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THE ROLE OF INSULIN RESISTANCE IN MENSTRUAL CYCLE DISORDERS IN ADOLESCENT GIRLS

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Abstract: Menstrual irregularities are among the most frequent reasons for adolescent girls to seek gynecological care. Although anovulation during the first years after menarche is often physiological, persistent oligomenorrhea, amenorrhea or heavy irregular bleeding may signal an endocrine-metabolic disorder in which insulin resistance (IR) plays a central role. To summarize current evidence on the contribution of IR and compensatory hyperinsulinemia to menstrual cycle disorders in adolescent girls and to outline practical diagnostic and therapeutic implications. Physiological pubertal IR, amplified by obesity, low birth weight, premature adrenarche and genetic susceptibility, promotes ovarian theca-cell androgen excess, disturbs follicular maturation, alters GnRH pulse dynamics and lowers hepatic synthesis of sex hormone-binding globulin, which together result in oligo-anovulation.

Keywords: insulin resistance, hyperinsulinemia, adolescents, menstrual cycle disorders, oligomenorrhea, polycystic ovary syndrome, metformin

Menstrual function is increasingly regarded as a vital sign of general health in girls and adolescents [1]. During the first years after menarche, irregular cycles are common and frequently reflect the physiological immaturity of the hypothalamic–pituitary–ovarian (HPO) axis: regular ovulatory cycles are established gradually, and a considerable proportion of early cycles are anovulatory [2]. Nevertheless, persistent oligomenorrhea, amenorrhea or heavy irregular uterine bleeding may be the first clinical manifestation of an underlying endocrine or metabolic disorder, most frequently polycystic ovary syndrome (PCOS) [3, 4].

Depending on the diagnostic criteria applied, the prevalence of PCOS in adolescents is estimated at approximately 3–11% [5]. Insulin resistance (IR) and compensatory hyperinsulinemia are recognized as key pathogenic components of the syndrome [6, 7]. Euglycemic–hyperinsulinemic clamp studies indicate that IR is present in the majority of affected women, in approximately 75% of lean and 95% of overweight individuals [8, 9]. The global increase in childhood and adolescent obesity, which is associated with earlier pubertal maturation and a greater metabolic burden [10], makes the interaction between IR and menstrual dysfunction a growing concern for pediatric and adolescent gynecologists.

The aim of this narrative review is to synthesize evidence from international guidelines, clinical investigations and mechanistic studies on the role of IR in the development of menstrual cycle disorders in adolescent girls, and to outline practical implications for diagnosis and management.

Puberty is accompanied by a transient, physiological decline in insulin sensitivity. Clamp-based studies have shown that insulin-mediated glucose disposal falls by approximately 30% in mid-puberty (Tanner stages 2–4) compared with prepubertal and adult values, and that compensatory

hyperinsulinemia maintains normal glucose tolerance [11, 12]. This phenomenon is attributed mainly to the pubertal surge of growth hormone and insulin-like growth factor-1 (IGF-1) and to increased lipolysis, and it usually resolves by the end of puberty.

In most girls this adaptation is harmless. However, in the presence of additional risk factors – obesity, low birth weight followed by rapid catch-up growth, premature adrenarche or pubarche, a family history of type 2 diabetes or PCOS, and certain ethnic backgrounds – IR may be exaggerated or may fail to resolve, and the resulting hyperinsulinemia can drive ovarian hyperandrogenism [10, 13]. Puberty therefore represents a window of vulnerability in which physiological IR may unmask or accelerate a latent predisposition to anovulatory dysfunction. Girls with a history of premature pubarche, for instance, have been shown to exhibit hyperinsulinemia and reduced concentrations of IGF-binding protein-1 (IGFBP-1) both before and during puberty [13].

The ovary is a principal target of hyperinsulinemia. Insulin acts through its own receptor on theca cells and enhances luteinizing hormone (LH)-stimulated androgen biosynthesis, in part by increasing the activity of cytochrome P450c17 (CYP17A1) [7, 14, 15]. A distinctive feature of the syndrome is "selective" IR: while metabolic signaling pathways (such as glucose uptake) are resistant to insulin, steroidogenic pathways in the ovary remain responsive, so that compensatory hyperinsulinemia continues to stimulate androgen production [16]. In granulosa cells, insulin acts synergistically with LH, promoting premature responsiveness to LH and luteinization of small antral follicles, which contributes to arrest of follicular growth and anovulation [17]. Intrafollicular androgen excess further impairs selection of a dominant follicle, so numerous small follicles accumulate while ovulation fails [17, 18]. Clinically, this is expressed as oligomenorrhea or amenorrhea.

Hyperandrogenemia and hyperinsulinemia may reduce the sensitivity of the hypothalamic GnRH pulse generator to the negative feedback of estradiol and progesterone, resulting in an accelerated GnRH and LH pulse frequency, a relative predominance of LH over FSH and further stimulation of ovarian androgen production [3, 18]. In adolescents, this may delay or prevent the establishment of regular ovulatory cycles after menarche. However, evidence for a direct effect of insulin on LH secretion in humans is less consistent [19], and neuroendocrine abnormalities are best regarded as contributing rather than initiating factors.

In the liver, insulin suppresses the synthesis of sex hormone-binding globulin (SHBG) [20, 21]. Lower SHBG raises the free fraction of circulating testosterone and thereby amplifies its peripheral effects, such as hirsutism and acne. Insulin also lowers IGFBP-1, increasing bioavailable IGF-1, which augments theca-cell androgen production [13]. Visceral adiposity, altered adipokine secretion (reduced adiponectin, increased leptin), increased free fatty acid flux and chronic low-grade inflammation further aggravate IR [7]. Importantly, IR is not confined to obese girls: lean adolescents with PCOS may also exhibit hyperinsulinemia, reduced insulin sensitivity and mitochondrial dysfunction [22]. Androgen excess, in turn, favors visceral fat deposition and worsens IR, creating a self-perpetuating cycle in which metabolic and reproductive disturbances reinforce each other [7, 18].

In adolescents, menstrual cycles are considered normal when they occur at intervals of 21 to 45 days and bleeding lasts up to seven days [1]. Cycles shorter than 21 days or longer than 45 days more than one year after menarche, any single cycle longer than 90 days, and primary amenorrhea by age 15 years (or more than three years after thelarche) are regarded as abnormal and warrant evaluation [9]. Cycle irregularity during the first year after menarche, in contrast, is usually a normal physiological variant.

IR-associated menstrual disorders most often present as oligomenorrhea or secondary amenorrhea resulting from chronic anovulation. Prolonged anovulation with unopposed estrogen stimulation may also lead to heavy, prolonged and unpredictable bleeding, classified by FIGO as

abnormal uterine bleeding of ovulatory dysfunction type (AUB-O) [23]. Typical accompanying findings include central obesity, acanthosis nigricans, hirsutism, persistent acne and, in a substantial proportion of girls, dysglycemia, dyslipidemia and non-alcoholic fatty liver disease. The metabolic syndrome is markedly more frequent in PCOS than in the general population [24], which underlines that menstrual irregularity in these girls is a visible sign of a systemic disorder.

The differential diagnosis includes pregnancy, thyroid dysfunction, hyperprolactinemia, non-classic congenital adrenal hyperplasia, Cushing syndrome, functional hypothalamic amenorrhea (energy deficiency, eating disorders, intensive sport) and premature ovarian insufficiency [3, 25].

Current international guidance emphasizes caution in adolescents. Because irregular cycles and polycystic-appearing ovaries may be normal in the years after menarche, a diagnosis of PCOS in this age group requires both irregular cycles (appropriate for the time since menarche) and clinical or biochemical hyperandrogenism, whereas pelvic ultrasound and anti-Müllerian hormone are not recommended for diagnosis within eight years of menarche [4, 5, 9]. Girls who show only some features may be considered “at risk” and reassessed over time, with lifestyle and metabolic guidance provided in the meantime. Table 1 summarizes a practical diagnostic approach.

Table 1. Suggested evaluation of an adolescent girl with menstrual irregularity and suspected insulin resistance

Domain	Assessment	Practical comment
History and anthropometry	Age at menarche, cycle pattern, birth weight, premature adrenarche, family history of type 2 diabetes or PCOS; BMI percentile, waist circumference, blood pressure	Central adiposity and family history increase the likelihood of IR
Skin signs	Acanthosis nigricans, hirsutism, acne, alopecia	Acanthosis nigricans is a marker of hyperinsulinemia
Hormonal profile	Total testosterone, SHBG (free androgen index), LH, FSH, TSH, prolactin, 17-hydroxyprogesterone, hCG	Excludes pregnancy and other causes of irregular cycles
Glycemic status	Fasting glucose, HbA1c, 75-g OGTT (± insulin)	HOMA-IR = fasting insulin (μU/mL) × fasting glucose (mmol/L) / 22.5
Lipids and liver	Lipid profile, alanine aminotransferase	Screening for dyslipidemia and fatty liver disease

The euglycemic–hyperinsulinemic clamp remains the reference method for measuring insulin sensitivity but is impractical in routine care. Surrogate indices, such as the homeostasis model assessment of insulin resistance (HOMA-IR) [26], are widely used; however, universal cut-off values for adolescents are lacking because of physiological pubertal IR and variation by Tanner stage, sex and ethnicity. Consequently, insulin concentrations are not required to establish the diagnosis and should be interpreted cautiously, whereas assessment of glycemic status by fasting glucose, HbA1c or an oral

glucose tolerance test is recommended in adolescents with PCOS or at risk of it, particularly in those with overweight or additional risk factors [5, 9].

Management should be individualized and multidisciplinary, involving the gynecologist, endocrinologist, dietitian and, where necessary, a psychologist, with attention to the psychological burden (anxiety, depression, disordered eating) that often accompanies the condition [9]. **Lifestyle modification** is the first-line approach. A balanced, energy-appropriate diet and regular physical activity improve insulin sensitivity, and even a modest reduction of body weight in overweight girls is associated with improved cycle regularity and reduced hyperandrogenism [27].

Insulin resistance, physiological in puberty and exaggerated in the presence of obesity and other risk factors, is a major and modifiable contributor to menstrual cycle disorders in adolescent girls. Through ovarian androgen excess, disturbed follicular development, altered GnRH pulsatility and reduced SHBG, hyperinsulinemia promotes oligo-anovulation and abnormal uterine bleeding and predisposes to long-term cardiometabolic complications. A careful, age-appropriate diagnostic approach that avoids premature labeling, together with early lifestyle intervention and individualized pharmacotherapy, can improve both immediate menstrual outcomes and long-term health. Further prospective studies, including those in Central Asian populations, are needed to define adolescent-specific thresholds of IR and to optimize treatment strategies.

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