BEDNARCZYK, Małgorzata Maria, KAROL, Michał, KOSESKA, Kamila, BOROWICZ, Jan, GÓRECKI, Bartosz, KLOCH, Kinga, ROMANIUK, Patryk, LOHIN, Mariia-Khrystyna, and STRAWIŃSKA, Aleksandra. Kisspeptin and Leptin as Treatments for Functional Hypothalamic Ammenorhea (FHA): Experimental Approach or Emerging Therapy?. Quality in Sport. 2026;49:67123. eISSN 2450-3118.
https://doi.org/10.12775/QS.2026.49.67123
https://apcz.umk.pl/QS/article/view/67123

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 09.12.2025. Revised: 15.12.2025. Accepted: 05.01.2026. Published: 08.01.2026.

Kisspeptin and Leptin as Treatments for Functional Hypothalamic Ammenorhea (FHA): Experimental Approach or Emerging Therapy?

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ABSTRACT

Functional hypothalamic amenorrhea (FHA) is a common cause of amenorrhea among women in reproductive age. The disturbance is often associated with stress and deficiency in energy availability caused by either intensive exercise or improper nutrition. Those factor affect the hypothalamic-pituitary-gonadal axis and further absence of ovulation and normal menstrual cycle. Treatment should be directed to treatment of the etiology, however sometimes it is not enough.

For this reason, novel therapies emerged to counteract the consequences of FHA to support restorating that lifestyle changes are not capable of. This review summarizes current knowledge

on the leptin and kisspeptin treatment, which recently gained more interest, due to it physiological basis in hypothalamic-pituitary-gonadal axis. Furthermore, paper evaluates clinical data, its limitations and safety consideration, and more importantly, the need for future research.

Keywords: leptin, functional hypothalamic amenorrhea, kisspeptin, reproduction, hypothalamic-pituitary-gonadal axis

Introduction

Functional hypothalamic amennorhea (FHA) is a common cause of both primary and secondary amenorrhea in women of reproductive age. After polycystic ovary syndrome (PCOS), it is the second most frequent cause of secondary amenorrhea, which consitutes for approximately 25–35% of cases. [1], [2]

The condition is associated with stress, restrictive eating behaviors, and excessive physical activity. Consequently, its prevalence is particularly high in athletes, among whom amenorrhea affects up to 30%. [2], [3]

Anovulation results from disrupted neuromodulatory signaling to the hypothalamus which can be either inhibitory or stimulatory, that further alters gonadotropin-releasing hormone (GnRH). [2], [4], [5] A reduced GnRH drive leads to insufficient pulsatile LH secretion and reduced FSH levels, ultimately failing to support folliculogenesis and, consequently, normal ovulatory function. [2], [6]

Low energy availability, whether due to nutritional restriction or excessive energy expenditure, suppresses the hypothalamic-pituitary-gonadal (HPG) axis, resulting in neuroendocrine, metabolic, and hormonal changes. [2] These alterations include reductions in appetite-regulating hormones such as leptin and insulin, accompanied by increases in fasting peptide YY and ghrelin. [5] Furthermore, leptin secretion is proportional to fat stores and signals adequate energy storage and satiety. However, women with FHA exhibit markedly reduced circulating leptin levels, contributing to GnRH suppression. [7], [8]

Additionally, stress also affects the HPG axis, although via a different mechanism, ultimately leading to similar reproductive suppression. In response to stress, the hypothalamic-pituitary gland-adrenal (HPA) axis is activated and increases secretion of corticotropin-releasing hormone (CRH), which stimulates adrenocorticotropic hormone (ACTH), thus cortisol release. Elevated CRH in patients with stress-related amenorrhea, which can directly inhibit GnRH secretion, which alters LH pulsation. [9], [10]

Kisspeptin and leptin in HPG axis

The KISS1 gene encodes the KISS1 protein, which is secreted by neurons localized in the preoptic area and in the arcuate nucleus of the hypothalamus. [11] Its secretion plays a crucial role in regulating puberty and reproduction by directly stimulating the HPG axis. In the hypothalamus, kisspeptin neurons stimulate GnRH secretion, regulating downstream of LH and FSH release. [12]

In energetic deficiency, the level of circulating kisspeptin is decreased. Kisspeptin serum concentration has been proven to have an inverse correlation with body mass index (BMI) and physical activity. [13], [14]

Leptin concentration is directly proportional to fat mass, and serves as a key signaling, linking energy storage to reproductive function. The link between leptin, and GnRH seemed to be faint, as GnRH neurons lack the isoforms for the leptin receptor, additionally, there is low expression of leptin receptors on kisspeptin neurons. [15], [16] However, neurons in the ventral premammillary nucleus (PMV) form a pathway, mediating leptin stimulation of kisspeptin neurons, which in turn stimulate GnRH pulsatile release. [17] Low energy availability decreases the leptin signals to the hypothalamus, which further suppresses the expression of KISS1, ultimately, inhibiting GnRH release and the pulsatile activity of gonadotropins. [18]

The neuroanatomical pathway linking leptin signaling to GnRH neurons is not yet fully understood. It is suggested that connection occur via kisspetitin neurons, which supposedly has a major role in stimulation of GnRH secretion. [15]

Health consequences of amennorhea in FHA

Both receptors for estradiol - ERα and ERβ are expressed widely as well, modulating a broad spectrum of physiological functions in the reproductive, skeletal, cardiovascular, and central nervous systems. ERα is highly expressed in the mammary glands and liver and is the predominant receptor in the ovarian cells, uterus, brain, heart, and bone. [19], [20]

FHA leads to low estrogen levels, which can cause a range of adverse effects similar to those seen in postmenopausal women. These include a higher risk of cardiovascular disease,

disturbances in bone metabolism such as osteopenia or osteoporosis, and impairments in cognitive and brain function, along with an increased vulnerability to psychiatric disorders. [21] However, despite same mechanism of action that come with low estrogen level in young women, there are not a lot papers that describe side effects among those in reproductive age.

There are only several studies that show, that amenorrhea in young women increases the serum concentration of cholesterol, and LDL which may contribute to the anthlesclerosis formation, thus increasing the cardiovascular risk. [22], [23], [24]

Lack of stimulation of osteoblasts by the estrogen, and promotion of osteoclasts, which is responsible for bone-resorption leads to diminished bone density, and may result in osteopenia or osteoporosis. [24] Additionally, low estrogen levels also contribute to poor absorption of calcium in the intestines, which decreases calcium avalibility for bone reabsobtion. [25] However, not only hypoestrogenemia, but its prolonged duration major risk factor for bone loss, thus reducing the strength, and increasing the risk of pathological fractures. [20], [26], [27], [28]

Other health risk include cardiovascular incidents, however the data is scarce, mental health disorders, which involve higher rates of depression, anxiety and mood swings which may be due to estradiol's role in the regulation of neurotransmitter systems encompassing the serotonergic, dopaminergic, and glutamatergic signaling pathways. [10], [24], [29]

Treatment approaches to FHA

Treatment aims to re-establish ovulation, thus to restore a regular menstrual cycle. Usually, treatment should be directed to eliminate the cause, such as decreasing chronic stressors, reducing excessive exercise, or gaining weight in order to improve energy availability.

Most women receive oral contraceptives, often perceived as an estrogen replacement therapy. This approach addresses symptoms rather than the underlying etiology. However, oral contraception does not restore menstruation, and may only cover the return of spontaneous menses. Furthermore, estrogen therapy may not be beneficial in counteracting all of the consequences of estrogen deficiency. [30], [31]

Usually, use of estrogen replacement should be considered after attempt to counteract the etiology of the FHA – modifying nutrition, CBT and easing on exercise, in order to compensate the deficiency of energy. Furthermore, it may be considered after 6 to 12 months after conservative interventions, especially in those patients with low bone density.

Other interventions may be worth considering, especially in patients who do not reestablish menstrual cycle or mitigate the consequences of low estrogen.

Other therapies include treatment with GnRH or pulsatile gonadotropins, as well as kisspeptin, and leptin.

Methods

The study selection, followed PRISMA guidelines and is based on the analysis of scientific articles selected for their relevance to treatment of FHA. The literature search was conducted using PubMed database, with keywords: functional amenorrhea, leptin, kisspeptin, treatment. 64 papers related to leptin treatment in FHA and 43 papers relating to kisspeptin as a possible treatment were identified. 78 papers were excluded due to them being duplicates, reviews, conference abstracts, animal studies, or papers unrelated to therapeutic interventions in FHA. 29 articles were further assessed, among which only 8 original studies were taken under consideration – 3 leptin clinical trials, and 2 with kisspeptin. Detailed inclusion criteria are presented in Table 1.

Table 1. Inclusion criteria for study selection.

Category	Inclusion criteria
Population	Women (≥ 18 years old) diagnosed with functional hypothalamic amenorrhea (FHA), defined by ≥3 months of amenorrhea (or ≥6 months of oligomenorrhea).
Study design	Interventional studies, either clinical trials, pilot trials. Both randomized and non-randomized designs are accepted.
Intervention	Administration of either recombinant leptin (metreleptin) or kisspeptin (KP-54 or analogs) any dosing or route.
Outcomes	Studies that report reproductive outcomes or lack thereof (either ovulation recovery or menstrual cycle resumption).
Language	Articles published in English.

Discussion

Only a few studies have described leptin and kisspeptin in FHA treatment. The idea of using either of the hormones is to replace the missing hormone to restore activation of the HPG axis, and thus the menstrual cycle in reproductive women.

The main idea behind using recombinant leptin is derived from the hypothesis that leptin deficiency causes reproductive and neuroendocrine dysfunction caused by low adiposity in women with hypothalamic amenorrhea. The use of leptin in women suffering from FHA was first reported by the Welt C.K. in 2004. The study enrolled 14 patients suffering from FHA for at least 6 months, among whom 8 received recombinant leptin, and six served as a control group. Subjects received treatment for approximately 2-3 months – if the subject had ovulated, the study was concluded at 2 months; if not, the dose of medication was increased. It was found that 3 subjects, among 8 that received the recombinant leptin, had an ovulatory menstrual cycle

during the treatment ($p<0.05$). Subjects that were able to ovulate also had levels of LH, FSH, and estradiol within normal range. Another two subjects that received r-metHuLeptin were able to develop a preovulatory follicle; however, they did not ovulate. Despite the lack of ovulation, an estradiol peak, without an increase in progesterone level, was observed. [32] An important finding is that recovery occurred within the first 1–2 months of treatment, which is shorter than in patients incorporating lifestyle changes, were menses restoration can take from 3 to 8 months. [33], [34]

Markers of bone formation – such as bone alkaline phosphate and osteocalcin- increased during the treatment; however, total bone density was not affected. Changes to bone metabolism, thyroid hormones, and cortisol levels were not statistically significant, which may be either due to the small intervention group or due to the short duration of the study, to notice any visible changes.

The advantage of the study is the presence of the control group, and clear inclusion and exclusion criteria of the subjects. Furthermore, clear control over other variables that can affect the results, such as daily exercise records and four-day food diaries, was established. Additionally, the ovulation was monitored not only by biochemical changes in hormones, but also via ultrasound, which is more precise than hormon monitoring. The weak sides of the study are a small study group that received medication, which may be the cause, why some results did not reach scientific significance. Additionally, the duration of the study does not allow us to observe long-term effect on the bone metabolism, and any longitual side effects that may be observed with longer administration of the recombinant leptin. Furthermore, the study's single-center design and the absence of randomization limit the reliability and generalizability of the findings.

Another study was conducted by Chou in 2011. He enrolled 20 subjects, and allocated them randomly either to the metreleptin-treated group (11 participants) or the placebo group (9 participants). In Chou's study, 7 out of 10 subjects that received metreleptin, over time, developed menstruation ($p = 0.0046$), in comparison to two in the placebo group. Menses appeared at various stages, ranging from 4 to 32 weeks; however, on average restoration of menses was earlier in women treated with metreleptin. Steroid hormones – estradiol and progesterone increased significantly in the participants treated with metreleptin as compared with the participants treated with placebo ($p = 0.0137$). However, there was no difference in gonadotropin levels between the 2 groups ($P = 0.40$ and $P = 0.70$, respectively).

Similarly to Welt study, there were no significant changes in thyroid hormones, cortisol level, and bone metabolism in comparison to the control group over 36 weeks of the treatment. [35]

The downside of the study was that only of biochemical analysis of the ovulation monitoring was used, rather than ultrasound, which is more accurate, and can also show the development of the preovulatory follicle. Additionally, the study included a very small cohort, which increases the risk that the findings may not reaching statistical significance; thus, similarly as with Welt's, results have to be generalized with caution. The treatment time, despite the fact that it is longer than Welt's, did not provide extended follow-up, making it difficult to evaluate potential long-term metabolic, reproductive, or immunological consequences of leptin replacement that may follow. Furthermore, there is no mention regarding monitoring other variables that may affect the HPA axis in FHA women – nutrition and exercise, which are the major components in FHA etiology. Thus, residual confounding cannot be excluded.

ame year, Sienkiewicz conducted the study with 20 participants (11 received metreleptin, and 9 received a placebo). He mainly focused on the effect of mereleptin administration on bone mineral density in women suffering from FHA. Sienkiewicz showed that mertleptin treatment, in fact, significantly increased both lumbar bone mineral content ($P = 0.04$) and lumbar bone mass density ($P = 0.03$); those changes were not observed in Chou's and Welt's studies, which may be due to the shorter observation time, smaller number of participants, or simply due to the study design. [36] However, the significant was not reached regarding total body, hip, and radial BMD and BMC.

The menstruation was restored metreleptin resulted in resumption of menses in 40% (2 out of 5) of the subjects during months 3 to 12 (the sixth subject received placebo during the first 9 months), in 50% (3 out of 6) of them at 18 months, and in 75% (3 out of 4) of them at 24 months. However, the change did not reach significance ($P = 0.161$; intention to treat: $P = 0.134$). [36] The study's focus on the ovulation restoration was superficial; the study did not use the ultrasound to observe the development of either the ovulatory or preovulatory follicle. The lack of significance, when monitoring menses restoration, may be due to the small sample size. The advantages of the study include long-term observation, which is 9 months, it is the longest observational duration in comparison to the other 2 studies.

There are no studies that explore the comparison between the leptin treatment and lifestyle modification, regarding the restoration of the ovulation, thus menstruation. Furthermore, there are no studies that compare the effect of such an intervention regarding bone density. Additionally, new studies should be conducted that take into consideration incorporating 2 interventions (treatment with leptin on top of lifestyle modification) to the single one, in terms of ovulatory and menstruation restoration, duration of recovery, and whether its effectiveness in increasing BMD is greater in comparison to the single intervention.

Detailed information regarding study design, dosage of leptin, number of participants and most important findings are presented in the Table 2.

Table 2. Summary of the studies that treated hypothalamic amenorrhea with recombinant leptin.

Author and year	Study type	Number of participants	Leptin dose	Duration of the study	Main findings
Welt et al., 2004	Single-center interventional study	14 patients enrolled, 8 received recombinant leptin, 6 were in control group	0.08–0.1 mg/kg/day s.c., given in the morning	2-3 months	• Three of eight subjects had an ovulatory menstrual cycle during r-metHuLeptin therapy (P<0.05 for the comparison with an expected rate of spontaneous ovulation of 10 percent). • Two treated subjects completed the study at two months, after meeting the primary end point of ovulation. • Overall, three of eight subjects had an ovulatory menstrual cycle during r-metHuLeptin therapy (P<0.05 for the comparison with an expected rate of spontaneous ovulation of 10 percent). • Two subjects who were treated with r-metHuLeptin had a preovulatory follicle (19.0 mm in one and 23.6 mm in the other) but did not ovulate. • Two weeks of r-metHuLeptin increased mean LH levels (P=0.017) and pulse frequency (P=0.058 by nonparametric analysis and P=0.049 by parametric analysis). • Changes to bone metabolism, thyroid hormones and cortisol level were not statistically significant.
Chou et al., 2011	double-blind, placebo-controlled	20 participants enrolled, 11 received	~0.04–0.08 mg/kg/day s.c., in the morning,	24–36 weeks, with one additional	• Seven of 10 subjects receiving metreleptin therapy developed menstruation during the

		metreleptin, 9 were receiving placebo drug. Seven of the 11 participants in the metreleptin-treated group and six of nine participants in the placebo-treated group completed the entire study.	dose increase after 12 weeks of not restoring menses to to 0.12 mg/kg	follow-up visit at 52 weeks	course of the study, and two of nine subjects on placebo developed menstruation (p = 0.0046). • Estradiol and progesterone levels increased significantly in the participants treated with metreleptin as compared with the participants treated with placebo (*P* = 0.0137 and *P* = 0.0342, respectively, by treatment effect). • No significant changes in thyroid hormones (*P* = 0.0137 and *P* = 0.0342, respectively, by treatment effect) , cortisol level and bone metabolism in comparison to the control group over 36 weeks of the treatment. • No difference in gonadotropins (LH and FSH) levels between the 2 groups (*P* = 0.40 and *P* = 0.70, respectively).
Sienkiewicz et al., 2011	randomized, double-blinded, placebo-controlled study	20 participants were enrolled, 11 were receiving metreleptin, 9 were receiving placebo drug. 7 participants dropped out of the study (4 from intervention	0.08 mg/kg/day s.c. If menstruation occurred during 12 weeks of treatment, the dose was continued, if not the dose was increased to 0.12 mg/kg/day	9 months followed by a 3-month washout period, after washout period, subjects could enroll for another 12 months	• Treatment with metreleptin significantly increased BMC and tended to increase BMD at the lumbar spine (time × treatment interaction: *P* = 0.034 and *P* = 0.069), but did not affect total body, hip, and radial BMD and BM • For those subjects who continued the

	group, 3 from control group). Overall 13 participants finished first phase of the study.		study after washout period, and completed the 2-year study (on-treatment: n = 4), treatment with metreleptin significantly increased BMD (*P* = .024) and BMC (*P* = .049) at the lumbar spine (range: 2.2% to 10.8% and 1.4% to 6.5% from baseline, respectively. • Estradiol concentration doubled in response to metreleptin treatment, but the overall change was not significant (*P* = 0.24). • Metreleptin resulted in resumption of menses in 40% (2 out of 5) of the subjects during months 3 to 12 (the sixth subject received placebo during the first 9 months), in 50% (3 out of 6) of them at 18 months, and in 75% (3 out of 4) of them at 24 months. However, the change did not reach significance (Cochran *Q* test: *P* = 0.161; intention to treat: *P* = 0.134)

Besides leptin, kisspeptin mechanism of action and its crucial presence in the HPA axis, became of interest. It seems that kisspeptin neurons in the hypothalamus stimulate GnRH secretion directly, which further affects LH and FSH release. The first papers of kisspeptin use have

shown that endogenous administration of kisspeptin stimulates the hypothalamic-pituitary-gonadal axis, the study showed an increase in both LH and FSH in comparison to the injection containing saline solution. The first study by Dhillo has shown the possibility of the endogenous use of kisspeptin may have on disorders regarding the reproductive system. [37], [38]

Hence, a novel therapeutic option with kisspeptin injection appeared to be the center of interest, as it may be the solution for infertility for those suffering from FHA.

Jayasena et al. have shown that injecting KP-54 does stimulate the release of reproductive hormones, as previous studies have proved; however, it does not restore menstrual cyclicity in women with hypothalamic amenorrhea. The study compared chronic and acute administration of kisspeptin. Firstly, the kisspeptin was administered in subcutaneous injections twice a day. Later on injection of kisspeptin was changes to twice a week, due to the significant reduction in response of reproductive hormone responses as compared with those on day 1. [39], [40]

Injecting twice a week still presented, with time, desensitization; however, it was not a profound one in comparison to daily injections. Despite partial desensitization, response to the injection was present over the entire duration of the 8-week study. The response was more significant with LH, rather than FSH, which is consistent with other studies, showing the use of KP-54. Furthermore, in the study group, 6 subjects developed a dominant follicle, under ultrasound, in comparison to the 3 of those that received saline, however, those results did not reach statistical significance. [40] Which may be due to amount of subjects that were enrolled in the study.

The study has several notable strengths, including the methodology and the random allocation of subjects, which decreases the bias that can be attributed to the final results. The control of the preovulatory follicle and ovulation follicles under the ultrasound was a helpful addition to the hormonal testing. Furthermore, the inclusion of a well-defined control group substantially strengthens the validity and interpretability of the study’s findings. Despite its strengths, the study is not without limitations. A small study group, despite being clearly defined, may be too small to make generalized conclusions. Additionally, the short duration of follow-up prevents making conclusions about long-term outcomes and further safety. Moreover, unmeasured variables such as exercise and nutrition were not mentioned in the methodology section. Additionally, weight was not measured, which might have added to the controllability of other factors that are crucial in hypothalamic amenorrhea. Thus, it cannot be excluded that those agents might have affected the final results. The detailed results and study design of Jayasena's study were presented in Table 3.

Table 3. Summary of the studies that treat hypothalamic amenorrhea with KP-54.

Author and year	Study type	Number of participants	Kisspeptin dose	Duration of the study	Main findings
Jayasena et al., 2010	A randomized, double-blinded, placebo-controlled	10 participants were enrolled in the study, 5 were receiving KP-54, 5 were receiving placebo drug.	6.4 nmol/kg twice a week	8-week period	• After 2 weeks of twice-weekly injections, LH responses after the KP-54 injection were significantly lower relative to those on day 1 (mean maximal LH increase (IU/l): baseline, 21.5 ± 10.7; 2 weeks, 10.0 ± 4.3; P < 0.001). However, no further significant reductions in LH KP-54 were observed after injection of KP-54 at 4 weeks (mean maximal LH increase: 9.0 ± 4.1 IU/l; P > 0.05 vs. response at 2 weeks), 6 weeks (mean maximal LH increase: 8.9 ± 3.5IU/l; P > 0.05 vs. response at 2 weeks), and 8 weeks (mean maximal LH increase: 7.9 ± 4.5 IU/l; P > 0.05 vs. response at 2 weeks). • No significant differences were observed at any stage during the 8-week protocol with respect to the number of follicles, the maximum size of the follicles, the volume of the ovary, and endometrial thickness between subjects who

	received KP-54 and those who received saline injections. • More dominant follicles were observed in subjects treated with KP-54 than in subjects treated with saline (six vs. three dominant follicles, respectively); however, no preovulatory follicles were observed in any subject during the study.

Additionally, Jayasena conducted another study, but instead of subcutaneous injection, she changed the route to the infusion. Infusion, also shown, temporarily increases in LH pulsatality in patients with HA; however, the restoration of the menstrual cycle was not measured. [41] Besides Jayasena, Abbara et al. in 2020 compared the use of KP-54, and its agonist – MVT-602. Agonist has caused an increase in the LH and FSH serum levels sooner, in comparison to the increase caused by the KP-54. This study has shown new possibilities that scientists may reach with aganoist, which has more favorable properties. [42]

A new study by Mills et al, have shown that the use of intranasal administration of kisspeptin also causes the rapid release of the GnRH, thus gonatropins. This may serve as a solution for any side effects that come with kisspeptin use. With the intranasal route, the response presented as an increase in LH levels was observed in patients with HA, in comparison to placebo. [43]

Only 1 study has shown effect of kisspeptin administration on ovulation, thus menstrual cycle.

Only 1 study has shown the effect of kisspeptin administration on ovulation, the menstrual cycle. There is registrated new trial, NCT07224438, that supose to show the effect of kisspeptin administration to patients with FHA, focusing mainly on ovulation, thus menses restoration; however, results are not published yet.

Safety of kisspeptin use

Kisspeptin is a fairly safe drug, and several side effects were only reported during its use. During the Jaysena study, were KP-54 was injected only twice a week, no significant side effects were observed. During the study of Mills et al. no side effects were observed; furthermore, no effect on blood pressure or heart rate measurements at any of the doses

administered. The reason behind it is probably due to the administration route that was chosen in the study.

Safety of leptin use

Metreleptin mimics the physiological effects of leptin by binding to and activating the human leptin receptor. Recombinant human methionyl leptin (metreleptin) is registered and currently approved for the treatment of the metabolic complications associated with lipodystrophy and leptin deficiency. The drug is not currently registered in the FHA, only as an off-label and experimental treatment. [44]

As with every drug, mentreleptin also carries possible side effects. In people treated with metreleptin, the most common side effects included weight loss, hypoglycemia, abdominal pain, and nausea. However, those were observed in subjects that suffered from lipodystrophy, which also had other metabolic disturbances, such as hyperglycemia at fasting, hypertriglyceridemia, and insulin resistance. [45], [46]

However, most side effects mentioned in the included studies involve a reaction at the injection site and loss of appetite. [32], [35] A

Additionally, as with all therapeutic proteins, with using metrileptin there is also a potential for immunogenicity. In Chou study, antileptin bodies developed in seven out of eight subjects. However, antibodies decreased slightly or were maintained at similar levels until the end of the study. Furthermore, antileptin antibodies were determined to be non-neutralizing antibodies. [35], [44]

Conclusion

Leptin, as well as kisspeptin, may be beneficial as an additional therapy in the restoration of ovulation and the menstrual cycle. It seems, that leptin itself is more effective in ovulation restoration. However, both of the drugs that mimic the action of hormones that are crucial in HPG axis, cause increases in gonadotropins and may be helpful in helping those suffering from infertility, despite adapting to life changes. However, there are more studies are needed to further explore the idea. The downside is that other conservative treatment, which involve lifestyle changes, seems to be easier to incorporate, and do not involve drug administration, and side effects that may follow.

Disclosure

The authors declare that they have no relevant financial or non-financial interests to disclose.

Author Contributions

Conceptualization: M.B. Methodology: M.B. Validation: M.B., Ka.K., J.B. Formal analysis: M.B.

Investigation: M.B., K.K., B.G., K.Kł., P.R., M.K.L., A.S. Resources: M.B., B.G., K.Kł. Data curation: J.B., M.K.L., A.S., M.B. Writing – original draft: M.B. Writing – review and editing: K.K., J.B., B.G., K.Kł., P.R., M.K. Visualization: A.S. Supervision: M.B. Project administration: M.K. Funding acquisition: none.

All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

Not applicable.

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