

# Leptin Deficiency: Addressing the Detrimental Effects of Stringent Calorie Restriction on Reproductive-Age Women through Patient Education and Counselling

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## ABSTRACT

Stringent calorie restriction, often pursued for weight loss, has significant repercussions for metabolic and reproductive health, primarily due to leptin deficiency (LD). Leptin is essential for regulating appetite, metabolism, and reproductive functions. This review explores the effects of LD from aggressive dieting on women's reproductive health and highlights the role of clinical pharmacists in managing these issues through patient education and counseling. This narrative review examines existing literature on leptin's role in female reproduction, its influence on puberty, menstruation, and energy balance, and assesses various dietary approaches affecting leptin levels. Caloric restriction significantly lowers leptin levels, disrupting the hypothalamic-pituitary-ovarian (HPO) axis, which impacts reproductive functions, delays puberty, and causes menstrual irregularities. LD also disrupts energy balance and can lead to broader metabolic disturbances. The review delves into the physiological impact of LD on reproductive health, including its effects on follicular development, endometrial function, and overall metabolism. It underscores the crucial role of healthcare professionals, especially clinical pharmacists, in managing these challenges through comprehensive patient care. Managing LD in women undergoing severe calorie restriction requires a multidisciplinary approach, including personalized nutrition plans, digital monitoring tools, and behavioral support. Clinical pharmacists are vital in patient education and collaborative care to mitigate the adverse effects of restrictive dieting.

**Keywords:** Caloric Restriction, LD, Menstrual Irregularities, Reproductive Health, Weight Loss, Women's Health

## 1. INTRODUCTION

An alarming consequence of modernization is the emergence of aggressive dieting patterns among women.[1]Extreme dietary habits can result in a deficiency of a vital hormone called leptin, which plays a crucial role in regulating appetite and metabolism.[2]Although leptin's involvement in the control of hunger, neuroendocrine function, and energy homeostasis is well-established, it also appears to have an impact on a number of other physiological processes.[3]LD can raise the risk of metabolic syndrome which is a severe life-threatening multifactorial metabolism-mediated chronic conditions.[4,5] To address the aforementioned issues, it is crucial to understand leptin's role comprehensively. This review aims to explore leptin's role and its potential negative impacts on women's reproductive health due to unhealthy or stringent dietary practices.

## 2. LD due to calorie restriction and its effect on female reproduction

The human reproductive system engages complex interactions of biological molecules and neuroendocrine pathways since it needs energy throughout the reproductive cycle. This pathway often involves the hypothalamic-pituitary-ovarian (HPO) axis.[6] This HPO axis is exclusive for the regulation of women's reproductive functions where it takes care of the communication process between the hypothalamus, pituitary gland, and ovaries. The gonadotropin-releasing hormone (GnRH) is released from the hypothalamus in a pulsatile manner which stimulates the pituitary gland to produce Follicle stimulating hormone (FSH) and luteinizing hormone (LH).[7] These two hormones are necessary for the growth and development of ovarian

follicles and the latter is responsible for the release of the matured egg from the ovary, in other words, it induces ovulation and promotes the formation of corpus luteum followed by the production of progesterone and estrogen by the ovaries. Overall, the HPO axis works via an intricately orchestrated interplay of hormones.[7] Leptin serves as a signal to the CNS about the body's energy stores. During aggressive dieting, there is a notable decrease in energy intake and a reduction in leptin levels. Since female reproduction involves the necessity of energy for the cycle to take place normally the decline in leptin levels may have a major impact.[8] Here's how aggressive dieting can affect leptin levels and subsequently influence female reproductive health.

### 2.1. Puberty and infertility

In women who aim to achieve weight loss by aggressive calorie restriction enter the stage of metabolic adaptation where due to decreased availability of leptin the body perceives it as a signal of energy deficiency and switches to energy conservation by decreasing the energy expenditure making weight loss more difficult.[9] Extreme calorie deficit or starvation in order to lose weight ends up in loss of muscle loss instead of fat loss and complexities or delay in puberty can be strongly affected due to low levels of leptin. When there is extreme inadequacy of leptin it leads to severe energy deficiency and suppression of the HPO axis. The scarcity of leptin fails to activate the production of Kisspeptin by acting on kiss1 neurons to release GnRH.[10] Likewise in the ovary, LD may cause leptin resistance which may hinder with the ovulation process via a negative feedback mechanism resulting in infertility, disruption, or delayed puberty with slow development of primary and secondary characteristics.[11] LD also causes changes in the endometrial epithelium where the normal decidualization of the endometrium is disrupted since leptin is responsible for the remodeling of the endometrium by proliferation and apoptosis in a balance.[12] Leptin, regulates in vitro development of pre-implantation embryos. In mice, physiological levels of leptin (10 ng/ml) enhance embryo development at early stages, while high levels (100 ng/ml) hinder growth at early stages but not at later stages. Leptin's effect depends on concentration and embryo stage. Sheep embryos show similar patterns, indicating species-specific sensitivity to leptin.[13] Reduced levels of leptin during fetal development can pose challenges to nutrient availability, as it disrupts various signaling and endocrine stimuli. This, in turn, can impact processes such as glucogenesis (the production of glucose) and tissue maturation during the later stages of gestation. Additionally, the establishment of neural pathways, which play a crucial role in maintaining energy balance, can also be affected by diminished leptin signaling.[14]

### 2.2. Menstruation

A previous study by Williams et al, conducted to investigate the interplay between diet, calorie restriction, and menstruation in females suggests that both calorie restriction and exercise produced energy deficiency and triggered menstrual disturbances.[15] Caloric restriction and exercise can lead to energy deficiency and decreased body fat, causing low leptin levels. LD disrupts the HPO axis, affecting follicular development, reproductive hormone production, and the release of GnRH, LH, and FSH. This disruption can result in irregular or absent menstrual cycles and menstrual disturbances.[16]

### 3. Influence of different dietary approaches on leptin secretion and energy balance

Leptin acts within the hypothalamus to reduce food intake and increase energy expenditure by inhibiting the expression of AgRP and NPY, while stimulating the expression of POMC.[17,18] When individuals are in an energy-balanced state at their usual weight, the secretion of leptin corresponds to their fat mass.[19] Consistent with its role as an indicator of energy depletion, leptin levels decrease significantly during dietary restriction,[20,21] and they are notably lower during active weight loss compared to weight loss maintenance.[22] Administering leptin to individuals at their baseline weight has minimal effect on body weight and appetite.[23] However, during an energy deficit, leptin administration reduces appetite.[24] Furthermore, in individuals who have achieved weight stability after weight reduction, restoring leptin levels to pre-weight loss values reverses many of the adaptive physiological changes affecting thyroid hormones, the autonomic nervous system, appetite, energy expenditure, and skeletal metabolism. The **Table 1** provides information on nine different studies related to the effects of diet composition, energy expenditure, appetite-regulating hormones, and weight loss.

### 4. Role of Healthcare Professionals in Managing LD Due to Calorie Restriction

Healthcare professionals have the potential to play an essential role in managing LD in reproductive-age women undergoing stringent calorie restrictions. Clinical pharmacists are equipped to ensure proper medication, including hormone therapies and psychological treatments while offering nutritional advice and collaborating with dietitians to create balanced meal plans. Dietitians are capable of designing nutrient-rich diets to address the effects of LD, while medical doctors are responsible for overseeing comprehensive treatment plans and monitoring patient progress. Psychological care providers are adept at addressing mental health issues, offering support for stress, anxiety, and depression exacerbated by restrictive dieting. Together, they are positioned to

provide thorough education on the risks of calorie restriction and its impact on reproductive health, integrating psychological support to ensure a holistic approach to treatment and optimal patient outcomes.

### **5. Strategies to Manage Stringent Calorie Restriction Among Women to prevent the negative effect of LD**

To innovatively manage stringent calorie restriction among women, personalized nutrition plans using genetic and metabolic profiling can tailor dietary needs, supported by smart meal planning apps. Integrating digital tools like wearables for real-time monitoring and virtual nutrition coaching can enhance management. Behavioral support through cognitive behavioral therapy and mindfulness practices addresses psychological impacts, while advanced nutritional interventions, including functional foods and customized nutrient timing, optimize health. Educational technologies, such as interactive modules and virtual reality, provide valuable insights on balanced eating. A multidisciplinary care approach, involving dietitians, pharmacists, psychologists, and doctors, ensures comprehensive management, supported by regular check-ins. Engaging in research and utilizing biomarker analysis further refines strategies, promoting effective calorie restriction while maintaining overall well-being.

### **6. CONCLUSION**

In conclusion, stringent calorie restriction in women can lead to significant LD, which disrupts the hypothalamic-pituitary-ovarian (HPO) axis, impairs reproductive functions, and affects overall metabolic health. This deficiency triggers hormonal imbalances, delays puberty, and contributes to menstrual irregularities, while also influencing energy expenditure and appetite regulation. The pathophysiological mechanisms involve reduced leptin signaling, which negatively impacts follicular development and endometrial function, potentially resulting in infertility and altered glucose metabolism. Innovative strategies, including personalized nutrition plans, real-time digital monitoring, and multidisciplinary care, can effectively manage these challenges. By leveraging advancements in technology and behavioral support, healthcare professionals can address the comprehensive needs of women facing LD due to aggressive calorie restriction, ensuring improved health outcomes and well-being.

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#### **Availability of data and materials Information**

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#### **Declarations Competing interests**

The author(s) declare that they have no conflict of interest.

#### **Ethical approval**

Not applicable.

#### **Consent to participate**

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#### **Consent to publish**

All the authors have approved the manuscript for publication

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### Graphical Abstract

