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Menstrual dysfunction in adolescent girls who are overweight: a literature review

Evgeniya A. Svidinskaya, Mikhail B. Ageev, Natal'ya V. Paleeva, Valeriya A. Mukhaeva, Elena A. Sosnova

I.M. Sechenov First Moscow State Medical University, Moscow, Russian Federation

ABSTRACT

This study aimed to review the modern literature on the problems of adolescent obesity and the pathogenesis of menstrual dysfunction in overweight adolescents and women of reproductive age. In recent years, a large number of works have been published on the relationship of hyperinsulinemia with ovarian hyperandrogenism. Most authors recognize that insulin resistance and hyperinsulinemia contribute to polycystic ovary syndrome formation. The formation of menstrual disorders in overweight girls is based on the violation of gonadotropin secretion, insulin resistance, and hyperinsulinemia, which over time lead to hyperandrogenism. A decreased level of somatotropic hormone and insulin-like growth factor and an increased level of leptin leads to malfunctions in the correct functioning of the hypothalamic-pituitary system. These changes disturb the ovulatory function and, consequently, adolescent reproductive health. The relationship between obesity and depression is actively discussed by foreign authors, and the obtained results often contradict each other. Most studies suggest that excessive weight gain during adolescence can lead to depression, negative mood, and low self-esteem.

This study analyzes the results of research by domestic and foreign authors on the issues of diagnosis and treatment. Menstrual disorder therapy against the background of overweight adolescent girls is a matter of dispute among clinicians. With weight loss in adolescents, a significant improvement is found in carbohydrate and lipid metabolism, decreased levels of hepatic transaminases, and a decreased severity of obstructive sleep apnea syndrome.

Keywords: obesity in adolescents; ovulatory dysfunction; hyperandrogenism; literature review.

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Нарушение менструальной функции у девочек-подростков с избыточной массой тела (обзор литературы)

Е.А. Свидинская, М.Б. Агеев, Н.В. Палеева, В.А. Мухаева, Е.А. Соснова

Первый Московский государственный университет им. И.М. Сеченова, Москва, Российская Федерация

АННОТАЦИЯ

В работе представлен обзор современной литературы по проблемам подросткового ожирения, патогенезу нарушений менструальной функции при избыточной массе тела, как у подростов, так и у женщин репродуктивного возраста. В последние годы опубликовано большое число работ, посвящённых взаимосвязи гиперинсулинемии с яичниковой гиперандрогенией. Большинство авторов признают, что инсулинорезистентность и гиперинсулинемия способствуют формированию синдрома поликистозных яичников. В основе формирования нарушений менструального цикла у девочек с избыточной массой тела лежат нарушение секреции гонадотропинов, инсулинорезистентность и гиперинсулинемия, которые с течением времени приводят к гиперандрогении. Снижение уровня соматотропного гормона, инсулиноподобного ростового фактора и повышение уровня лептина приводят к сбоям в корректном функционировании гипоталамо-гипофизарной системы. Эти изменения могут вызывать нарушения овуляторной функции и, следовательно, репродуктивного здоровья подростков. Связь ожирения и депрессии активно обсуждается зарубежными авторами, а полученные результаты часто противоречат друг другу. Большинство исследований свидетельствуют о том, что чрезмерное увеличение массы тела в подростковом возрасте может обусловить депрессию, негативное настроение и низкую самооценку.

В работе проанализированы результаты исследований отечественных и зарубежных авторов по вопросам диагностики и лечения. Терапия нарушений менструального цикла на фоне избыточного веса у девочек-подростков — предмет спора среди клиницистов. При снижении веса у подростков отмечается значительное улучшение показателей углеводного и липидного обмена, снижение уровней печёночных трансаминаз, уменьшение выраженности синдрома обструктивного ночного апноэ.

Ключевые слова: ожирение у подростков; овуляторная дисфункция; гиперандрогения; обзор литературы.

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ЭКО•ВЕКТОР

Obesity is currently one of the most pressing medical and social problems in the younger generation; however, it is poorly covered and is becoming increasingly threatening. In recent decades, there has been a rapid increase in the number of obese children and adolescents worldwide. Overweight and obesity have become one of the most common endocrine disorders in children and adolescents; among schoolchildren, the incidence of fat metabolism disorders currently reaches 25–30% [1–6].

There has been an increase in the number of obese children in Russia. For the pediatric population in the northwest European part of Russia and the Urals, the prevalence of overweight and obesity in 1994–2005 was 4–9%, whereas in 2008–2018, it increased to 12.9–26.1% [7].

According to Rosstat, 31% of children aged 3–13 years in Russia are overweight, and every 9th child of this age is diagnosed with obesity. Moreover, 15% of adolescents aged 14–18 years are overweight.

At the beginning of the 20th century, H. Evans and K. Bishop have actively studied the effects of fatty foods on animal fertility. Numerous observations have led to the discovery of vitamin E, and scientists have identified a relationship between obesity and women's reproductive health and noted the restoration of fertility with weight normalization. Stein and Leventhal have described polycystic ovary syndrome and confirmed the association between obesity and reproductive dysfunction.

Menstrual irregularities in overweight girls is based on impaired gonadotropin secretion, insulin resistance (IR), and hyperinsulinemia, which over time lead to hyperandrogenism. A decrease in somatotropic hormone and insulin-like growth factor levels and an increase in leptin levels result in incorrect functioning of the hypothalamic–pituitary system. These changes may explain ovulatory dysfunction and consequently impairment of reproductive health in adolescents [8–11].

In recent years, the role of leptin in the regulation of reproductive function has been actively discussed. Significant weight loss, especially due to adipose tissue, can lead to amenorrhea or infertility. According to some authors, leptin can serve as a signaling hormone for the reproductive system to provide an adequate supply of adipose tissue. There is evidence that leptin levels in animals increase only before the onset of puberty, which can be accelerated by the administration of exogenous leptin.

During the normal course of puberty, leptin production increases and adipose tissue accumulates. At the age of ~10–11 years, healthy girls experience adrenarche, a physiological growth spurt that coincides with an increase in leptin levels. This indicates that a certain level of adipose tissue content has been reached in the body, and the body is ready for menarche and completion of sexual development. Leptin receptors were found on the surfaces of granulosa, theca, and interstitial cells of the ovaries.

Furthermore, the neuropeptide kisspeptin plays a crucial role in the correct functioning of the reproductive system. Kisspeptin acts on GPR54 receptors in the brain, activating neurons that release the gonadotropin-releasing hormone which controls the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [2–4].

Several authors consider adipose tissue as an endocrine gland that is actively involved in the metabolism of sex hormones; in addition, data have been obtained on the synthesis of a certain set of cytokines by adipose tissue. In obesity, leukocytes and macrophages infiltrate the adipose tissue, which is called the "adipose tissue inflammation phenomenon". This aseptic inflammation eventually leads to IR through the activation of pattern recognition receptors (Toll-like receptors, TLRs). TLRs are found on the surface of macrophages, dendritic and mast cells, neutrophils, basophils, and nonimmune cells (fibroblasts, epithelial cells, keratinocytes). Additionally, adipose tissue cells participate in TLR expression, leading to a chronic inflammatory response in adipose tissue. The presence of TLR2 and/or TLR4 is critical for the infiltration of adipose tissue by macrophages. In adolescent girls with oligomenorrhea and obesity, an association was noted between an increase in body weight and increased monocyte counts expressing TLR2, TLR4, and TLR6. Carriers of the Gly allele of the *TLR4* gene have an increased risk of menstrual dysfunction and IR, whereas the Asp/Asp genotype is protective because it is less common in obese patients and oligomenorrhea than in healthy girls and obese patients with a regular menstrual cycle. Activation of TLR4 leads to IR. Allelic variants of the *TLR4* gene at the Asp299Gly polymorphism points can be considered as a genetic marker of menstrual disorders in obese adolescent girls [12–16].

The researchers concluded that menstrual irregularities in obese adolescent girls were accompanied by significant changes in cytokine levels. One of the cytokines, TNF-α, is synthesized mainly by monocytes and macrophages. This cytokine is multifunctional, as it leads to IR, endothelial dysfunction, and dyslipidemia and disrupts the normal functioning of the ovaries, leading to anovulation and luteal phase failure [17]. An increase in soluble receptor for tumor necrosis factor α (sTNF-α-R1) level in female patients can be considered a protective reaction against the development of IR; that is, sTNF-α-R1, by inhibiting the activity of TNF-α, provides subcompensation in the progression of IR and the development of persistent menstrual irregularities [18].

Another significant cytokine formed during excess weight is interleukin-6 (IL-6); its concentration directly depends on the content of adipose tissue in the body. Interleukin-6 has been found to have a direct effect on metabolic processes in the liver, reducing the sensitivity of insulin receptors, and is an auto- and paracrine regulator of adipocyte function. An increase in IL-6 concentration leads to an increase in IR, disruption of the hypothalamic–pituitary system, hyperandrogenism, and menstrual irregularities. One of the main sources of IL-6 (the second largest after the immune system) is adipose tissue, which produces up to 10–35% of the circulating cytokine [19–22], which is formed in adipose tissue cells

and macrophages. Adipocyte hypertrophy, which is common in inflammation, can lead to increased IL-6 production. IL-6 can block insulin-induced glycogen synthesis, inhibit the metabolic effects of insulin, and have a direct effect on the formation of IR at the level of liver cells through the production of SOCS proteins (suppressor of cytokine signaling). In addition, IL-6 inhibits the secretion of adiponectin in fat cells, indirectly affecting the development of IR. It has been proven that the level of increase in IL-6 correlates with the severity of IR, and the degree of increase in the blood concentration of IL-6 is a more significant indicator of an increase in the mass of adipose tissue in the body compared with the severity of IR [19–23].

In recent years, the development of ovarian hyperandrogenism against hyperinsulinemia has been actively discussed. Most researchers have revealed that IR and hyperinsulinemia can lead to the development of polycystic ovary syndrome.

Hyperandrogenic ovarian dysfunction leads to chronic anovulation [24–27]. One study has revealed a 4–18% incidence of hyperandrogenic conditions in obese girls. In addition, obesity has been proven to be an additional factor in the formation of hyperandrogenic ovarian dysfunction, which aggravates the course and prognosis of this pathology [24]. Androgens disrupt the normal development of follicles, leading to multiple atresias. The increasing concentration of androgens in the ovary causes the gradual elimination of estrogen-producing granulosa cells, followed by hyperplasia of thecal cells and luteinization of the interstitial tissue of the ovary, which is the site of androgen production. This explains why stimulation of ovarian steroidogenesis by insulin manifests itself predominantly in the form of hyperandrogenism.

According to a study that included 130 obese teenage girls, obesity can cause psychopathological disorders in girls, which are influenced by the personality characteristics of the patients. The state of emotional distress in adolescents causes neurohormonal disruption, which results in disruption of the menstrual cycle [25].

The association between obesity and depression has been actively discussed by international authors, and the results often contradict each other. Most studies have shown that excessive weight gain during adolescence may be associated with depression, negative mood, and low self-esteem [26–30]. Moreover, other studies have revealed a negative relationship between BMI and obesity and indicators of depression and anxiety. This means that the higher your weight, the lower your levels of depression, anxiety, and perceived stress. Overweight is probably no longer a trait that stigmatizes anyone, especially if the entire family is obese or overweight and an increasing number of peers are overweight. Another possible explanation is the subjective positive self-esteem of body image, which could eliminate negative self-esteem [31–33]. Long-term obesity, from early childhood, can also lead to a feeling of "addiction" to this body image, which does not affect self-esteem.

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in adult women with characteristic signs of anovulation and clinical and biochemical hyperandrogenism. PCOS onset occurs in adolescence; however, in teenage girls, the clinical aspects of the syndrome may be less pronounced or borderline with adolescent physiology. However, in adolescents, the quality of life appears to be affected by the same signs and symptoms of PCOS as in adult women, namely, excess weight, clinical hyperandrogenism, menstrual irregularities, and infertility [33–35]. The risks of menstrual irregularities and development of PCOS are significantly higher in women who have been persistently overweight or obese since childhood. Excess weight in adulthood is considered a major risk factor for the development of cardiometabolic diseases. Some researchers have revealed that early menarche is associated with the development of cardiometabolic risk factors. These women had high triacylglycerols (TAG) levels and low high-density lipoprotein levels and were 1.55 times more susceptible to metabolic syndrome.

CHARACTERISTICS OF ANAMNESIS

The onset of puberty in girls occurs at the age of 8–9 years and depends on various factors, including heredity, nutrition, and physical activity. The average age of menarche in Russia is 12–13 years; however, in adolescent girls with excess body weight, puberty begins earlier than in girls with normal body weight, possibly isolated thelarche, and menarche occurs earlier. Yu.V. Kovaleva has analyzed menstrual function in adolescents and noted that with excess body weight, menarche begins 1.4 ± 0.2 years earlier than in girls with normal body weight, i.e. the age of menarche decreases to 9–11 years. Acceleration of the rate of puberty does not correlate with the development of the uterus and ovaries. The author considers the early age of menarche as an independent prognostic factor for the increase in BMI and other complications of obesity [32].

In another study of obese adolescent girls aged 11–15 years, pubertal development was characterized by early onset (average, 10.8 ± 0.8 years), with an average height of 171 ± 3 cm and a BMI ranging from 31.2 kg/m^2 to 43 kg/m^2 (average 37.1 ± 5.9 kg/m^2). The age of the menarche was from 9.9 to 13.5 years. Menstrual irregularities were noted in 70% of the girls examined, most often (60%) of the oligomenorrhea type. The proportion of patients with secondary amenorrhea and acyclic uterine bleeding during puberty was the same (20 and 20%, respectively) [2]. In addition, deviations in the order of appearance of sexual characteristics were observed in overweight girls; therefore, the incidence of isolated pubarche was 33%, whereas in the population this figure was 15%. The endocrine basis for the untimely manifestation of sexual hair growth is androgen excess.

Approximately half of the symptomatic menstrual irregularities are due to neuroendocrine immaturity, and half

are associated with elevated androgen levels. The former manifests as aluteal or short/deficient luteal phase cycles and usually resolves spontaneously, and the latter appears to be associated with PCOS because adolescent androgen levels are associated with adult androgens and ovulatory dysfunction.

Menstrual irregularities, such as oligomenorrhea, secondary amenorrhea, and abnormal uterine bleeding, occur more often among overweight girls than in the general population. Some authors have noted manifestations of hypercortisolism in the form of stretch marks, increased blood pressure, follicular hyperkeratosis, and acanthosis nigricans.

EXAMINATIONS

According to the clinical recommendations of the Russian Association of Endocrinologists, in all obese and overweight children, it is recommended to measure the height, weight with the calculation of standard deviations of BMI (standard deviation score, SDS), and waist circumference; assess the nature of the distribution of subcutaneous fat; measure the blood pressure and evaluate it considering gender, age, and height; determine the presence and nature of striae, follicular keratosis, acanthosis nigricans, and androgen-dependent dermopathy; assess the stage of sexual development; and identify specific phenotypic features.

N.V. Bolotova et al. [2] have described characteristic changes in the pelvic organs detected in obese girls, namely, densification of the stroma and tunica albuginea of the ovaries, small cystic inclusions, and absence of a dominant follicle (noted in 52.5% of obese patients). When analyzing the hormonal profile, a decrease in FSH content and an increase in the level of other tropic hormones (LH, LH/FSH index, androgens, estrogens, insulin, and IR) were noted, indicating activation of the neuroendocrine system.

TREATMENT

The standard treatment of menstrual disorders in adolescent girls remains controversial. Most doctors limit themselves to the use of cyclic vitamin therapy or herbal preparations to correct oligomenorrhea and other disorders. As a rule, doctors avoid prescribing hormonal therapy or other medications for age-related functional disorders of menstrual function and tend to use nondrug treatment methods.

N.V. Bolotova et al. have reported that the use of transcranial magnetic therapy in the complex treatment of patients with hypothalamic syndrome in the pubertal period provided significant positive results and led to an improvement in the clinical and hormonal status of adolescent girls with obesity [2].

According to clinical recommendations for the treatment of obesity in children, the use of medications (in combination with lifestyle changes) in obese children and adolescents is advisable after the age of 12 years if measures aimed at developing a healthy lifestyle, which lasted for at least 1 year, are ineffective. The only drug approved for the treatment of obesity in children is orlistat. The widely used drug metformin for the treatment of IR in patients with PCOS is not approved for the treatment of obesity in either children or adults; it belongs to the first line of treatment for type 2 diabetes mellitus (DM). In this regard, the prescription of metformin in pediatric practice is approved in the over 10 years age group only in patients diagnosed with type 2 DM.

This drug has been proven effective for the treatment of PCOS in patients with obesity and those with normal body weight; metformin reduces the incidence of anovulation and testosterone levels. Off-label metformin therapy is beneficial for patients with hyperandrogenism and menstrual irregularities who are at risk of developing polycystic ovary syndrome [1]. In recent years, surgical methods for the treatment of morbid obesity (e.g., bariatric surgery) in adolescents have become widespread worldwide. The main advantages of this method are rapid weight loss, improvement of metabolic parameters, reduction of psychological discomfort in patients, and a significant increase in the quality of life of patients with morbid obesity. According to the clinical guidelines of the International Endocrine Society, bariatric surgery is the treatment of choice in adolescents with morbid obesity [1].

CONCLUSION

Overweight and obesity in adolescence not only affect appearance and cause the development of many diseases but also have a detrimental effect on the proper functioning of the entire reproductive system, which in turn affects a woman's health in adulthood. Obesity in childhood increases the probability of being overweight or obese in adulthood, disability, or untimely death. In addition to problems with menstrual regularity, obese adolescent girls may suffer from hypertension, shortness of breath, limited physical activity, and psychological problems.

The pathology that develops over time is characterized by a large set of clinical symptoms and leads to disruption of the processes of formation of the reproductive system in girls because the reproductive system is unstable in the puberty period and is particularly sensitive to the effects of unfavorable exogenous and endogenous factors, particularly obesity.

Drawing attention to the problem of childhood and adolescent obesity will help maintain health and avoid various health problems in adulthood through weight correction.

ADDITIONAL INFO

Author's contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work. The concept and design of the study — N.A. Svidinskaya, M.B. Ageev; collection and processing of the material — N.V. Paleeva, V.A. Mukhaeva; writing of the text — E.A. Svidinskaya, M.B. Ageev; editing — E.A. Sosnova.

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AUTHORS INFO

***Evgeniya A. Svidinskaya,** MD, Cand. Sci. (Med.),
assistant at Department of Obstetrics and Gynecology № 1;
address: 8 Trubetskaya str., build. 2, Moscow, 119991, Russian Federation;
ORCID: 0000-0002-2368-1932;
e-mail: svidinskaya@gmail.com

Mikhail B. Ageev, MD, Cand. Sci. (Med.);
ORCID: 0000-0002-6603-804X;
e-mail: ageev_m_b@staff.sechenov.ru

Natal'ya V. Paleeva, V-year student;
ORCID: 0000-0002-7842-479X;
e-mail: npaleeva4@gmail.com

Valeriya A. Mukhaeva, V-year student;
ORCID: 0000-0001-5507-3299;
e-mail: vvaleriamuhaeva@gmail.com

Elena A. Sosnova, M.D., Dr. Sci. (Med.), Professor;
ORCID: 0000-0002-1732-6870;
eLibrary SPIN: 6313-9959;
e-mail: sosnova-elena@inbox.ru

* Corresponding author / Автор, ответственный за переписку

ОБ АВТОРАХ

***Свидинская Евгения Александровна,** к.м.н., ассистент каф. акушерства и гинекологии № 1;
адрес: 119991, г. Москва, ул. Трубецкая, д. 8, стр. 2, Россия;
ORCID: 0000-0002-2368-1932;
e-mail: svidinskaya@gmail.com

Агеев Михаил Борисович, к.м.н., доцент;
ORCID: 0000-0002-6603-804X;
e-mail: ageev_m_b@staff.sechenov.ru

Палеева Наталья Вячеславовна, студентка V курса;
ORCID: 0000-0002-7842-479X;
e-mail: npaleeva4@gmail.com

Мухаева Валерия Арифовна, студентка V курса;
ORCID: 0000-0001-5507-3299;
e-mail: vvaleriamuhaeva@gmail.com

Соснова Елена Алексеевна, д.м.н., профессор;
ORCID: 0000-0002-1732-6870;
eLibrary SPIN: 6313-9959;
e-mail: sosnova-elena@inbox.ru