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Pathogenetic substantiation of a differential approach to the treatment of endometrial hyperplasia in women with abdominal obesity

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Abstract

Background: Endometrial hyperplasia is a precursor to endometrial adenocarcinoma. According to the Global Cancer Observatory 2019, endometrial cancer affects 382,000 women worldwide per year. With timely detection and treatment of endometrial hyperplasia and modification of the factors that lead to excessive proliferation of the internal lining of the uterus, it will be possible to reduce the incidence and preserve the fertility of women of reproductive age. Excessive estrogen is the main cause of endometrial hyperplasia. While the leading mechanism of excessive endometrial proliferation is a disruption in the cyclical change in the ratio of production of the main female hormones estrogen/progesterone. Obesity is a pandemic of the 21st century. Abdominal obesity is the most metabolically dangerous variant of it, as it is characterized by distorted endocrine function, which disrupts the normal functioning of the hypothalamic-pituitary-ovarian system in women. and is also involved in impaired cellular sensitivity to insulin and low-grade chronic inflammation.

Methods: This literature review summarizes the impact of abdominal obesity on the female reproductive system and explains the pathogenetic influence of abdominal obesity on the development, progression and recurrence of endometrial hyperplasia.

Results: This review summarizes the importance of modern pathogenetic treatment of endometrial hyperplasia in women with abdominal obesity

Conclusion:. It was found that the use of first-line drugs together with drugs that increase insulin sensitivity, lifestyle modification and the use of herbal remedies containing Vitex agnus castus can have a positive effect on the treatment of endometrial hyperplasia, and also report a positive effect on improving the quality of life and avoiding recurrence of the disease in women with abdominal obesity.

Key words: **endometrial hyperplasia; insulin resistance; abdominal obesity; THF-alpha; leptin; sex hormone binding protein; hyperandrogenism; aromatase; endometrium; levonorgestrel; metformin; oxidative stress; cytokines; Vitex agnus castus; "Epigallocatechin"; "cucurmin".**

Introduction

Endometrial hyperplasia

Endometrial hyperplasia is an abnormal proliferation of endometrial glands with an increase in the ratio of glands to stroma compared to normal proliferative endometrium. [1].

Endometrial hyperplasia is clinically important because it is often a precursor to endometrial adenocarcinoma.

In 2014, the WHO published a new simplified classification of endometrial hyperplasia, which consists of only two categories and is based on morphological criteria

1) hyperplasia without atypia

2) atypical hyperplasia/endometrial intraepithelial neoplasia [1].

Numerous studies indicate that the leading mechanism of endometrial hyperplasia is chronic exposure to estrogen without counteraction.

This means that conditions accompanied by hyperestrogenism without progestogen counteraction cause excessive endometrial proliferation with a violation of the gland to stroma ratio, which is normally 1:1.

The endometrium is a highly dynamic tissue controlled by ovarian steroids, estrogen and progesterone, and prolonged estrogen stimulation without progesterone antagonism is a key factor in the development of endometrial hyperproliferative conditions.

Risk factors for endometrial hyperplasia include endogenous or exogenous hyperestrogenism. Endogenous factors include chronic obesity, chronic anovulation, hormone-secreting tumours, and early menarche and late menopause.

Obesity is characterised by an increased amount of estradiol produced from androgen precursors in peripheral tissues (for a more detailed mechanism, see the section on abdominal obesity) and by increased adrenal secretory activity.

Chronic anovulation, as a risk factor, leads to a disruption in the cyclicity of sex hormone production, which leads to an increase in estrogen and a lack of progesterone counteraction. As a result, the endometrium constantly proliferates and is not rejected.

Hyperprolactinemia can be the cause of chronic anovulation and inhibits the production of gonadotropin-releasing hormone (GnRH). It can be of exogenous origin (taking antipsychotics, neuroleptics) and endogenous origin (PCOS, obesity, prolactinoma) [2,3].

Polycystic ovary syndrome (PCOS) is characterised by excessive androgen synthesis and impaired folliculogenesis and accumulation of a large number of preovulatory follicles. This leads to chronic anovulation and impaired endometrial rejection, resulting in endometrial hyperplasia.

Studies also indicate that the endometrium of women with PCOS is less receptive to progesterone. The endometrium of women with PCOS is characterised by increased levels of pro-inflammatory cytokines (TNF-a), which lead to excessive proliferation, chronic inflammation and impaired insulin and glucose signaling. Women with PCOS and endometrial hyperplasia are at increased risk of endometrial cancer. In addition to the pathophysiological effects of hyperandrogenism, oxidative stress, insulin resistance and distortion of endometrial receptivity typical of PCOS, which together contribute to carcinogenesis, recent studies have reported a possible link between tumorigenesis and excessive luteinising hormone (LH) secretion in PCOS, which is also characteristic of endometrial cancer. [4,5]

Estrogen therapy, for example, tamoxifen, is a factor in the occurrence of exogenous hyperestrogenism and, as a result, endometrial hyperplasia.

Lynch syndrome is a genetic disorder inherited in an autosomal dominant pattern. t Due to mutations in DNA mismatch repair (MMR) genes such as MSH2, MLH1, MSH6 and PMS2, leading to microsatellite instability (MSI), patients with HNPCC have a 40-60% risk of developing atypical hyperplasia [6].

Abdominal obesity

Abdominal obesity is characterised by the deposition of excess fat in the abdomen.

The abdominal type of obesity is determined by anthropometric data such as waist circumference, waist-to-hip ratio, and waist-to-height ratio [7].

Regardless of body mass index (BMI), people with central or abdominal obesity, compared to people with peripheral (gluteal-thigh) obesity, are at a higher risk of developing health problems. This is because abdominal obesity is characterised by distorted endocrine function and leads to metabolic disorders. Most studies show that visceral obesity is associated with insulin resistance (hyperinsulinemia), fat metabolism disorders (leptin and adiponectin disorders), hyperglycaemia, hyperlipidaemia, chronic inflammation and hyperandrogenism-hyperestrogenism.

Adiposopathy has a direct and indirect effect on the female reproductive system. The leading mechanisms associated with endometrial hyperplasia in obese women are

Conditions associated with hyperandrogenism-estrogenism

Conditions accompanied by insulin resistance and fat metabolism disorders

Conditions accompanied by the circulation of pro-inflammatory cytokines and causing chronic low-grade inflammation.

Disorders in the regulation of the hypothalamic-pituitary-ovarian system lead to a number of endocrinological and gynecological pathologies of the reproductive system. It is known that sex hormones are synthesized in a woman's body from a cholesterol molecule in the endocrine glands of the body.

Adipose tissue has the ability not only to convert steroids but also to initiate the process of steroid hormone formation The main mechanisms of hyperestrogenemia in obesity are the aromatase pathway of androgen conversion to estrogens, as well as de novo synthesis of estrogens from precursors obtained from the bloodstream [8].

In addition, visceral obesity causes hyperinsulinemia, which can reduce the synthesis of sex hormone binding protein (SHBG) by increasing the bioavailability of insulin-like growth factor-1 (IGF-1), leading to increased estrogen levels. [9]

An increase in circulating insulin levels leads to proliferative processes, as insulin is a known growth factor, has the ability to bind to endometrial receptors and has mitotic activity, which leads to hyperplastic processes [11, 12, 13, 14].

Insulin resistance and hyperinsulinemia lead to significant ovarian dysfunctions, such as premature follicular arrest and anovulation. In addition, hyperinsulinemia plays an important role in enhancing LH-induced androgen production by theca cells in the ovaries [15, 16]. In particular, insulinemia causes a pulsatile production of GnRH, which promotes LH secretion from the anterior pituitary gland, while limiting FSH secretion, resulting in a relative FSH

deficiency. Increasing the frequency and amplitude of LH pulses leads to excessive LH production, which stimulates androgen production by ovarian theca cells and further stimulates androgen production by the ovaries, increases androgen production by the adrenal glands and inhibits hepatic synthesis of steroid-binding protein, thereby contributing to hyperandrogenism. Relative deficiency of FSH leads to a halt in follicular growth.

Hyperandrogenism, in turn, leads to increased insulin resistance and dyslipidemia, impaired endometrial regeneration, and may also cause hyperestrogenemia through the aromatase pathway of androgen conversion to estrogen. Excess estrogen via the reverse pathway of endocrine regulation stimulates LH and suppresses FSH secretion, promoting theca cell hyperplasia. In turn, this will increase the synthesis of androgens, which again serve as substrates for extraovarian aromatisation, reinforcing this cycle of hyperestrogenism-hyperandrogenism in obese women [17, 18].

Obesity and chronic inflammation

Abdominal obesity is accompanied by the circulation of cytokines (TNF-α) and leptin, which leads to chronic inflammation.

Inflammation is associated with insulin resistance, tumor necrosis factor (TNF)-alpha can affect glucose uptake and TNF has been shown to induce insulin resistance. Insulin-mediated glucose uptake was significantly reduced during TNF infusion, suggesting that (TNF)-alpha plays a leading role in the development of insulin resistance in obesity. Recent studies indicate that TNF a has the ability to molecularly exacerbate the dysfunction of pancreatic β-cells and can competitively bind to leptin receptors at the molecular level, which disrupts leptin regulation by inhibiting the leptin receptor LepRb and, thus, causing excessive insulin secretion associated with hyperinsulinemia, which is believed to be the cause of insulin resistance and leptin resistance [19, 20, 21].

Pro-inflammatory mediators and leptin are known to induce aromatase. Moreover, free leptin stimulates estrogen production by increasing aromatase expression and activity in human luteal granulosa cells and adipose stromal cells. Leptin, in turn, also affects disorders in the hypothalamic-pituitary-ovarian system. The ability of leptin to disrupt the cyclic release of gonadoliberin and, as a result, to disrupt the secretion of gonadotropin-releasing hormone, which in turn dysregulates the production of LH\FSH and leads to anovulatory cycles, has been proven [22, 23, 24].

(TNF)-alpha is also involved in the regulation of SHBG, a sex hormone binding protein, reducing its concentration in the circulating blood [25, 26].

TNFα affects estrogen metabolism and endometrial cells and has been shown to enhance local estrogen biosynthesis in human endometrial glandular cells and to direct estrogen metabolism into more hormonally active and carcinogenic metabolites. These effects can affect many physiological and pathological processes occurring in the endometrium [27, 28].

Results and discussion

Thus, due to the significant impact of abdominal obesity on the female reproductive system and the presence of proven mechanisms of influence on the pathogenesis of endometrial hyperplasia, this cohort of patients requires a differentiated approach to treatment in order to avoid recurrence of the disease, normalise the state of the hypothalamic-pituitary-ovarian system, preserve reproductive function, prevent malignancy and improve quality of life.

The leading areas of treatment for such women are the combination of first-line drugs (IUD levonorgestrel) with insulin sensitizers, lifestyle modification (weight loss by more than 5%), and intriguingly, herbal remedies containing biologically active substances from the extract of common vetch (Vitex agnus-castus L.), epigallocatechin, and cucurmin.

According to the analysis of women with a histological diagnosis of endometrial hyperplasia with or without atypia, who were compared to LNG-IUDs with non-intrauterine progestogens, placebo, surgery or no conservative treatment, it was proved that LNG-IUD treatment used for three to six months is more effective than non-intrauterine progestogens in eliminating GH in the short term (up to six months) and long term (up to two years). Also, according to a Cohrane review, the regression of endometrial hyperplasia after LNG-IUD treatment is 85% to 92%.[29, 30, 31]

Based on the analysis of randomized trials, there is currently insufficient evidence to support or refute the use of metformin alone or in combination with standard therapy for the treatment of endometrial hyperplasia. However, recent studies indicate that the addition of metformin in combination with progestin in the treatment of women of reproductive age leads to fewer recurrences and more pregnancies than when treated with progestin alone [32, 33, 34].

According to the literature, the mechanism is to increase sensitivity to progestins and prevent the development of resistance to progesterone drugs [20]. Metformin is able to block the action of TNF-α, restoring signaling to endogenous insulin and leptin in endometrial cells [35, 36].

Lifestyle modification in women with abdominal obesity leads to a reduction in the manifestations of the disease, prevents recurrence and improves quality of life. Lifestyle modification is about losing weight, namely losing weight by changing eating habits and

increasing physical activity, which results in a decrease in waist circumference. In the literature, we find studies that prove the existence of a link between diet and the risk of endometrial hyperplasia and cancer. It has been shown that there is a positive relationship between a diet with a high glycaemic index and the risk of endometrial cancer [37, 38].

Reducing obesity is associated with a decrease in the secretion of pro-inflammatory cytokines (IL-6, TNF-α and IL-1β) and an increase in anti-inflammatory mediators (IL-10 and adiponectin). In addition, a decrease in adipose tissue leads to a decrease in the synthesis of androgen precursors and, as a result, a decrease in estrogen levels. In turn, there are studies that describe the effect of exercise on 5'-AMP-activated protein kinase (AMPK), a signaling molecule that directly affects transcriptional regulators that suppress IR and regulate cell growth and survival. The increase in AMPK activity associated with exercise may thus inhibit endometrial hyperplastic processes [39, 40].

Numerous studies have reported a beneficial effect of a low-carbohydrate and ketogenic diet on endometrial hyperplastic processes in women with abdominal obesity [41].

The researchers attribute this effect to the fact that ketone bodies, which are the source of energy in a ketogenic diet, theoretically create an unfavourable environment for cell proliferation, and it is known that a ketogenic diet also affects insulin resistance, with a significant reduction in fasting insulin and C-peptide concentrations, as well as unchanged concentrations of insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein (IGFBP), respectively, and a decrease in circulating insulin concentrations, which leads to a cascade of disorders of female endocrine regulation [42, 43, 44]. The literature also describes that a ketogenic diet has the ability to reduce chronic low-grade inflammation caused by adiposopathy [45, 46].

A promising area at the present stage is the addition of Vitex agnus-castus to the therapy of women with endometrial hyperplasia and abdominal obesity. Vitex agnus-castus is a medicinal plant of the verbena family, which has

antioxidant and pro-diabetic effects as it is an effective inhibitor of α-amylase and α-glucosidase, which can be useful for reducing postprandial glucose levels They also increase cellular glucose sensitivity, thereby reducing insulin resistance and circulating insulin levels [47, 48], and are a powerful antioxidant that can reduce oxidative stress and inflammation in obesity [49]. The effect of preparations containing Vitex agnus-castus on reducing prolactin levels, which are elevated in abdominal obesity, is known [50].

Studies have reported a therapeutic effect of adding Epigallocatechin Gallate to the treatment on glycaemic levels, insulin resistance and weight loss [51, 52].

A positive effect on the restoration of insulin resistance and reduction of circulation of chronic inflammatory mediators is observed when adding to the main therapy of drugs containing cucurmin. [53, 54]

Conclusions

After analysing the review of modern literature, it was found that

Firstly, abdominal obesity has a pathogenetic relationship to the occurrence of menstrual irregularities, which leads to chronic anovulatory cycles, impaired endometrial rejection and regeneration

Secondly, taking into account insulin resistance and hyperandrogenism, chronic low-grade inflammation accompanying abdominal obesity and ovulation disorders, it can be argued that abdominal obesity is one of the most important etiological factors in the development of not only endometrial hyperplasia but also polycystic ovary syndrome.

The pathogenesis of endometrial hyperplasia in women with abdominal obesity involves many factors that form strong interactions with each other and turn a woman's body into a vicious circle for the development, progression and recurrence of these diseases. That is why a differentiated approach to the treatment of these women is very important.

Further studies should determine the effectiveness of a differential treatment approach to endometrial hyperplasia in women with abdominal obesity, namely to determine the effectiveness and impact on the endometrial state, hypothalamic-pituitary-ovarian system, insulin resistance and low-grade chronic inflammation, quality of life, and disease recurrence.

1)combination of levonorgestrel IUD with insulin sensitizers (metformin)

2) combination of lifestyle modification with Vitex agnus, Epigallocatechin Gallate, cucurmin herbal medicine

Conflicts of interest

The authors declare having no conflicts of interest.

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