of conception. Studies outside the United States were included, however statistics regarding infertility and ART was only gathered from US studies. Articles pertaining to male fertility and energy balance were excluded. Article language was limited to English.

Fertility

Fertility is defined as “the ability to conceive and bear children or the ability to become pregnant through normal sexual activity” (MedicineNet, 2012). Conception requires proper interaction between not only a male and female, but also between the human hypothalamus, pituitary gland, and gonads, which make up the hypothalamic-pituitary gonadal axis (HPG axis). The HPG axis is a complex network of tissues and hormones that drive a number of human reproductive functions including menstruation, ovulation, and conception in women. In women, reproductive hormones including gonadotropin releasing hormone (GnRH), follicle stimulating hormone (FSH), luteinizing hormone (LH), estrogen, and progesterone play an intricate role in stimulating and inhibiting various gonadal reproductive functions through positive and negative feedback loops. Appropriate function of the HPG axis leads to female menstruation, ovulation, and the ability to conceive, however alterations female reproductive hormones or hormones can result in significant physiologic dysfunction including infertility (Nestor, Kelly, & Ronnekleiv, 2014).

HPG axis pathway.

The hypothalamus is a central nervous system (CNS) structure responsible for regulating a number of physiologic processes including reproduction. It’s role in female reproduction consists of receiving messages from gonadal hormones, estrogen and progesterone, and secreting GnRH. GnRH is secreted by the hypothalamus in a pulsatile fashion when estrogen and progesterone is decreases. The hypothalamus also secretes prolactin-inhibiting factors (PIFs) such as dopamine.

Follicle stimulating hormone (FSH) and luteinizing hormone (LH) are pituitary hormones stored in anterior lobe cells called gonadotrophs. GnRH can stimulate synthesis and storage of FSH and LH or directly stimulate synthesis and secretion of the pituitary hormones (Hacker, Hobel, & Gambone, 2010). Luteinizing hormone (LH) is a hormone secreted by the anterior lobe of the pituitary gland that in the female stimulates ovulation and the development of corpora lutea. FSH is a "hormone produced by the anterior lobe of the pituitary gland that stimulates the growth of the ovum-containing follicles in the ovary and activates sperm-forming cells" (Merriam-Webster Medical Dictionary Online (2015a). Thus, FSH and LH propagate the HPG axis by stimulating gonadal development and function.

Ovarian steroids include estrogens and progesterone, which are secreted from the ovaries when stimulated by LH and FSH. Estrogen and progesterone circulate bound to plasma proteins in the blood stream. Unbound estrogen and progesterone stimulate reproductive organs (breast, uterus, vagina). These hormones typically inhibit gonadotropin secretion (FSH and LH), but at the time of ovulation will stimulate gonadotropin release (Brzyski & Knudtson, 2013). Therefore, FSH and LH are simulated by GnRH and typically inhibited by estrogen and progesterone.

Positive and negative feedback loop.

A positive feedback loop involves elevated rate of production when the quantity of the product is increased. Negative feedback involves a reduction in the rate of production when the quantity of the product is elevated. Both types of feedback loops are seen in reproduction. Female gonadal steroids, estrogen and progesterone, act on the hypothalamus and pituitary through a negative feedback loop. When estrogen and progesterone are sufficiently elevated,

GnRH and gonadotropin expression are inhibited. The exception to this is the GnRH surge release caused by circulating estradial during the pre-ovulatory period. Reduced levels of estrogen and progesterone stimulates a negative feedback reaction on the hypothalamus to secrete GnRH. Pulsatile GnRH release stimulates a positive feedback reaction on the anterior pituitary to synthesize and release FSH and LH. The positive feedback continues as coordinated gonadotrophic elevations initiate ovarian processes. These coordinated fluctuations in FSH and LH, as well as estrogen and progesterone, will be discussed further in the "conception" section. At the end of menstrual cycle, estrogen and progesterone decrease and incite the activation of another cycle through negative feedback on the hypothalamus (Tsutsumi & Webster, 2009).

GnRH pulsatility.

The concept of negative feedback dominates the process of stimulation and release of hormones in the HPG axis. In the case of gonadotrophs, the preceeding, stimulating hormone is important to their function. "GnRH is released in a pulsatile manner to avoid the down-regulation of the GnRH receptor in the pituitary" (Tsutsumi & Webster, 2009, p.2). Constant elevation of GnRH would inhibit expression of gonadotrophs. The frequency and amplitude of GnRH pulses are important to FSH and LH release. LH is favored by fast pulse frequencies, while FSH is favored by slow pulse frequencies, which helps to coordinate release throughout the menstrual cycle (Tsutsumi & Webster, 2009). See figure 1.

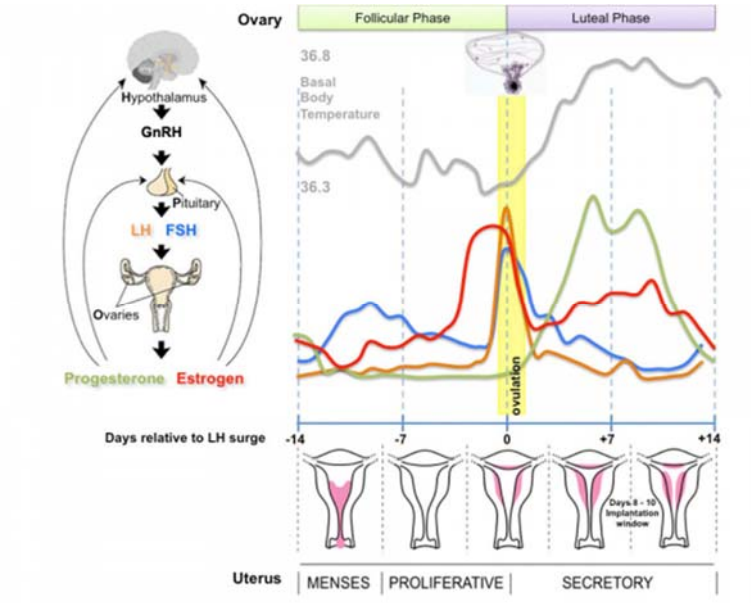

Figure 1: Female Reproductive Physiology. This diagram portrays the female reproductive axis and menstrual cycle. "Female - Hypothalamus Pituitary Gonad (HPG) Axis." From University of New South Wales. https://embryology.med.unsw.edu.au/embryology/index.php/2011_Lab_8_-_Postnatal

Conception.

With an understanding of the tissues and hormones are involved in reproduction, as well as the mechanism of propagation through the HPG axis, further knowledge of conception can be obtained by understanding how the quantity and timing of hormone fluctuations makes conception successful. The menstrual cycle can be divided into two phases; the first phase being the follicular phase, followed by the luteal phase, which begins after the initiation of ovulation.

At the beginning of the follicular phase, gonadotrophs contain very little FSH and LH. Estrogen and progesterone production is low. This low steroid hormone number stimulates GnRH expression and thus FSH synthesis, which drives development of primordial follicles in a step-wise fashion (Brzyski & Knudtson, 2013). Women are born with a set number of primordial follicles. One of these primordial follicles develops to become a dominant follicle that ovulates

and is termed the graafian follicle. This mature graafiain follicle contains granulosa cells, follicular fluid, and the primary oocyte (Hacker et al., 2010). While FSH is maturing the dominant follicle and eventual egg, LH slowly increases during the follicular stage. As the ovarian follicles mature, they increase estradiol production, which stimulates FSH and LH synthesis (Brzyski & Knudtson, 2013).

Ovulation marks the rupture of the graavian follicle. At this time, estradiol levels peak and progesterone begins to increase. LH surges and FSH increases to a lesser degree. High estradiol levels, GnRH, and progesterone cause the LH surge. The LH surge causes reduction of estradiol, progression of progesterone increase, and the release of the oocyte from the graafian follicle (Brzyski & Knudtson, 2013). Remaining follicles present undergo atresia. The remaining graafian follicle is called the corpus luteum, which will go on to produce progesterone in the second half of the menstrual cycle called the luteal phase (Hacker et al., 2010).

During the luteal phase, the corpus luteum involutes and causes a peak in progesterone. This progesterone is responsible for influencing the secretion of glycogen, mucus, and development of other substances that organize the endometrium. Progesterone's functions and a second peak of estrogen allow the endometrium to organize itself and prepare for implantation (Hacker et al., 2010).

If the oocyte (egg) is fertilized, an embryo forms and the corpus lutuem goes on to support the developing embryo. Human chorionic gonadotropin is produced by the maturing embryo and facilitates development of the fetus. If the oocyte is not fertilized, the corpus luteum degenerates and becomes a small portion of scar tissue on the ovary termed the corpus albicans. Progesterone and estrogen decline and the endometrium involutes. At this time, the endometrium

prepares to slough off the organized lining of the endometrium and begin the next menstrual cycle (Hacker et al., 2010).

Infertility

Infertility vs. infecundity.

According to data provided by the National Health Statistics Report (NHSR), infertility is defined as "a lack of pregnancy in 12 months … despite having had unprotected sexual intercourse in each of those months with the same husband or partner" (Chandra, Copen, & Stephen, 2013, p. 1). This study defined impaired fecundity as "physical difficulty in either getting pregnant or carrying a pregnancy to live birth" (Chandra et al., 2013, p. 1). In some circumstances, a woman may be considered to have impaired fecundity if she is surgically sterile or if her partner is infertile.

In 2002, about 12% of women in the United States had impaired fecundity. The NHSR showed no correlation between economic class, marriage status, education level, or poverty level and a significant reduction in fertility status. However, Asian women appeared to have lower infecundity rates than African American, Hispanic and non-Hispanic white women. The study confirmed that age is an independent risk factor for primary infertility and infecundity. Infecundity rates, regardless of parity, among women ages 15-24 is around 7%, while women ages 25-44 have infecundity rates around 13%. There was a significant difference in infecundity among women 25-29 and those ages 40-44, however the difference is only among nulliparous women. The rates of nulliparous women with impaired fecundity was about 14% in women ages 25-29. This number dramatically increases to 30% in nulliparous women aged 40-44 (Chandra et al., 2013). For the purposes of this literature review, the focus will be on physiological causes of fertility status.

Anatomical causes of infertility.

Anatomical causes of female infertility include tubal damage, endometriosis and uterine anomalies. Abnormalities of the uterine cavity may be congenital or acquired with the potential to prevent implantation and thus also cause recurrent pregnancy loss or infertility. A septate uterus is the most common uterine malformation and has the poorest reproductive outcomes. This uterine malformation is associated with "pregnancy losses of more than 60% and fetal survival rates reported to be as low as 6-28%" (Abrao, Muzii, & Marana, 2013, p. 4). All uterine malformations have the risk of causing recurrent pregnancy loss, preterm labor, abnormal fetal presentation, and infertility (Abrao et al., 2013).

Tubal disease is found in 25-35% of women that present for infertility evaluation. The most common cause of tubal disease or damage is pelvic inflammatory disease (PID). Tubal infections can cause proximal tubal occlusion (PTO), periadnexal adhesions, and distal tubal occlusion (DTO). Because of the detrimental impact pelvic infections may have on the fallopian tubes, checking tubal patency is an important part of pre-fertility treatment evaluation. The effects of tubal disease may be bypassed by in vitro fertilization (IVF), however this does not repair the underlying tubal disease. The chances of conception are higher with IVF than with reconstructive surgery to the fallopian tubes, however there are more risks associated with IVF than with reconstructive surgery (Abrao et al., 2013). Parents remain responsible for the decision of whether to surgically fix the pathologic tube or implant a fertilized egg into the uterus, knowing the complications and success rates of both procedures.

Between 5-15% of women of reproductive age have endometriosis, a disease in which endometrial glands and stroma exist outside the uterine cavity. The clinical manifestations of the disease consist of dysmenorrhea, dyspareunia, chronic pelvis pain, abnormal uterine bleeding,

intestinal disorders and infertility. The pathophysiology behind the disease and its effect on fertility status are not clearly understood. Studies show increased rates of conception in women suffering from infertility secondary to endometriosis who have undergone laparoscopic treatment when compared to women with endometriosis who use laparoscopy for diagnostic purposes alone. The rates of conception in endometriosis patients using IVF are also higher in those who have had surgical treatments prior to fertility treatments than those who were not surgically treated. There are a number of suggested etiologies behind endometriosis infertility such as "impaired folliculogenesis, ovulatory dysfunction, sperm phagocytosis, impaired fertilization, defective implantation, toxicity against early embryonic development, and alterations within the oocyte" (Abrao et al., 2013, p. 3-4).

Biological causes of infertility.

Female fertility status may be impaired due to disorders within the physiologic process of conception that lies within the endocrine system. Disorders involving tissues, hormones, and peptides within the HPG axis are included in this set of etiologies. Some tissues, such as the adrenal glands and thyroid, have effects on the reproductive axis through inputs from outside the hypothalamic pituitary and gonadal cycle (Weiss & Clapauch, 2014).

One of the most common causes of infertility is anovulation, which accounts for about 25-50% of female infertility. Anovulation is the failure of the ovary to release a mature oocyte. This can lead to irregular menstrual cycles and hormone insufficiencies. While anovulation is a common precursor to conception difficulties, it is standard protocol to check for common anatomical etiologies such as those within the fallopian tube and endometrial cavity before initiating any fertility treatments (Weiss & Clapauch, 2014).

A variety of endocrine conditions may diminish fertility status through disruption of the ovulatory cycle and an imbalance of the hormones involved in ovulation. Premature ovarian failure and hypothalamic amenorrhea involve amenorrhea and hormone imbalances that cause ovulation failure. Premature ovarian failure is due to an early overuse or dysfunction of a woman's follicle supply. Hypothalamic amenorrhea is characterized by defects in the ability of the hypothalamus to secrete GnRH in a pulsatile manner, amount of GnRH, or other defects in the hypothalamus function. Prolactinomas and acromegaly are pituitary defects that have been associated with reproductive insufficiency. Cushing's disease and polycystic ovarian syndrome (PCOS) are complex conditions with correlations with infertility. Characteristics of obesity and sex hormone imbalance affect menstrual function and reproduction in these patients. Both hyper- and hypothyroid conditions are correlated with impaired reproductive outcomes including infertility and increased miscarriage rates. Studies investigating the link between thyroid complications and fertility have found that both conditions have the ability to cause irregular menstrual cycles and hormone regulation. Adrenal dysfunction exhibited in congenital adrenal hyperplasia and Addison's disease has been associated with infertility, however are not completely understood (Weiss & Clapauch, 2014).

Modifiable risk factors.

Apart from spontaneous pathologic causes of infertility, there are numerous modifiable factors that can affect fertility such as smoking, age, obesity, and timing of intercourse. Research has shown that smoking in any amount has harmful effects on female reproduction (Chandra et al., 2013). In a review by Meeker and Benedict (2014), a study showed that "women seeking IVF treatment found decreased pre-retrieval serum estradiol concentrations, lower numbers of

retrieved oocytes, fewer embryos, and a 50% reduction in implantation rate among smokers compared to women who had never smoked" (p. 4). The same review found that ovarian follicles are damaged when exposed to smoke either actively or passively. Active smoking exposes follicular fluid to cotinine, a substance found in cigarettes, which increases follicular lipid peroxidation. Both active and passive smoking increases the risk of DNA damage in granulose-lutein cells. Increased exposure of cotinine to follicular fluid (>20ng/ml) was associated with lower fertilization rates than follicles exposed to lower (<20ng/ml) levels of cotinine. Impaired oocyte quantity, function, and viability have also been associated with IVF patients who smoke. Infertility has been identified in women with unintentional smoke exposure such as that of secondhand smoke. Increased follicular prolactin levels and dysmenorrhea are among some of the effects seen in women exposed to secondhand smoke, which could impair fertility (Meeker & Benedict, 2013).

The basis of age as a modifiable factor is due to the ability to attempt to conceive at a particular age. As previously mentioned in the National Health Statistics Report by Chandra et al. (2013) the rates of infecundity considerably increase in women as they reach their thirties and forties.

As the rates of obesity increase, the focus on its effect on fertility has also raised attention. In 2014, it was reported that more than two-thirds of American adults are overweight or obese (Ogden, Carroll, Kit, & Flegal, 2014). A high body mass index (BMI) has been associated with lower pregnancy and live birth rates and increased infertility and miscarriage rates (Kesmodel, 2012). Specific details of how excess weight impacts the reproductive axis are to be discussed in further sections.

Anatomical and physiologic etiologies to infertility discussed in this paper are limited to

female origin. Fertility troubles arise about equally from females and males. When there are preventable factors standing in the way of a couple's reproductive success, implementing strategies to handle these modifiable factors becomes an important initial treatment method. Both men and women have the ability to control some aspect of their conception odds through lifestyle behaviors.

Nutritional Status

Measuring nutritional status.

Nutritional status is comprised of a number of factors including weight, body composition and circumferences, height, age, function, laboratory values, and dietary intake. A person's nutritional status is commonly judged by his or her BMI, a calculation of one's weight compared to his or her height. In order to obtain a well-rounded perception of one's nutritional status, their functional status, body composition, and dietary behaviors must also be included.

Body mass index (BMI) calculations are commonly performed in a variety of settings such as schools and healthcare facilities in attempt to quickly understand one's weight. The formula for BMI is calculated by a person's weight (in kilograms) and dividing by height (in meters squared). This number is then squared to calculate the final BMI value and interpreted (see chart). BMI provides a quick way to assess one's weight, however it does not take into consideration a person's lean body mass. Careful interpretation must be given when evaluating people strictly on body mass index. Body composition investigates body weight, height and the amount of fat versus lean mass. In addition, macro and micronutrient intake, gastrointestinal absorptive abilities, and body function in relation to dietary intake may also be evaluated when investigating one's nutrition status.

Table 1: BMI classification.

BMI	Weight Status
Below 18.5	Underweight
18.5-24.9	Normal or Healthy Weight
250.0-29.9	Overweight
30.0 and Above	Obese

The CDC classifies BMI into the following weight classes. "Adult BMI," Centers for Disease Control and Prevention, 2015, https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/

Measuring energy balance.

There are a number of hormones that can be identified and measured to assess metabolism, including ghrelin, leptin, and insulin. These hormones have the ability to connect an individual's metabolism with energy balance. Normal production and signaling of the hormones are involved in regulating several other physiologic processes including reproduction and appetite. Interruptions or impairment in the transmission of the hormones may result in irregular appetite signals and changes in reproduction stimulation.

Leptin.

Leptin is a secretory protein found mostly in white adipose tissue and circulates throughout the body in both a free and a protein bound form. Leptin is released in a pulsatile manner by adipocytes, and its major roles involve energy balance and reproduction (Nestor et al., 2014). With regards to energy balance, leptin is responsible for signaling a state of adequate energy intake or abundance. The amount of leptin is increased with positive energy balance and decreased with negative energy balance or starvation (Vazquez, Romero-Ruiz, & Tena-Sempere, 2015).

Leptin receptors are found centrally in the hypothalamus and pituitary and peripherally in the gonads. Centrally, leptin acts on the hypothalamus to regulate energy expenditure. Leptin elevations trigger messages to the central nervous system that there are adequate stores and energy expenditure is permitted. In times of starvation when leptin is low, the hypothalamus is signaled to conserve energy and reduce expenditure. In the periphery, leptin has an antagonistic relationship with pancreatic insulin, regulating fat and glucose metabolism. As energy stores and

food intake increases, leptin increases and pancreatic insulin secretion is decreased (Brewer & Balen, 2010).

Leptin is also responsible for integrating the signal of energy balance into the reproductive axis. Reproduction requires ample amounts of energy. Leptin interprets the amount of available energy stores into a message sent to the reproductive system indicating whether the stores are sufficient for procreation. When there are adequate energy stores, leptin stimulates the HPG axis. Yet, excessive leptin, as seen with obesity, can have an inhibitory effect on the HPG axis (Brewer & Balen, 2010).

Adipocytes in overweight and obese women become hypoxic as BMI increases, leading to increased secretion of proteins called adipokines. Leptin is one of the many adipokines secreted by adipocytes and increases with increased fat cells. High leptin levels may actually result in leptin resistance, which is commonly observed in obese patients (Brewer & Balen, 2010). Deletions of leptin receptors on the hypothalamus have been associated with obesity in mice, likely due to the inability to detect the signal of adequate energy stores. Damage or mutation to leptin signaling centers are correlated with excess body weight (Nestor et. al, 2014). In addition, defective leptin signaling is associated with delay or absence of puberty and compromised fertility (Vazquez et al., 2015). Therefore, damage or deficiencies in leptin signaling centers is linked with obesity and impaired pubertal development, both of which can lead to fertility struggles. In contrast, obesity increases leptin levels substantially. Excessive leptin levels are also associated with compromised reproductive function. "High leptin concentrations, when accompanied by obesity, are associated with leptin resistance" (Nestor et al., 2014, p. 110). This results in impaired energy balance signaling, appetite discrepancies, and improper reproductive stimulation. Leptin levels and associated signaling is a sensitive process

relying on genetics and nutrition status to function properly.

Leptin also plays a critical role in pubertal development. Women with leptin mutations or leptin deficiency do not undergo puberty. Young women supplemented with leptin experience an induced pubertal state (Brewer & Balen, 2010). Impaired leptin physiology beginning at puberty may create a medium in which conception becomes difficult later on in life.

Adiponectin.

Adiponectin is one of many proteins secreted by adipocytes. Unlike leptin, adiponectin is secreted at higher rates during times of weight loss and reduced energy stores. Reduced levels are observed with obesity and insulin resistance. It is suggested that adiponectin is involved in insulin sensitivity regulation as levels are inversely related to levels of insulin resistance. As with insulin sensitivity control, this may also infer more control of ovulation. Adiponectin can be found within the ovary, follicular fluid, oocyte, corpus luteum, theca cells, and granulosa cells, however the function of adiponectin within these gonadal sites remains unclear (Brewer & Balen, 2010).

Ghrelin.

Ghrelin is defined by Merriam-Webster Medical Dictionary Online (2015b) as a "28-amino-acid peptide hormone that is secreted primarily by stomach cells with lesser amounts secreted by other cells (as of the pancreas), and acts to stimulate appetite and the secretion of growth hormone." It is an orexigenic peptide secreted by the stomach, which sends a hunger signal to the central nervous system when the body has insufficient energy stores. Thus elevated ghrelin indicates hunger or negative energy balance. Since reproductive physiology requires

abundant energy, ghrelin has a role in controlling the stimulation of the HPG axis when elevated (Celik, Aydin, Celik, & Yilmaz, 2015).

Insulin.

Insulin is an anabolic hormone secreted by pancreatic beta cells to control blood glucose levels. Insulin acts through the insulin receptor and the insulin-like growth factor 1 receptor (IGF1). These receptors have been detected in gonadal tissues and the pituitary. Within the gonadal tissues (including granulosa, theca and ovarian stroma tissue), insulin stimulates ovarian steroidogenesis and upregulates the LH receptor. At the pituitary, insulin upregulates the GnRH receptor on gonadotroph cells, increasing ovarian steroidogenesis. The hormone is also responsible for increasing the bioavailability of sex hormones by inhibiting production of sex-hormone binding globulin (SHBG) and IGF binding protein 1 (IGFBP1), thereby increasing circulating free sex hormones. At normal insulin levels, there is proper stimulation of reproductive tissues and hormone synthesis (Brewer & Balen, 2010).

Abundant amounts of insulin have the ability to over-stimulate tissues, leading to an imbalance of hormones and a state that is incompatible for reproduction (Brewer & Balen, 2010). Insulin is found at high levels in obese individuals, which leads to insulin resistance. According to a review by Kesmodel (2012), hyperinsulinaemia and insulin resistance are speculated to alter levels of SHBG. Obesity, specifically central adiposity, is associated with reduced levels of SHBG, which increases the amount of circulating free sex steroids, particularly androgens, and also metabolic clearance of the steroids. This induces synthesis of androgens and eventually produces hyperandrogenism. The changes lead to defects in the menstrual cycle including anovulation and fertility trouble. As seen in the original study by Kiddy et al., a “weight loss of

5% or more in obese subjects has been demonstrated to favorably change insulin (decrease), IGF (decrease), SHBG (increase) and menstrual cyclicity in women with PCOS" (Brewer & Balen, 2010, p. 350).

Because insulin is a critical component to conception, educating women about controlling health conditions like diabetes and following a balanced diet is one way to all them to control part of their own fertility status.

Energy balance and fertility.

In a number of studies reviewed by Brewer and Balen (2010), it was discovered that obese woman are at two to three times the risk of infertility compared to woman with normal BMI values. Overweight and obese woman have increased incidents of anovulation, which precipitates fertility complications. The Collaborative Perinatal Project, an American retrospective study, measured fertility rates in only women with normal menstrual cycles. This study found that within the population, overweight and obese women still had reduced fecundity (Brewer & Balen, 2010).

Many studies focus on the impact obesity has on one's ability to spontaneously conceive, however, there is a new emphasis on the impact of excess weight on assisted reproductive technology (ART). "Prolonged ovarian stimulation, increased gonadotrophin dose requirement, increased incidence of follicular asynchrony, and increased cancellation rates" are among the reported means that obesity may weaken ART success (Brewer & Balen, 2010, p. 356).

A study by van der Steeg et al. (2008) studied the rates of spontaneous pregnancy in subfertile, ovulatory women according to their age. Women with a BMI above 29 kg/m^2 were associated with a statistically significant lower probability of spontaneous ongoing pregnancy

than those women with a BMI between 21 and 29 kg/m^2. They also found that for every BMI unit above 29 kg/m^2, there was a 5% reduction in the probability of spontaneous pregnancy. Despite limitations of this study, including intercourse frequency and male BMI, the results conclude that weight plays a significant role on a woman's fertility status (Brewer & Balen, 2010).

Excess weight and fertility.

Obesity creates an unsuitable and dysfunctional platform for conception. A proper LH:FSH ratio is required for folliculogenesis. An increase in LH production and increased LH:FSH ratio has been demonstrated in obese infertile women. The quantity and quality of oocyte maturation proves to be impaired in obese patients through a variety of methods. The structure and steroid composition within the endometrium of obese women may be impaired due to high levels of estrogen in these patients. Elevated inflammatory markers seen in obesity can also damage the endometrium, reducing implantation success in obese women. After comparing the consistency among studies reviewing obesity and factors that lead to infertility, Brewer and Balen (2010) conclude that oocyte quality is likely more strongly associated with poor conception outcomes than endometrial factors. Obese women require more gonadotrophin stimulation to stimulate the ovaries; this is termed gonadotrophin resistance. Some studies suggest that overstimulation and increased levels of gonadotrophins may impair oocyte and embryo quality, however there is insufficient evidence to consistently prove that obesity impairs embryo quality. While some features require further research, there are several means by which obesity can weaken fertility through ovarian function, implantation structure, and the viability of the oocyte (Brewer & Balen, 2010).

In addition to ovulation, obesity can affect oocyte maturation, endometrial development, uterine receptivity, implantation and survival of the fetus. Excess weight has the ability to alter one's chances of a successful pregnancy. Therefore, weight loss through diet and exercise has become an evidence based first-line therapy in obese women seeking fertility treatment (Brewer & Balen, 2010)

Neuropeptides

Kisspeptin.

Kisspeptin, also known as metastin, is a reproductive protein encoded by the Kiss1 gene in humans. It was originally discovered as a protein able to suppress human metastasis genes (Nestor et. al, 2014). The reproductive neuropeptide has been found to be the most potent activator of GnRH neurons identified thus far (Martin et al., 2014). In addition to regulating GnRH and gonadotrophin secretion, kisspeptin also mediates the onset of puberty and fertility status. Kisspeptin acts upstream of GnRH with its activity controlled by sex steroid feedback as well as metabolic signaling (Skorupskaite, George, & Anderson, 2014). “Kisspeptin-54 is the endogenous ligand of GPR54, a receptor that is highly expressed in GnRH neurons. When administered centrally, kisspeptin stimulates GnRH and gonadotropin secretion in both prepubertal and adult animals” (Nestor et. al., 2014, p. 112).

A recent study including male and females autopsies confirmed that the kisspeptin neurons are located mostly within the infundibular nucleus (also termed the arcuate nucleus in some species) of the hypothalamus with a second large group of kisspeptin neurons in the rostal preoptic area (POA). The infundibular nucleus and the POA are generally known as the pre-optic area of the hypothalamus, to which most kisspeptin cell bodies can be found (Skorupskaite et al., 2014). Kisspeptin is part of a neuronal network named kisspeptin-neurokinin B-dynorphin (KNDy), which consists of kisspeptin, neurokinin B, and dynorphin. Neurokinin B is mostly stimulatory while dynorphin is mostly inhibitory. Infundibular or arcuate nucleus (ARC nucleus) neurons that express all three of these neuropeptides are called KNDy neurons. “KNDy neurons are typically found in the indfundibular region in humans, but POA neurons did not express KNDy neuropeptides” (Javed, Qamar, & Sathyapalan, 2015). KNDy neurons are known as a

special subclass of kisspeptin neurons which “autosynaptically, modulate the pulsatile secretion of kisspeptin and GnRH” (Javed et al., 2015, p. 535-536). Dynorphin’s inhibitory tone and neurokinin-B’s stimulatory action collaborate to balance and control kisspeptin secretion. Kisspeptin then regulates the pulsatile release of GnRH and LH.

Kisspeptin was discovered as GnRH neurons’ pulsatility modulator through multiple studies identifying anatomical, functional and pharmacological evidence to support the idea. GnRH pulsatility is proposed to originate in the ARC nucleus where most kisspeptin neurons are located. Studies show that when kisspeptin is antagonized, GnRH pulsatility is stopped. Pharmacologic studies exhibit increased gonadotrophin pulsatile release, particularly LH, when kisspeptin-1- and kisspeptin-54 are injected into humans (Javed et al., 2015).

Like GnRH, kisspeptin requires pulsatile release to properly function. Research study participants receiving continuous kisspeptin administration were unable to produce neither LH or FSH after just two weeks of treatment. Participants receiving pulsatile kisspeptin administration were able to stimulate LH and FSH release. The suppression of the reproductive axis caused by continuous kisspeptin is likely due to desensitization of kisspeptin receptors since research participants were still responsive to GnRH (Javed et al., 2015).

Kisspeptin and feedback loops.

Kisspeptin is thought to have a large role in mediating the interactions between sex steroids and GnRH. GnRH neurons do not express androgen or estrogen receptors, but the majority of GnRH neurons express kisspeptin receptors. Yet, most kisspeptin neurons express estrogen, androgen, and progesterone receptors (d'Anglemont de Tassigny & Colledge, 2010). Kisspeptin receives both positive and negative feedback signals from sex steroids, which

determines the action kisspeptin has on GnRH. Animal studies reveal increased expression of GnRH mRNA by GnRH neurons and elevated GnRH firing rates after the animals had been exposed to kisspeptin. Research studies on rats “revealed increased expression of Kiss1 mRNA in the hypothalamus of both male and female rates after gonadectomy, with a parallel increase in levels of circulating gonadotrophins” (Javed et al., 2015, p.537). When sex steroids were replaced, Kiss1 mRNA expression dropped. Further research localized the changes to the arcuate or induibular nucleus and also revealed that the changes also took place in humans after menopause.

Furthermore, a specific method by which estrogen blocks kisspeptin-GnRH stimulation has been reviewed. Kisspeptin expresses increased amounts of neurokinin B when responding to low levels of estrogen, demonstrating that kisspeptin and neurokinin B act synergistically to facilitate estrogen negative feedback. Parallel with this, administering kisspeptin antagonist resulted in a failure to increase LH levels in rodents. “These findings imply that estrogen mediates its negative feedback loop by suppressing kisspeptin and neurokinin B release from KNDy neurons, which reduces their stimulatory input to GnRH neurons” (Skorupskaite et al., 2014, p. 7).

To observe the positive feedback response by kisspeptin, animals with similar hypothalamic structures to humans were involved. These studies provided evidence that sex steroids peaks (such as those seen in the menstrual cycle) may be associated with and possibly caused by elevations in hypothalamic kiss1-mRNA expression (Javed et al., 2015). Kisspeptin action on GnRH neurons is dependent on sex steroid release, relying on mostly a negative feedback loop to propel the HPG axis.

GnRH Stimulation.

Kisspeptin predominantly incites GnRH depolarization by activating transient receptor potential canonical (TRPC) channels within GnRH neurons (Nestor et al., 2014). This is independent of intracellular calcium store release. TRPC4 is the main transcript in GnRH neurons, responsible for the majority of GnRH stimulation. Phosphatidylinositol 4,5-bisphosphate (PIP2) regulates TRPC channels. PIP2 inhibits TRPC4 channels, resulting in suppression of kisspeptin's activation of GnRH. Once kisspeptin stimulates GnRH neurons through TRPC4 channels, the stimulatory GnRH signal is conducted through calcium-activated slow after hyperpolarization current (IsAHP). IsAHP currents regulate GnRH firing through two different channels, one of which is as well as prolonging the firing of GnRH by inhibiting the other IsAHP current in GnRH neurons. (Nestor et al., 2014).

About 36-40% of female guinea pigs and mice kisspeptin cells contain leptin receptors (LRb), indicating a direct effect of leptin on kisspeptin. Reduced food intake results in low leptin levels and thus low kisspeptin mRNA expression. Female kisspeptin neurons express many more LRb receptors than male kisspeptin neurons (Nestor et al., 2014). Kisspeptin's leptin receptors and direct relationship with leptin imply direct communications between the two peptides. However, later discussion of leptin interaction with gabaminergic neurons reveals a more complex relationship between leptin and kisspeptin (Nestor et al., 2014).

Pro-opiomelanocortin (POMC) Neurons.

Pro-opiomelanocortin (POMC) neurons have synaptic interactions with GnRH neurons, proposing a direct influence on GnRH secretion (Celik et al., 2015). POMC neurons are made up of many compounds. Two of the main compounds relative to energy homeostasis and

reproduction include a-melanocyte stimulating hormone (a-MSH) and B-endorphin. a-MSH has anorexigenic effects on melacortin-Y receptor (MC4R), its binding site. B-endorphin has an inhibitory effect on gonadotropin release.

Leptin receptors are found on about 50% of POMC neurons. Leptin has also been proven to increase POMC expression and the release of a-MSH. This results in increased GnRH secretion and an anorexigenic outcome. In a study involving mice, the knockout of LRb in POMC cells led to increased weight gain, but had no noticeable impact on fertility (Nestor et al., 2014). Celik et al. (2015) discovered that when mice POMC neurons lack the leptin and insulin receptor, they have severe reproductive deficiency. The same article proposes that POMC neurons work together with kisspeptin and NPY to balance and regulate leptin's effect on reproduction (Celik et al., 2015). While there are insufficient studies to conclude the impact of POMC neurons on fertility, the direct connection between POMC neurons and GnRH neurons suggests a meaningful association.

Neuropeptide Y.

Neuropeptide Y (NPY) is a peptide that stimulates increase food consumption by activating Y1 and Y5 G-coupled protein receptors. Agouti-related peptide (AgRP) is a type of NPY neuron that antagonizes melancortin-3 and -4 receptors. This reveals an anti-anorexigenic affect, opposite of that of leptin and POMC neurons (Nestor et al., 2014). "AgRP neurons release AgRP, neuropeptide Y, and GABA and are important in regulating body weight" (Javed et al., 2015, p. 535-536).

The antagonist to NPY and AgRP is gamma-aminobutyric acid-a (GABAa). a-MSH has also been shown to oppose the effects of NPY (Nestor et al., 2014). When GABA transporters

are deleted from AgRP neurons in mice, the mice are “lean, resistant to obesity and have an attenuated hyperphagic response to ghelin” (Tong et al., 2008, p. 1). Tong et al. (2008) also noted that deleting NPY neurons without altering GABA activity in mice had little effect on body weight. The review concluded that GABAnergic activity may also be important in weight control (Tong et al., 2008).

NPY suppresses reproductive pathways; alterations in NPY by a multitude of neuropeptides results in improved fertility. NPY knock out mice are typically fertile and lean, while obese mice with an infertile phenotype have reportedly high NPY levels. NPY is associated with reduced LH secretion in obese mice. Deprivation of NPY neurons or ablation of AgRP neurons resulted in more fertile mice (Celik et al., 2015).

There is an inverse relationship between leptin and NPY neurons. Fasting reveals decreased leptin and increased NPY concentrations. Leptin has a direct effect on NPY neurons with LRb receptors being expressed on NPY neurons. When leptin is administered, NPY mRNA expression is reduced and fertility is improved in obese mice (Nestor et al., 2014).

There is a reciprocal effect between kisspeptin and NPY. Kisspeptin initiates gonadotrophin release and fertility while NPY has suppressive effects on the HPG axis. Kisspeptin was found to inhibit NPY neuronal activity by exciting presynaptic GABA release (Fu & van den Pol, 2010).

NPY neurons also express estrogen receptors with estradiol (E2), the most active estrogen, having a suppressive effect on NPY. Altogether, leptin, kisspeptin, and estradiol block the suppressive actions of NPY on reproduction (Nestor et al., 2014).

Connections between Energy Balance and the HPG Axis

Alterations in energy stores produce changes in a variety of hormones and neuropeptides, which signal feedback to the central nervous system so as to control metabolism and fertility (Celik et al., 2015). There is potential to use these correlations to predict one's fertility status according to their nutrition status. While there are many intricate interactions between energy balance and reproduction, these sensitive pathways operate in a manner that facilitates conception when appropriate. In opposition, disturbances within these interactions between nutrition and fertility may alter one's ability to conceive.

Estrogens.

Estradiol (E2) is the most active pre-menopausal estrogen secreted by the female ovarian follicle. There are numerous roles of estradiol including regulating GnRH secretion and stimulating LH and FSH synthesis (Brzyski & Knudtson, 2013). In addition to reproductive physiology functions, estradiol is also "involved in the regulation of appetite, energy expenditure, body weight, and adipose tissue deposition and distribution in females" (Nestor et al., 2015, p. 109-110). Depleted estrogen levels result in weight gain, as often seen with menopause.

Studies involving ovarectomized female guinea pigs show that estradiol up regulate the expression of B-endorphine protein in POMC neurons while estradiol reverses elevated NPY mRNA expression (Nestor et al., 2015). STX is a selective G-coupled membrane estrogen receptor (Gq-mER) ligand (Smith, Bosch, Wagner, Ronnekleiv, & Kelly, 2013). Estradiol (E2) and STX desensitize the coupling of $GABA_B$ receptors to G protein-coupled inward rectifying K channels (GIRKs) by increasing the excitability of POMC neurons, thus creating an overall

stimulatory influence on reproduction (Smith et al., 2013). In addition to stimulating reproduction, the excitatory effects of STX on POMC neurons also helps control energy homeostasis, since POMC neurons have anorexigenic effects. Smith et al. (2013) concluded that STX may provide hormonal influence needed in post-menopausal women providing an additional weight control component without the negative side effects seen with hormone replacement therapy (HRT) (Smith et al., 2013).

Estradiol has opposing effects on NPY compared to the hormone's effect of POMC neurons. Smith et al. (2013) were the first group of researchers to confirm that estradiol is able to inhibit NPY/AgRP function by signaling $GABA_B$ in a study conducted on mice. The study found that STX enhanced $GABA_B$ signaling at higher rates and also reduced food consumption in guinea pigs. Smith et al. (2013) concluded that the receptor by which STX attaches (G1-mER) "regulates NPY/AgRP and POMC neurons in a reciprocal manner by enhancing or attenuating $GABA_B$ and GIRK channel coupling, respectively" (p.7).

Overall, proper estrogen concentrations are a vital component to both energy balance and fertility (Nestor et al., 2015).

Leptin.

Energy stores are responsible for ensuring there is sufficient energy to carry out reproduction. Among the chemicals involved in sending nutrition status messages to the HPG axis include leptin and ghrelin. A positive energy balance will signal leptin to the hypothalamus, which stimulates GnRH. In contrast, a negative energy balance stimulates ghrelin, which suppresses GnRH (Celik et al., 2015).

GnRH neurons do not express leptin receptors. Therefore, it is suggested that the actions of leptin are indirect and there are intermediate players that connect signals of metabolic state with the reproductive axis (Celik et al., 2015). Neuronal networks like kisspeptin, POMS, and NPY are among the intermediate players that are thought to be involved in connecting leptin and GnRH. In an article reviewed by Celik et al. (2015), it was found that eliminating all leptin signaling in GnRH neurons did not impact reproductive performance; however eliminating leptin receptors in the entire forebrain did impair fertility. In addition, "leptin deficient, obese mice are in general infertile with low sex steroid and gonadotropin levels" (Celik et al., 2015, p.35). This reestablished the idea of intermediate factors playing a role in leptin's stimulatory effect on GnRH with leptin still having a large impact on GnRH.

Each direct interaction between leptin and the neuronal mediators is customized. Leptin stimulates POMC neurons directly by activating TRPC neurons. Leptin hyperpolarizes NPY cells by activating Katp channels. STX enhances the inhibitory capabilities of GABAa receptor on NPY neurons (Nestor et al., 2015). About 40% of kisspeptin neurons contain leptin receptors through which leptin stimulates kisspeptin. Since kisspeptin has its own receptors on GnRH neurons, the leptin-kisspeptin-GnRH connection stands as a possible network through which leptin's signal is transferred to GnRH (Celik et al., 2015).

There is evidence to suggest that leptin-kisspeptin signaling is impacted by weight. Leptin deficient obese mice have also been shown to have significantly fewer kisspeptin mRNA levels. When leptin was restored in these mice, kisspeptin levels remained inadequate. Deficient or excessive energy stores expressing insufficient leptin concentration may have other mediators signaling the nutrition status message to the hypothalamus. The study's inability to restore leptin and kisspeptin levels might indicate that the energy store issue must be solved before the central

nervous system will allow for reproduction (Celik et al., 2015). A different review by Martin et al. (2010) concluded that when leptin levels are low, kisspeptin is also low. This review suggests leptin may be the upstream activator of the Kiss1 gene. It requires properly functioning leptin to increase kisspeptin and thus increase GnRH. The same review found that Kiss1 gene expression is reduced in food-deprived rats and obese mice, which exhibits leptin's sensitivity to both food deprivation and excessive energy stores. Despite the need for leptin to activate kisspeptin, studies show that removing leptin receptors from kisspeptin neurons did not alter puberty and fertility, possibly due to compensatory actions (Martin et al., 2014).

Leptin receptors have also been identified on the ovaries, suggesting a direct stimulatory effect on ovulation in a LH-independent manner. Vazquez et al. (2015) hypothesized that elevated leptin, as seen in obesity, may actually inhibit leptin's effect on the ovaries.

Leptin is responsible for transmitting a positive energy balance or satiety signal from peripheral tissue stores to the hypothalamus. In terms of reproduction, leptin serves as a checkpoint to continue down the HPG pathway. If adequate, leptin is suggested to then stimulate a variety of intermediate peptides, which have a direct role in stimulating GnRH. These mediators respond differently according to the leptin levels. Overall, leptin is responsible for ensuring there is sufficient energy to carry out conception and pregnancy through indirect contact with GnRH.

Leptin and GABAergic neurons.

Gabaminergic neurons have mostly inhibitory properties in the human body. Within the reproductive axis, gabaminergic neurons suppress reproductive function and puberty development. The inhibitory neurons also decrease kisspeptin, gonadotropin production, and

inhibit positive feedback response to sex steroids. Some gabaminergic neurons express leptin receptors, which are thought to inhibit the transmission of leptin's information to the HPG axis. If leptin is able to bind to the GABA receptors they can inhibit the suppressive effects of gabaminergic neurons (Martin et al., 2014). This is another way that adequate leptin levels are able to advance the reproductive pathways. Without leptin responsive receptors or enough leptin, leptin is not able to attach and inhibit the suppressive properties of GABA neurons. This results in difficulties responding to negative feedback and reduced concentration of LH and FSH. GABA neurons that are not suppressed by leptin or have mutated leptin receptors have been correlated with reduced kisspeptin levels (Martin et al., 2014). Only about 40% of female kisspeptin neurons possess leptin receptors. While kisspeptin's leptin receptors may serve as a direct contact for leptin, kisspeptin, and GnRH connection, the role of GABA neurons within the leptin-kisspeptin network has produced the question of whether this network has a direct or indirect connection.

Leptin is believed to act centrally at the hypothalamus prior to kisspeptin interaction in the HPG axis. Research supports the idea that the interactions between leptin and gabaminergic neurons are upstream of kisspeptin and its contact with GnRH. A study supplementing kisspeptin-10 (Kp10) to GABA malfunctioning mice resulted in improved LH and FSH production. Researchers concluded that kisspeptin is able to independently improve GnRH stimulation and gonadotropin production despite malfunctioning GABA neurons. The role of leptin on gabaminergic neurons within the reproductive axis is substantial, yet there is evidence that defects to the leptin-GABA linkage may be resolvable with ample amounts of kisspeptin (Martin et al., 2014).

There may be a functional role of gabaminergic neurons with leptin receptors in reproduction. Mice without GABAergic neurons containing leptin receptors had poorer reproductive function and vaginal development critical for fertility. “Female mice lacking functional leptin receptors in GABA neurons have hypogonadotropic hypogonadism, similar to leptin-deficient and resistant mice” (Martin et al., 2014, p. 6053). These mice have ovarian failure and anovulation (Martin et al., 2014).

GABAergic Neurons Impact on Nutrition and Fertility.

There are multiple neuropeptides involved in the function of GABAergic neurons with an overall inhibitory synaptic activity on the hypothalamus. Estradiol and STX have been proven to stimulate or minimize the GABA signaling, which then determines the expression of the involved neuropeptides. Among these peptides are leptin, POMC neurons, and NPY. In this manner, reproductive hormones connect peptides conveying one’s nutritional status.

Proper balance and function of the hormones and peptides part of the HPG axis is critical for energy balance and fertility. Over or under-expression may send inappropriate messages to the central nervous system about one’s energy stores, ensuing not only an unhealthy body composition, but could also compromise fertility status.

GABA signaling affects each peptide discussed previously in a specific way in order to relay the proper message to the CNS. While the effects of GABAergic neurons are overall inhibitory, the action is necessary to regulate energy balance and fertility. Deleting GABA receptors from NPY/AgRP neurons has shown to produce lean mice whom are resistant to obesity (Smith et al., 2013).

Adipose tissue signals.

Energy status is distinguished based on the amount of available adipose tissue. Adipose tissue and its signaling is one way the body connects energy status to reproduction. Adipose tissue sends metabolic signals such as hunger, satiety, and obesity to the hypothalamus mainly through peripheral peptides part of adipose tissue and the GI tract. When the amount of energy or adipose stores changes, a signal is sent to the hypothalamus through fluctuations in leptin, ghrelin, kisspeptin, NPY and insulin to translate the message. The HPG axis receives the signals from the hypothalamus and determines how this will effect that person's reproductive axis (Celik et al., 2015).

Ghrelin.

Ghrelin is an indicator of negative energy balance and hunger. It antagonizes GnRH neurons, resulting in decreased GnRH. The hormone is secreted from the stomach and applies its effect on the ARC nucleus. "Unlike leptin deficient mice, ghrelin knockout mice are neither obese or reproductively impaired" (Celik et al., 2015, p. 36). Ghrelin has been shown to control kisspeptin expression. Supplementation of injected ghrelin resulted in LH pulsatility and hypothalamic Kiss1 expression. NPY Y5R antagonist is able to inhibit ghrelin's effects. Ghrelin functions to suppress reproductive processes when adequate energy stores are unavailable unless the NPY Y5R antagonist is able to suppress ghrelin (Celik et al., 2015).

Insulin.

It is known that insulin facilitates reproduction by exciting reproductive tissues and hormones. In a review by Celik et al. (2015), the researchers concluded that insulin signaling in

the hypothalamus improves fertility and regulates GNRH neurons, however insulin's effect on the reproductive axis is thought to be indirect. Rather than insulin directly stimulating GNRH neurons, kisspeptin likely mediates insulin's effect on the HPG axis (Celik et al., 2015).

Another key aspect of insulin's role on reproduction is the nutritional status of the patient. Insulin levels are controlled by weight, diet behaviors, and other comorbidities such as diabetes. As previously mentioned, deficient or excessive insulin levels dramatically alters insulin's function on the reproductive axis, resulting in changes in fertility status.

Application to Clinical Practice

There is strong evidence to support the role of energy status in reproduction through a variety of hormones and peptides, each having individual roles within the HPG axis. The intricate physiology of these relationships can be deciphered into concepts useful for clinical practice.

Estrogen.

Estrogen acts as a stimulatory hormone within the HPG, axis with functions expanding past its part in the negative feedback loop, propelling the ovarian cycle. In addition to low estrogen levels directly signaling GnRH secretion, estrogen has also been proven to regulate appetite, body weight, energy expenditure and adipose tissue deposition. Altogether, estrogen helps to maintain a healthy body weight. Estrogen's inhibitory and stimulatory role on NPY and POMC neurons, respectively, assists in reproduction excitation while also controlling body weight. Limiting NPY inhibits orexigenic signals, while stimulating POMC neurons incites an anorexigenic state, thus controlling appetite and weight gain (Brzyski & Knudtson, 2013; Nestor et al., 2015; Smith et. al., 2013)

A study completed by Souter et al. (2011) reported the effects of a woman's BMI on superovulation/intrauterine insemination cycles. The study found an inverse relationship between BMI and estrogen levels. Overweight and obese women had significantly lower estrogen levels compared with women of normal BMI. Each BMI categories success rates were based on the same number of cycles. The obese class required higher doses of hormone medication for conception. The "medium and high BMI groups had better odds of achieving pregnancy and live births compared with the lowest BMI group" (Souter et al., 2011). Once high-BMI women were

given doses to compensate for weight, their success rates were similar to normal BMI participants. Weight can have a sizeable influence on estrogen, yet this is just one component of metabolic-induced infertility.

Estrogen's multi-excitatory role in fertility compels a significant concept for clinicians caring for couples trying to conceive. Understanding these functions in entirety may guide professionals to assess a woman's hormone profile, especially if she struggles with body composition. Evaluation of women's weight, body fat, endocrine function as well as the anatomy and physiology of reproductive organs may be part of an appropriate plan for reproductive assistance as each may influence estrogen.

Leptin.

When leptin acts appropriately, the peptide encourages a positive fertility status by using a number of mediators to indirectly stimulate GnRH release. Leptin signifies positive energy balance, stimulates POMC neurons, inhibits NPY, and has various kisspeptin effects, all of which excite the HPG axis.

Insufficient or excessive energy stores express inadequate leptin concentrations. Deficient energy stores do not have enough adipose tissue to signal proper amounts of leptin. In opposition, excessive amounts of adipose tissue are associated with leptin resistance in which the hypothalamus becomes less sensitive to leptin. In the case of leptin resistance, mediators (such as kisspeptin, NPY, and POMC) are not able to read leptin's signal and stimulate GnRH. The arcuate nucleus then requires higher amounts of leptin to recognize the adipocyte's signal, resulting in impaired signaling to the hypothalamus. In addition to leptin's hypothalamic receptors, its ovarian receptors may also be suppressed with excessive leptin. Due to improper

leptin levels and signals, abnormal weight and adipose tissue stores may cause problems with fertility (Celik et al., 2015).

Accurate levels of leptin are crucial to enhancing GnRH stimulation required for conception. Whether a woman is underweight or overweight may impact her ability to conceive based solely on the ability for her body to recognize that her energy stores are appropriate for conception. When counseling women on non-invasive strategies to improve her fertility status, it is important for providers to encourage healthy behaviors. Without proper education, patients may overindulge in certain foods or exercise or follow extremely low calorie diets. Referring couples to physicians, advanced practice providers, or dietitians with reproductive nutrition experience may help women formulate a healthy lifestyle individualized for her body. While it's not common at the time in the United States, examining a woman's leptin profile may help clinicians assess their patient's fertility status based on metabolic factors (Celik et al., 2015).

Ghrelin.

Ghrelin acts as an inhibitory hormone in reproduction. Individuals who are malnourished or underweight transmit more ghrelin as a signal of limited energy stores. This signals the HPG axis that nutrition is inadequate for conception and restricts the body's ability to conceive. Appropriate energy stores or moderate weight gain lowers ghrelin and increases leptin. As long as the weight gain is not abundant, leptin will not become resistant and will stimulate the HPG axis for proper fertility function (Celik et al., 2015). Table 2 displays normal levels of ghrelin and leptin in adult females according to nutrition status.

Knowing this importance of weight management, women may use this idea for diet and exercise purposes. A sudden loss in energy stores will increase ghrelin and prohibit HPG

stimulation. Contrary to this, excessive weight gain, may exaggeratedly elevate leptin, disabling its effect on reproduction.

Within fertility, many of the nutritional treatment strategies are aimed at weight loss. However, there is marked evidence that shows negative energy balance plays a negative role on reproductive capabilities. Patients must be educated about a healthy lifestyle as opposed to a starvation diet. Extremely low calorie diets and an underweight BMI greatly disable the stimulus necessary for conception as seen with the inhibitory effects of substances like ghrelin.

Table 2. Normal leptin and ghrelin levels. The above table lists the normal values of female leptin and ghrelin levels according to the Mayo Clinic.

Population	**Ghrelin**	**Leptin**
Normal weight	520-700 pg/mL	3.3-18.3
Obese – prior to diet	340-450 pg/mL	
Obese – post weight loss	450-600 pg/mL	
Obese – post gastric-bypass surgery	Up to 120 pg/mL	

"Ghrelin Total, Plasma," by Mayo Clinic: Mayo Clinical Laboratories, 2016. http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/57902.
"Leptin," by Mayo Clinic: Mayo Clinical Laboratories, 2016. http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/91339.

Kisspeptin.

Kisspeptin's role in reproduction appears to be controlled by energy balance and leptin signaling. Research has proven that without enough kisspeptin signaling, there is less stimulation to the HPG axis, demonstrating its significance. The amount of kisspeptin is correlated with energy balance. Deficient leptin levels, as seen with negative energy balance, are related to low

kisspeptin levels. Leptin resistance, in which excessive energy stores alter the body's response to leptin, is also associated with low kisspeptin. In order to manage the leptin and kisspeptin profile in abnormal energy balance states, the nutrition status must first be resolved as opposed to chemically supplementing peptide levels. The relationship between leptin and kisspeptin supports the idea that a woman's diet and energy stores may strongly influence her ability to conceive. Helping women maintain a nutritious and active lifestyle, with a goal of a normal BMI and appropriate body fat composition, may ultimately have a substantial impression on her fertility status (Celik et al., 2015; Nestor et. al, 2014).

Kisspeptin is being supplemented in research studies to help with various reproductive conditions. As mentioned previously, the rate and dose of kisspeptin determine the effectiveness of the neuropeptide. Continuous high doses of parenteral kisspeptin infusion often initiate tachyphylaxis, resulting in suppression of the HPG axis. In contrast, an intermittent bolus infusion of kisspeptin increases kisspeptin levels and stimulates GnRH production. Given this concept, the use of intermittent kisspeptin administrations has been shown to help initiate ovulation and augment the success of reproduction assistance. Prague and Dhillo (2014) examined the clinical uses of kisspeptin in a recent review. The review confirmed success in using intermittent kisspeptin administration in both healthy women and women with hypothalamus amenorrhea (termed sub-fertile) to stimulate an LH surge. Kisspeptin administration is most effective when given in the pre-ovulatory stage when an LH surge is crucial. Researchers hypothesize that appropriate timing may improve egg maturation in women undergoing IVF. This idea was tested in one of the reviewed studies that involved injection of kisspeptin in women receiving IVF therapy. "A single subcutaneous injection of kisspeptin-54 was used to trigger egg maturation after standard preparation with recombinant FSH injection

and a GnRH antagonist to achieve superovulation and prevent premature ovulation. ” (Prague and Dhillo, 2014, p.241).

Prague and Dhillo’s 2014 study states:

> Participants received four doses of kisspeptin…with the majority of patients receiving the three highest doses (6.4, 9.6, and 12.7 nmol/kg) in an adaptive design for dose escalation. Serum kisspeptin, LG, FSH and progesterone levels all increased after the trigger injection. Egg maturation was observed with each dose of kisspeptin; however, the two higher doses improved the ease of egg collection. Biochemical pregnancy occurred in 40% and clinical pregnancy was achieved in 23% (12 of all 53 patients treated). Ten of these women had live births and 12 healthy babies were born. (p.241)

Research evidence is increasing the knowledge of kisspeptin’s reproductive role and the potential fertility success couples may have with regulating its concentration. The social and psychological stress as well as the possible complications of IVF therapy is a concern for sub-fertile couples. Yet, the ability of kisspeptin to make fertility treatments more successful and require less stimulation creates better hopes for couples using IVF (Prague & Dhillo, 2014). Because of this achievement, there is potential for kisspeptin to be monitored and regulated more commonly in the clinical setting.

GABA.

GABAergic neurons play a primarily inhibitory role within reproduction. Metabolic and neuronal peptides either stimulate or inhibit the actions of GABA based on one’s nutrition status. If there are adequate stores needed for reproduction, the peptides regulate GABA in a way that

allows for reproduction. Therefore, GABA can be seen as a switch, either turned on or off by metabolic peptides in order to regulate reproduction (Martin et al., 2014).

A woman's energy status controls whether GABA drives inhibitory or stimulatory signals to the HPG axis. Underweight women may not produce proper metabolic peptides to affect GABA signaling thus maintaining the inhibitory function. Overweight women may have abundant or resistant metabolic peptides that are unable to alter GABAergic neurons. Either case may cause unsuitable or insufficient messages to be relayed to the HPG axis and result in reproductive difficulties (Martin et al., 2014; Nestor et al., 2015; Smith et al., 2013).

The positive effects of proper nutrition on conception may be seen as the driving force for encouraging a healthy lifestyle for reproductive assistance therapy. However, the negative consequences that an unhealthy energy status has on a woman's reproductive axis are important for understanding what is decreasing her chances of becoming pregnant. If women are seeking natural fertility treatment through diet and exercise, they need to understand how any current unhealthy behaviors are affecting their reproductive system. Simply suggesting a specific diet, exercise regimen, or weight loss goal does not teach patients the reasons for why change is needed. In order to reverse a currently depressed reproductive axis towards a stimulated, more fertile status, the inhibitory components must be addressed. In the case of elevated GABAergic neuron concentrations, altering a woman's diet may provide success (Martin et al., 2014; Nestor et al., 2015; Smith et al., 2013).

Adipose Tissue.

Adipocytes send a variety of signals through metabolic peptides (leptin, ghrelin, insulin). These messages are read by neuropeptides including kisspeptin, POMC, and NPY. Reproduction

relies on adipocytes to transmit messages that signify that energy stores are adequate or inadequate for conception processes. The amount of adipocytes determines whether the message sent to the hypothalamus is inhibitory or stimulatory (Celik et al., 2015).

Clinical application of adipocyte signaling may be more complex than simply eating a balanced diet. Adjusting calorie intake and implementing an exercise routine is a good starting point. However, if the amount of adipocytes is not modified, one may not see a difference in fertility status. Initial body fat assessment, metabolism evaluation, and a more specific diet may be necessary. There are differences in the way people metabolize and absorb foods and rates in which they lose weight through exercise. Hormone levels may alter body fat composition. The time and type of exercise will determine the amount of fat burned. Because of the multifaceted approach, professionals that are experienced in specific diet and exercise routines targeting body fat may be necessary for women with fertility struggles in which body fat is a suspected contributor.

Insulin.

Insulin has a primarily stimulatory role within the reproductive system when available in sufficient amounts executing its functions properly. However, women may face difficulties with conception if insulin function is disturbed. Diabetes, persistent spikes in blood sugar, and impaired pancreatic function may reduce the amount of accessible insulin. Conditions such as diabetes, metabolic syndrome, and obesity increase the risk of causing insulin resistance due to the effects of one's genetics, insulin levels, diet, and/or weight. This leads to the demand for increased insulin and a balanced, limited carbohydrate diet (Celik et al., 2015).

Couples and clinicians should understand the impact of insulin levels on fertility success. Implementing a healthy diet in which carbohydrates are monitored closely would help regulate insulin and one's weight. Lab tests that assess a woman's glucose, $HgbA_1C$, insulin, and lipase would likely diagnose diabetes, pre-diabetes, or pancreatic disease that may not have been previously noted. Discovering abnormal lab values related to insulin function would allow providers to develop appropriate treatment strategies based on what may challenge reproductive outcomes. While it is not practical to draw labs on all women trying to conceive, a simple blood draw may provide better insight for women struggling to get pregnant. If abnormal labs are found that indicate insulin-based etiology, non-invasive interventions such as weight and nutrition management have the potential to improve a woman's fertility.

Energy balance based treatment.

While there is a common theme of formulating healthier lifestyle behaviors to improve reproductive status, there seems to be specific approaches that lead to such fertility success. Immense research supports the use of particular diets, BMI classifications, and surgeries to reach conception. A review by Sim et al. (2014), examined seven studies that looked at the effect of "dietary intervention (excluding exclusive use of VLED) in overweight and/or obese women prior to assisted reproduction treatment" (ART) (p. 841-842). These studies also incorporated exercise and behavioral support. Four of the seven studies discovered statistically significant increases in pregnancy rates and/or live births. The review also noted decreased number of ART cycles needed, regularization of menstruation, and increase in natural conception. Within the four studies, one used a very low energy diet (VLED) for six weeks followed by a hypocaloric diet. The results were less desirable with lower pregnancy rates (48%) compared with that of the

other three studies (75-85%). Another VLED study delivered poor outcomes despite an average weight loss of 5.6 kg. Out of six participants in the VLED study, none of the women became pregnant and “half of the participants did not achieve a single fertilization” (Sim et al., 2014, p. 845).

“The Fertility Fitness Program,” founded by Dr. Norman in Australia, is a 6-month program of weekly group sessions targeting behavioral changes that include exercise and diet” (Duval et al., 2015, p. 2). The program has lead overweight, infertile, anovulatory women to lose weight, restore ovulation, and in a study of 13 women, 11 became pregnant (Duval et al., 2015).

A review by McLean and Wellons (2012) examined various research studies uncovering the effect of lifestyle modifications on fertility. The studies concluded that a weight loss reduction of at least 5-10% impacts fertility. A number of the studies included diet, exercise or both as beneficial treatment strategies, however there was insufficient evidence to designate an optimal diet or exercise routine (McLean & Wellons, 2012).

Most studies to date concerned with the effects of nutrition status on fertility interpret the success of low calorie, moderation-based diets. Very few studies have analyzed the outcomes of specific diets. For example, there is only one formal study examining the ketogenic diet and its use in fertility, however it showed mixed outcomes. The ketogenic diet is composed of a mostly fat-based diet, restricting most carbohydrate and protein foods. In a study of overweight and obese women with PCOS who followed a ketogenic diet, there was a decrease in body weight, fasting insulin, LH/FSH ratio, and testosterone. Forty percent of participants who completed the diet became pregnant within 24 weeks of the study. However, there was a high drop out rate within this study with only 5 of 11 participants completing the study. There is question as to whether the potential success of a ketogenic diet is based on weight loss or due to the

composition of the diet. The disadvantages of a high-fat diet include the risk of ovulatory dysfunction associated with consuming high amounts of trans-unsaturated fats. Increasing the amount of fat in one's diet puts a women at risk for consuming abnormally high amounts of trans-unsaturated fats, commonly found in prepared or packages foods and certain animal fats. Following a strict diet, such as the ketogenic diet, requires close monitoring by a skilled clinician to educate the woman about proper nutrition choices (Kulak & Polotsky, 2013).

The detrimental effect of obesity and insulin resistance on the reproductive system is the foundation of a study conducted by Becker, Passos, and Moulin (2015). This was another example of a specific diet; this time instead of focusing on just restricting calories, carbohydrate intake was also modified. The study involved a random block-design controlled trial of 26 overweight or obese infertile women in Brazil. The women were either assigned to a hypocaloric, low glycemic index (LGI) diet or a control group for 12 weeks. All dietary advice was given by a qualified dietitian who recommended a calorie range of 20 kcal/kg of current body weight, instructed participants about the proper use of the glycemic index, and provided other healthy diet tips such as portion control. Nutrition guidelines were based on the hypothesis that a weight loss of about 5.5% prior to the IVF cycle would improve outcomes (Becker et al., 2015).

All participants completed a thorough 3-day food record at week 6 and 12. All women had a BMI greater than 25 kg/m^2 and were less than 40 years old. Anthropometric data and dietary assessments were done at week 0, week 6 and week 12. Blood samples and consistent body composition measurements were taken at each assessment period. Nutritional advice and compliance was reinforced at week six and IVF was initiated immediately after the follow up visit on week 12 (Becker et al., 2015).

At the conclusion of the 12 week trial, the low glycemic index (LGI) group had a “greater reduction in body mass, BMI, percentage of body fat, waist:hip ratio, and hip circumference” than participants in the control group. The LGI diet group also had a 26% decrease in leptin levels as opposed to the control group, which did not see a change in leptin levels. There was not a significant difference in ghrelin level changes between the two groups. “The LGI-diet group had 85.4% more oocytes retrieved than did the control group” (Becker et al., 2015, p. 1369). The study also discovered a “moderate negative correlation between the number of oocytes retrieved with BMI, percentage of body fat, and leptin concentration” (Becker et al., 2015, p. 1369). Of the 14 patients in the LGI diet group, 3 women had spontaneous pregnancies during the follow-up, each of which resulted in live births. No pregnancies were generated from the control group. Becker et al. (2015) suggested that the results of the study were predominantly due to energy status signaling on the reproductive axis. Reductions in leptin concentrations were associated with increased oocytes when coupled with a balanced diet. While the research exhibited evidence to support their hypothesis, there were limitations such as small sample size and short duration of the trial. Closer diet monitoring would also be helpful to predict specific diet-induced therapies. As a whole, this trial supports the recommendation for overweight women to attempt weight loss through a balanced diet prior to beginning ART (Becker et al., 2015).

Various weight loss procedures deliver better success with reproductive therapies. Women who participated in medical procedures and bariatric surgery reported the greatest weight losses, and also had better fertility outcomes. In the review by Sim et al. (2014), “88% of women in the studies became pregnant and 83% achieved a live birth”, which is comparable to those who used lifestyle interventions for weight loss” (p. 845). The women involved in these studies had previous, unsuccessful attempts with spontaneous conception and experience using

ART or IVF. Within the 88% of women who attained a pregnancy after weight loss, conception occurred either within one year by spontaneous pregnancy, IVF, or ART.

Sim et al. (2014) concluded that within their reviews "reproductive improvements were evident in women who were still classified as obese after the weight loss intervention" (p. 846). This expands the idea of weight loss versus improved body weight classification. Weight loss, as opposed to a specific BMI class may be more necessary. Encouraging behaviors that help women reach a healthier weight seem to show better fertility outcomes.

A woman's age may change the importance of certain reproductive assistance strategies. Some women may not have the "time" to go through with behavioral changes and turn to fertility treatments. In a review conducted by Sim et al. (2014), BMI appears to impact fertility status greatest in younger women. The effect of BMI on fertility is much less pronounced in women over 37 years of age. In older women, age has a greater impact than BMI as the ovarian reserve is more depleted. The study suggests that weight loss strategies such as diet modifications, exercise, and weight loss surgery should be reserved for younger women who are less time-sensitive (Sim et al., 2014). Despite age having a greater impact on one's fertility after a certain age, nutrition status still plays a role. Thus, incorporating healthy lifestyle behaviors in addition to assisted reproduction therapies in older women may further enhance a couple's ability to conceive.

Conclusion

The data collected in this literature review concludes that energy status does have an impact on fertility status. Multiple metabolic peptides are capable of capturing one's nutrition profile and communicating this message to the neuropeptides involved in reproduction regulation. The complex relationships between energy status and reproduction are known, yet the peptides have yet to be used in the clinical setting to gauge fertility status. Nor have definitive, fertility-enhancing peptide levels been established. Successful fertility outcomes in the included studies were recorded in women of various body habitus' and BMIs as well as range of diet and intervention formulations. Therefore, it may be more appropriate to establish recommended fertility marker levels based on each individual woman's body type and metabolism, rather than strict guidelines for all women. Further research is needed to evaluate fertility marker levels in women of various body types and determine levels that promote conception. Research should also focus on nutrition therapy's ability to improve fertility status in overweight or underweight women desiring pregnancy who have not yet undergone assisted reproduction therapy. While there are several benefits to using nutrition-based therapy as a first-line infertility treatment, significant reproductive outcomes must be discovered to declare these peptides as routine fertility markers.

Discussion

Multiple etiologies for impaired fertility status involve metabolic conditions and body configuration. According to recent findings, the first-line solution in most cases is to make lifestyle changes including diet, exercise, and weight management. These interventions may be used to treat different hormonal or peptide dysfunctions, yet together, these interventions have the potential to create a normal panel of physiologic components that promote reproduction. Lifestyle modifications are less expensive and less invasive than fertility treatments. Implementing healthier choices also promotes a nutritious, preventative way of life past conception. The intervention characteristics make them appealing options for couples experiencing fertility struggles.

Because of the number of physiologic factors impacted by lifestyle modifications as well as the success rates noted by numerous research studies, the role of healthy behaviors may serve as a turning point in reproductive assistance. Clinicians who care for women trying to conceive may use this knowledge to educate patients about the impact that their diet, metabolism, and weight have on conception success rates. Advanced practice providers and physicians managing patient care plans would likely need to educate themselves about weight management and healthy nutrition choices. Providers uncomfortable discussing the topic with patients may refer women to a dietitian or fertility specialist that can counsel her about healthy behaviors. Employing dietitians within practices such as family, obstetrics, and fertility medicine would be an option for helping couples achieve fertility prior to more costly, invasive interventions. In conclusion, there is pronounced evidence that suggests a noteworthy role of nutrition and healthy lifestyle behaviors in regulating a woman’s reproductive system and improving her fertility status.

Physicians, physician assistants, and nurse practitioners have an important role of educating patient's about their reproductive anatomy, physiology, and abnormally functioning components within the system. It is the provider's responsibility to discover how they can help their patients become pregnant while keeping in mind their overall health and safety. Lifestyle changes like nutrition and exercise are changes frequently reviewed in the primary care setting to which physician assistants commonly work. Incorporating this discussion of making lifestyle changes prevent disease and improve fertility status is a crucial responsibility that mid-level providers should do.

Key Points

1. A number of energy balance markers communicate with neuropeptides that regulate the hypothalamic pituitary gonadal (HPG) axis. There appears to be changes in reproductive function reflective of one's nutritional behaviors and body composition. This process has been interpreted as a protective mechanism to ensure there are adequate nutrients to support a growing fetus.
2. Estrogen, leptin, insulin, and kisspeptin, are among a group of metabolic and neuroendocrine peptides that stimulate the HPG axis act to enhance fertility when in appropriate amounts and functioning properly. A woman's body composition and energy status creates a platform for these peptides to function as so.
3. While a positive energy status may be beneficial to reproduction, overabundant stores can lead to insulin and leptin resistance, which impairs the body's ability to respond to the hormones.
4. Depleted energy stores results in the elevation of several metabolic and neuroendocrine peptides, which act to inhibit activation of the HPG axis. These include ghrelin and GABAergic neurons.
5. The body composition in which fertility is enhanced or impaired is not well defined and seems to be individualized. In many cases, women improving their lifestyle and moving towards a healthier weight resulted in reproductive enhancement. "Healthy" body compositions and lifestyle behaviors are consistently associated with better fertility outcomes than highly restrictive behaviors.

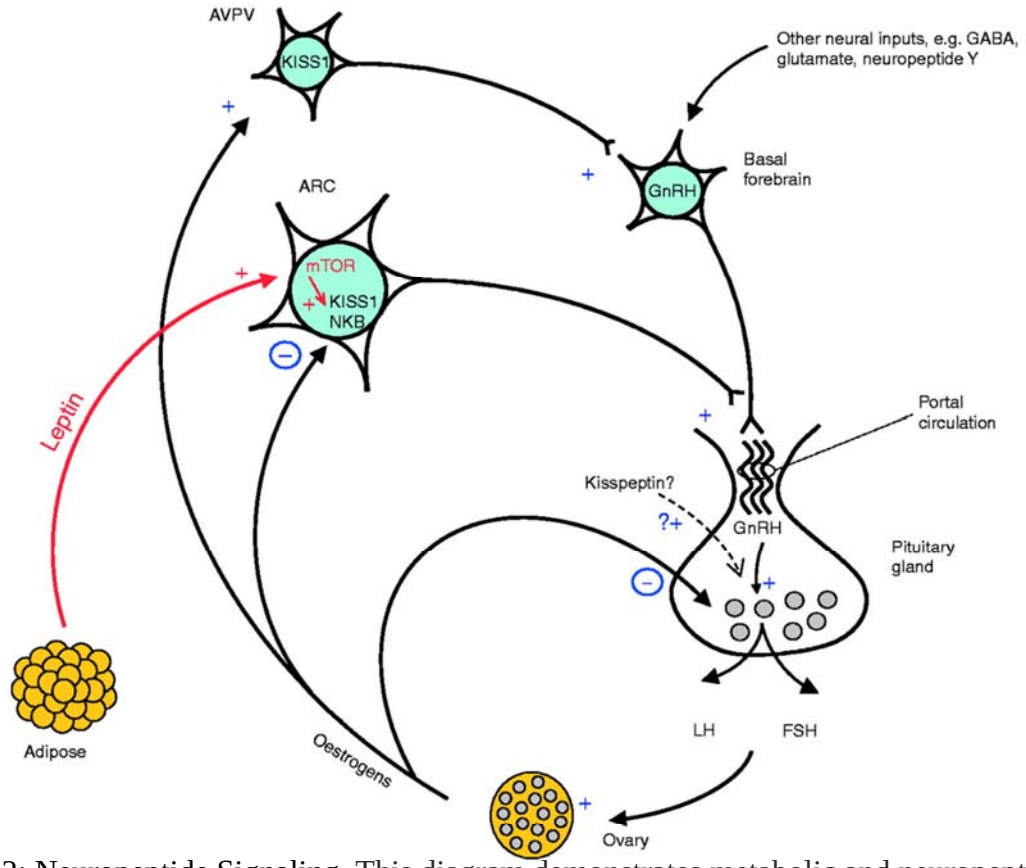

Figure 2: Neuropeptide Signaling. This diagram demonstrates metabolic and neuropeptide signaling within the female central nervous system. From "Kisspeptin and fertility," by S. Hameed, C.N. Jayasena, & W.S. Dhillo, 2011, *Journal of Endocrinology, Volume* 208, 97-105. http://joe.endocrinology-journals.org/content/208/2/97/F1.expansion.html.

References

Abrao, M. S., Muzii, L., & Marana, R. (2013). Anatomical causes of female infertility and their management. *International Journal of Gynaecology and Obstetrics, 123*(Suppl 2), S18-24. doi:10.1016/j.ijgo.2013.09.008

Becker, G. F., Passos, E. P., & Moulin, C. C. (2015). Short-term effects of a hypocaloric diet with low glycemic index and low glycemic load on body adiposity, metabolic variables, ghrelin, leptin, and pregnancy rate in overweight and obese infertile women: A randomized controlled trial. *American Journal of Clinical Nutrition, 102*(6), 1365-1372. doi:10.3945/ajcn.115.117200

Brewer, C. J., & Balen, A. H. (2010). The adverse effects of obesity on conception and implantation. *Reproduction, 140*(3), 347-364. doi:10.1530/REP-09-0568

Brzyski, R. G., & Knudson, J. (2013). Female reproductive physiology. In *Merck Manual: Profession Version*. Retrieved from http://www.merckmanuals.com/professional/gynecology-and-obstetrics/female-reproductive-endocrinology/female-reproductive-endocrinology

Celik, O., Aydin, S., Celik, N., & Yilmaz, M. (2015). Peptides: Basic determinants of reproductive functions. *Peptides, 72*, 34-43. doi:10.1016/j.peptides.2015.05.016

Centers for Disease Control and Prevention. (2015). *Adult BMI.* Retrieved from https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/

Chandra, A., Copen, C. E., & Stephen, E. H. (2013). Infertility and impaired fecundity in the United States, 1982-2010: Data from the National Survey of Family Growth. *National Health Statistics Report, 67*, 1-18.

d'Anglemont de Tassigny, X., & Colledge, W. H. (2010). The role of kisspeptin signaling in reproduction. *Physiology (Bethesda), 25*(4), 207-217. doi:10.1152/physiol.00009.2010

Duval, K., Langlois, M. F., Carranza-Mamane, B., Pesant, M. H., Hivert, M. F., Poder, T. G., . . . Baillargeon, J. P. (2015). The Obesity-Fertility Protocol: A randomized controlled trial assessing clinical outcomes and costs of a transferable interdisciplinary lifestyle intervention, before and during pregnancy, in obese infertile women. *BMC Obesity, 2*, 47. doi:10.1186/s40608-015-0077-x

Fu, L. Y., & van den Pol, A. N. (2010). Kisspeptin directly excites anorexigenic proopiomelanocortin neurons but inhibits orexigenic neuropeptide Y cells by an indirect synaptic mechanism. *Journal of Neuroscience, 30*(30), 10205-10219. doi:10.1523/JNEUROSCI.2098-10.2010

Hacker, N. F., Gambone, J. C., & Hobel, C. J. (Eds.). (2010). *Essentials of obstetrics and gynecology* (5th ed.). Philadelphia, PA: Saunders Elsevier.

Hameed, S., Jayasena, C. N., & Dhillo, W. S. (2011). Kisspeptin and fertility. *Journal of Endocrinology, 208*(2), 97-105. doi:10.1677/joe-10-0265

Javed, Z., Qamar, U., & Sathyapalan, T. (2015). The role of kisspeptin signalling in the hypothalamic-pituitary-gonadal axis - Current perspective. *Endokrynologia Polska, 66*(6), 534-547. doi:10.5603/EP.2015.0066

Kulak, D., & Polotsky, A. J. (2013). Should the ketogenic diet be considered for enhancing fertility? *Maturitas, 74*(1), 10-13. doi:10.1016/j.maturitas.2012.10.003

Martin, C., Navarro, V. M., Simavli, S., Vong, L., Carroll, R. S., Lowell, B. B., & Kaiser, U. B. (2014). Leptin-responsive GABAergic neurons regulate fertility through pathways that result in reduced kisspeptinergic tone. *Journal of Neuroscience, 34*(17), 6047-6056. doi:10.1523/JNEUROSCI.3003-13.2014

Mayo Clinic Clinical Laboratories. (2016a). *Ghrelin total, plasma.* Retrieved from

http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/57902.

Mayo Clinic Clinical Laboratories. (2016b). *Leptin.* Retrieved from http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/91339.

McLean, M., & Wellons, M. F. (2012). Optimizing natural fertility: The role of lifestyle modification. *Obstetric and Gynecology Clinics of North America, 39*(4), 465-477. doi:10.1016/j.ogc.2012.09.004

MedicineNet. (2012). *Medical definition of fertility*. Retrieved from http://www.medicinenet.com/script/main/art.asp?articlekey=3412

Meeker, J. D., & Benedict, M. D. (2013). Infertility, pregnancy loss and adverse birth outcomes in relation to maternal secondhand tobacco smoke exposure. *Current Women's Health Review, 9*(1), 41-49.

Merriam-Webster Medical Dictionary Online. (2015a). *Follicle stimulating hormone.* Retrieved from http://www.merriam-webster.com/dictionary/follicle%20stimulating%20hormone

Merriam-Webster Medical Dictionary Online. (2015b). *Ghrelin.* Retrieved from http://www.merriam-webster.com/medical/ghrelin

Merriam-Webster Medical Dictionary Online. (2015c). *Gonadotropin releasing hormone.* Retrieved from https://www.merriam-webster.com/dictionary/gonadotropin%20releasing%20hormone

Merriam-Webster Medical Dictionary Online. (2015d). *Leptin.* Retrieved from https://www.merriam-webster.com/dictionary/leptin

Merriam-Webster Medical Dictionary Online. (2015e). *Luteinizing hormone.* Retrieved from http://www.merriam-webster.com/dictionary/luteinizing%20hormone

Merriam-Webster Medical Dictionary Online. (2015f). *Obesity*. Retrieved from https://www.merriam-webster.com/dictionary/obesity#medicalDictionary

Nestor, C. C., Kelly, M. J., & Ronnekleiv, O. K. (2014). Cross-talk between reproduction and energy homeostasis: Central impact of estrogens, leptin and kisspeptin signaling. *Hormone Molecular Biology and Clinical Investigation, 17*(3), 109-128. doi:10.1515/hmbci-2013-0050

Ogden, C. L., Carroll, M. D., Kit, B. K., & Flegal, K. M. (2014). Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA, 311*(8), 806-814. doi:10.1001/jama.2014.732

Prague, J. K., & Dhillo, W. S. (2015). Potential clinical use of kisspeptin. *Neuroendocrinology, 102*(3), 238-245. doi:10.1159/000439133

Sim, K. A., Partridge, S. R., & Sainsbury, A. (2014). Does weight loss in overweight or obese women improve fertility treatment outcomes? A systematic review. *Obesity Reviews, 15*(10), 839-850. doi:10.1111/obr.12217

Skorupskaite, K., George, J. T., & Anderson, R. A. (2014). The kisspeptin-GnRH pathway in human reproductive health and disease. *Human Reproduction Update, 20*(4), 485-500. doi:10.1093/humupd/dmu009

Smith, A. W., Bosch, M. A., Wagner, E. J., Ronnekleiv, O. K., & Kelly, M. J. (2013). The membrane estrogen receptor ligand STX rapidly enhances GABAergic signaling in NPY/AgRP neurons: Role in mediating the anorexigenic effects of 17beta-estradiol. *American Journal of Physiology. Endocrinology and Metabolism, 305*(5), E632-640. doi:10.1152/ajpendo.00281.2013

Souter, I., Baltagi, L. M., Kuleta, D., Meeker, J. D., & Petrozza, J. C. (2011). Women, weight, and fertility: The effect of body mass index on the outcome of superovulation/intrauterine insemination cycles. *Fertility and Sterility, 95*(3), 1042-1047. doi:10.1016/j.fertnstert.2010.11.062

Tong, Q., Ye, C. P., Jones, J. E., Elmquist, J. K., & Lowell, B. B. (2008). Synaptic release of GABA by AgRP neurons is required for normal regulation of energy balance. *Nature Neuroscience, 11*(9), 998-1000. doi:10.1038/nn.2167

Tsutsumi, R., & Webster, N. J. (2009). GnRH pulsatility, the pituitary response and reproductive dysfunction. *Endocrine Journal, 56*(6), 729-737.

Vazquez, M. J., Romero-Ruiz, A., & Tena-Sempere, M. (2015). Roles of leptin in reproduction, pregnancy and polycystic ovary syndrome: Consensus knowledge and recent developments. *Metabolism, 64*(1), 79-91. doi:10.1016/j.metabol.2014.10.013

van der Steeg, J. W., Steures, P., Eijkemans, M. J., Habbema, J. D., Hompes, P. G., Burggraaff, J. M., . . . Mol, B. W. (2008). Obesity affects spontaneous pregnancy chances in subfertile, ovulatory women. *Human Reproduction, 23*(2), 324-328. doi:10.1093/humrep/dem371

Weiss, R. V., & Clapauch, R. (2014). Female infertility of endocrine origin. *Arquivos Brasileiros de Endocrinologia e Metabologia, 58*(2), 144-152.

Abstract

American obesity rates continue to be a growing epidemic with concerns regarding its long list of associated complications, including fertility. This review analyzes a multitude of research studies and reviews discussing the relationship between nutrition status and female reproductive function. This intricate relationship depends on the function of metabolic and reproductive peptides to regulate signals between the two networks. Inadequate or excessive energy stores have the ability to alter the function and response of these neuropeptides and in return, may alter a woman's ability to conceive. Nutrition therapies have the potential to improve fertility status using noninvasive strategies that spare one's overall wellbeing and wallet. The information gathered reveals the importance for providers to educate patients about proper diet and exercise in attempt to appropriately regulate the reproductive axis. The metabolic-reproductive network and its neuropeptides may significantly change the way infertility is handled with more focus on modifiable lifestyle behaviors.