

## Keywords

adolescent obesity; menstrual cycle disorders; reproductive endocrinology; insulin resistance; precision medicine; lifestyle intervention; adolescent gynecology; personalized healthcare.

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# Optimization of the Management of Adolescent Girls with Menstrual Cycle Disorders Associated with Obesity: An Integrated Clinical and Metabolic Approach

## Abstract

Obesity has become one of the most prevalent chronic health conditions among adolescent girls worldwide and is increasingly recognized as a major contributor to menstrual cycle disorders through complex endocrine, metabolic, and inflammatory mechanisms. Early menstrual dysfunction during adolescence may adversely affect reproductive health, increase the risk of polycystic ovary syndrome, infertility, and future cardiometabolic diseases, highlighting the need for comprehensive and individualized management strategies. This study aimed to optimize the clinical management of adolescent girls with obesity-associated menstrual cycle disorders by developing an integrated assessment model that combines metabolic, hormonal, clinical, and lifestyle factors to support personalized therapeutic decision-making. A prospective comparative clinical study was conducted involving adolescent girls aged 12–18 years diagnosed with obesity and menstrual irregularities. Participants underwent comprehensive anthropometric evaluation, hormonal profiling, metabolic assessment, pelvic ultrasonography, and lifestyle analysis. Individualized multidisciplinary interventions consisting of nutritional counseling, structured physical activity, behavioral modification, and endocrine management were implemented, while clinical outcomes were evaluated using standardized statistical analyses and predictive modeling techniques. The findings demonstrated that integrated multidisciplinary management was associated with significant improvement in menstrual regularity, hormonal balance, metabolic parameters, and ovarian morphology compared with conventional management. Insulin resistance, hyperandrogenism, elevated body mass index, and poor lifestyle adherence emerged as the strongest predictors of persistent menstrual dysfunction. The principal originality of this study is the development of the Integrated Adolescent Menstrual Health Optimization Framework (IAMHOF), a novel conceptual model that integrates obesity severity, endocrine function, metabolic biomarkers, pelvic ultrasonography, digital health monitoring, and personalized lifestyle interventions into a unified clinical decision-making framework. This approach advances existing management strategies by emphasizing individualized risk stratification and precision adolescent gynecological care. In conclusion, comprehensive multidisciplinary management supported by the IAMHOF model may improve reproductive and metabolic outcomes in obese adolescent girls, facilitate earlier intervention, and provide a practical evidence-based framework for optimizing adolescent reproductive healthcare in both clinical practice and preventive public health programs.

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## INTRODUCTION

Adolescent obesity has emerged as one of the most significant global public health challenges of the twenty-first century, affecting physical, metabolic, endocrine, and reproductive health during a critical period of growth and development. According to the latest international estimates, the prevalence of overweight and obesity among children and adolescents has increased dramatically over recent decades, with obesity now recognized as a major contributor to chronic noncommunicable diseases and long-term reproductive dysfunction. Excess adiposity during adolescence is associated not only with metabolic syndrome, insulin resistance, and cardiovascular risk but also with disturbances of pubertal maturation, menstrual cyclicity, and future fertility. These reproductive consequences have become increasingly important because adolescence represents the period during which the hypothalamic–pituitary–ovarian (HPO) axis matures and establishes normal ovulatory function. Consequently, metabolic disturbances occurring during this developmental window may have lasting effects on reproductive health throughout adulthood. (PubMed Central (PMC))

Menstrual disorders are among the most frequent gynecological problems encountered during adolescence. Although irregular menstrual cycles are common during the first years after menarche because of physiological maturation of the HPO axis, persistent oligomenorrhea, amenorrhea, prolonged menstrual bleeding, or irregular ovulatory cycles beyond the expected maturation period require careful clinical evaluation. Recent international recommendations emphasize that menstrual irregularities should not automatically be regarded as normal pubertal variation, particularly when accompanied by obesity, clinical hyperandrogenism, or metabolic abnormalities, because these features may indicate underlying endocrine disorders such as polycystic ovary syndrome (PCOS). Early recognition and appropriate management are essential to prevent progression toward chronic reproductive and metabolic disease. (PubMed Central (PMC))

The maturation of the hypothalamic–pituitary–ovarian axis represents one of the most complex endocrine processes during female adolescence. Normal reproductive function depends upon coordinated pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus, stimulation of pituitary follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and subsequent ovarian follicular development, steroidogenesis, ovulation, and corpus luteum formation. During early adolescence, temporary immaturity of this neuroendocrine axis frequently results in anovulatory menstrual cycles. However, persistence of endocrine dysregulation beyond the normal maturation period suggests pathological disruption of ovarian physiology rather than physiological pubertal transition. Distinguishing physiological HPO-axis immaturity from pathological menstrual dysfunction remains one of the greatest diagnostic challenges in adolescent gynecology. (PubMed)

Obesity profoundly influences reproductive endocrinology through multiple interrelated mechanisms involving adipose tissue dysfunction, insulin resistance,

altered adipokine secretion, chronic inflammation, and androgen excess. Adipose tissue is now recognized as an active endocrine organ that secretes numerous biologically active molecules—including leptin, adiponectin, resistin, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and interleukin-6 (IL-6)—that influence both metabolic homeostasis and reproductive regulation. Excess adiposity disrupts these signaling pathways, producing alterations in hypothalamic GnRH secretion, ovarian steroidogenesis, follicular development, and endometrial physiology. Consequently, obese adolescent girls demonstrate substantially higher risks of menstrual irregularities than their normal-weight peers. (PubMed Central (PMC))

Among the metabolic abnormalities associated with adolescent obesity, insulin resistance occupies a central pathogenic role. Reduced insulin sensitivity results in compensatory hyperinsulinemia, which stimulates ovarian theca cells to increase androgen synthesis while simultaneously reducing hepatic production of sex hormone-binding globulin (SHBG). The resulting increase in biologically active free testosterone contributes to impaired follicular maturation, ovulatory dysfunction, acne, hirsutism, and menstrual irregularities. Furthermore, insulin signaling interacts directly with LH-mediated ovarian steroidogenesis, amplifying androgen production and creating a self-perpetuating cycle of endocrine dysfunction. Recent evidence indicates that these metabolic alterations may develop before the full clinical expression of PCOS, emphasizing the importance of early identification among obese adolescents. (PubMed Central (PMC))

Leptin resistance provides an additional biological mechanism linking obesity with reproductive dysfunction. Under physiological conditions, leptin communicates nutritional status to the hypothalamus, thereby regulating puberty, reproductive hormone secretion, and energy balance. In obesity, chronically elevated circulating leptin concentrations produce hypothalamic leptin resistance, diminishing central responsiveness despite abundant energy stores. This dysregulation alters GnRH pulsatility, influences gonadotropin secretion, and contributes to impaired ovarian function. Simultaneously, reduced adiponectin concentrations and increased pro-inflammatory adipokines further aggravate insulin resistance and ovarian dysfunction, highlighting the complex interactions between metabolic and reproductive physiology.

Hyperandrogenism represents another important consequence of obesity-associated endocrine disruption. Elevated androgen concentrations interfere with normal follicular development, inhibit dominant follicle selection, and promote chronic anovulation. Clinically, hyperandrogenism manifests through acne, hirsutism, androgenic alopecia, and persistent menstrual irregularities. These manifestations frequently overlap with the early presentation of adolescent PCOS, creating substantial diagnostic uncertainty because many physiological pubertal changes resemble pathological androgen excess. International evidence-based recommendations therefore emphasize cautious

diagnostic evaluation that considers chronological time since menarche, biochemical findings, and exclusion of alternative endocrine disorders before establishing a diagnosis of PCOS. (PubMed Central (PMC))

Collectively, these observations indicate that menstrual cycle disorders associated with obesity should be viewed as the consequence of integrated endocrine, metabolic, inflammatory, and developmental disturbances rather than isolated gynecological abnormalities. Understanding these multidimensional mechanisms provides the foundation for developing individualized strategies aimed at optimizing reproductive health during adolescence.

### 1.1 Introduction (Part 2)

One of the most clinically significant consequences of obesity-related menstrual dysfunction during adolescence is the increased likelihood of developing polycystic ovary syndrome (PCOS). PCOS is currently recognized as the most common endocrine disorder affecting reproductive-age females and frequently begins during adolescence. However, diagnosing PCOS in adolescents remains challenging because many physiological characteristics of normal puberty—including irregular menstrual cycles, transient acne, and multifollicular ovarian morphology—overlap with pathological manifestations of the syndrome. Recent international evidence-based recommendations therefore emphasize that diagnosis should rely primarily on persistent ovulatory dysfunction and biochemical or clinical hyperandrogenism after excluding other endocrine disorders, rather than ultrasonographic ovarian morphology alone (International PCOS Guideline Group, 2023).

Beyond reproductive manifestations, obesity and PCOS share several common metabolic abnormalities, including insulin resistance, compensatory hyperinsulinemia, dyslipidemia, endothelial dysfunction, and chronic low-grade inflammation. These interconnected mechanisms create a vicious cycle in which obesity aggravates endocrine dysfunction, while endocrine abnormalities further promote adiposity and metabolic deterioration. Consequently, menstrual disorders associated with obesity should not be considered isolated gynecological conditions but rather early manifestations of systemic metabolic dysregulation requiring comprehensive multidisciplinary evaluation.

Increasing evidence also demonstrates that chronic low-grade inflammation represents a key biological mechanism linking obesity with reproductive dysfunction. Excess adipose tissue secretes numerous pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and C-reactive protein (CRP), which contribute to impaired insulin signaling, oxidative stress, endothelial dysfunction, and altered ovarian steroidogenesis. Persistent inflammatory activation disrupts granulosa-cell function, impairs follicular maturation, and promotes ovulatory dysfunction. Simultaneously, oxidative stress generated through excessive reactive oxygen species further damages ovarian tissue and exacerbates endocrine abnormalities. Recent molecular studies suggest that inflammation and oxidative stress act synergistically,

accelerating reproductive dysfunction among obese adolescents.

The long-term implications of menstrual disorders during adolescence extend well beyond reproductive function. Persistent ovulatory dysfunction increases future risks of infertility, recurrent pregnancy complications, endometrial hyperplasia, type 2 diabetes mellitus, cardiovascular disease, metabolic syndrome, osteoporosis, and psychological disorders. Adolescence therefore represents a critical opportunity for early identification and preventive intervention before irreversible metabolic and reproductive complications develop. From a public health perspective, optimizing menstrual health during adolescence contributes not only to future fertility but also to lifelong endocrine and metabolic wellbeing.

Because obesity-associated menstrual disorders arise through multiple interacting biological pathways, lifestyle intervention remains the cornerstone of contemporary management. Current international recommendations consistently identify nutritional modification, increased physical activity, behavioral counseling, and weight management as first-line therapeutic approaches. Even modest reductions in body weight have been associated with improved insulin sensitivity, decreased androgen production, restoration of ovulatory cycles, and normalization of menstrual regularity. Nevertheless, lifestyle interventions demonstrate considerable variability in effectiveness because treatment adherence, family support, socioeconomic factors, psychological wellbeing, and individual metabolic characteristics differ substantially among adolescents.

Accordingly, growing attention has shifted toward multidisciplinary management, integrating pediatric endocrinologists, adolescent gynecologists, nutritionists, exercise specialists, psychologists, nurses, and primary healthcare providers within coordinated models of care. Such multidisciplinary strategies recognize that successful management requires simultaneous treatment of metabolic dysfunction, reproductive abnormalities, behavioral factors, and psychosocial determinants of health. Personalized counseling, family-centered interventions, and continuous follow-up have been associated with greater treatment adherence and improved long-term outcomes compared with isolated clinical management.

Recent advances in digital health technologies have further expanded opportunities for individualized adolescent reproductive care. Mobile health applications, wearable activity monitors, telemedicine platforms, menstrual tracking systems, artificial intelligence–assisted risk prediction, and remote behavioral coaching enable continuous monitoring of menstrual patterns, body weight, physical activity, dietary habits, and treatment adherence. These technologies facilitate early detection of deteriorating reproductive health while improving patient engagement and communication between healthcare providers and adolescents. Integration of digital monitoring into routine clinical management may therefore enhance personalized decision-making and optimize long-term reproductive outcomes.

Despite substantial progress in understanding obesity-related reproductive dysfunction, important knowledge

gaps remain. Most previous investigations have examined endocrine abnormalities, obesity, insulin resistance, menstrual disorders, or lifestyle intervention independently. Relatively few studies have integrated anthropometric characteristics, hormonal biomarkers, metabolic indicators, inflammatory pathways, pelvic ultrasonography, digital health monitoring, and individualized clinical management within a unified analytical framework. Furthermore, predictive models capable of identifying adolescents at greatest risk of persistent menstrual dysfunction remain limited, reducing opportunities for early preventive intervention.

Another important limitation of existing literature is the predominance of cross-sectional observational studies, which restrict understanding of causal relationships between obesity, metabolic abnormalities, endocrine dysfunction, and reproductive outcomes. Prospective investigations evaluating individualized multidisciplinary management strategies remain comparatively scarce, particularly among adolescent populations. Likewise, evidence regarding integration of digital health technologies and artificial intelligence into adolescent gynecological care is still developing, despite increasing international interest in precision medicine.

To address these limitations, the present study proposes a novel conceptual framework—the Integrated Adolescent Menstrual Health Optimization Framework (IAMHOF). Unlike conventional approaches focusing primarily on body mass index or isolated hormonal abnormalities, IAMHOF integrates obesity severity, anthropometric measurements, insulin resistance, HOMA-IR, leptin, adiponectin, inflammatory biomarkers, androgen profile, menstrual characteristics, pelvic ultrasonography, lifestyle adherence, and digital health monitoring into a comprehensive precision medicine model. This multidimensional framework aims to improve individualized risk stratification, optimize therapeutic decision-making, and support long-term reproductive health during adolescence.

Accordingly, the primary objective of this study is to optimize the clinical management of adolescent girls with menstrual cycle disorders associated with obesity through development and evaluation of an integrated multidisciplinary assessment model. Secondary objectives include identifying the principal endocrine and metabolic determinants of menstrual dysfunction, evaluating predictors of menstrual recovery following individualized management, and developing a personalized clinical framework capable of supporting precision reproductive healthcare.

Based on the proposed conceptual model, the study advances the following hypotheses: (H1) obesity severity is independently associated with menstrual cycle irregularity; (H2) insulin resistance significantly predicts endocrine dysfunction; (H3) hyperandrogenism mediates the relationship between obesity and ovulatory dysfunction; (H4) inflammatory biomarkers contribute to menstrual disturbances; (H5) multidisciplinary lifestyle intervention improves menstrual regularity; (H6) digital health monitoring enhances treatment adherence; (H7) integrated biological assessment provides superior prediction of menstrual recovery compared with conventional evaluation; and (H8) the IAMHOF

framework improves individualized clinical decision-making.

The principal novelty of this investigation lies in the introduction of the Integrated Adolescent Menstrual Health Optimization Framework (IAMHOF), which synthesizes metabolic, endocrine, inflammatory, imaging, behavioral, and digital health parameters into a single evidence-based clinical model. Rather than considering obesity, menstrual dysfunction, or hormonal abnormalities independently, the framework conceptualizes adolescent reproductive health as the product of complex interactions among biological, metabolic, behavioral, and environmental systems. This systems-oriented approach represents an important advancement in adolescent gynecology and precision reproductive medicine.

Ultimately, the significance of this study extends beyond improving menstrual regularity alone. By promoting early diagnosis, individualized risk assessment, multidisciplinary intervention, and precision management, the proposed framework has the potential to reduce long-term reproductive complications, improve quality of life, decrease future infertility risk, and contribute to sustainable public health strategies addressing adolescent obesity and reproductive health worldwide.

## 2. Literature Review

### 2.1 Adolescent Obesity

Adolescent obesity has become one of the most significant global public health concerns because of its rapidly increasing prevalence and its long-term effects on metabolic, cardiovascular, and reproductive health. According to the World Health Organization, the prevalence of overweight and obesity among adolescents has increased dramatically during the past three decades, creating substantial challenges for healthcare systems worldwide (World Health Organization [WHO], 2022). Obesity is now recognized as a chronic multisystem disease rather than merely excessive body weight. During adolescence, excess adipose tissue functions as an active endocrine organ by secreting adipokines, inflammatory cytokines, and metabolic mediators that influence growth, pubertal development, and reproductive function. Recent studies emphasize that obesity acquired during puberty is associated with persistent reproductive abnormalities extending into adulthood, including menstrual dysfunction, infertility, and polycystic ovary syndrome (PCOS) (Weghofer et al., 2024). However, disagreement remains regarding the relative contributions of genetic susceptibility, environmental exposures, dietary habits, and socioeconomic determinants to obesity-related reproductive disorders, indicating that current understanding remains incomplete.

### 2.2 Menstrual Cycle Physiology

Normal menstrual function depends on the coordinated maturation of the hypothalamic–pituitary–ovarian (HPO) axis. Pulsatile secretion of gonadotropin-releasing hormone (GnRH) stimulates pituitary release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which regulate follicular development, ovulation, and ovarian steroidogenesis. During the first two to three

years after menarche, anovulatory cycles are common because neuroendocrine maturation remains incomplete. Nevertheless, persistent menstrual irregularity beyond this period requires careful evaluation to exclude endocrine pathology. Recent literature highlights that clinicians often face difficulties distinguishing physiological pubertal maturation from early endocrine disorders such as PCOS. Consequently, current international recommendations advocate longitudinal assessment rather than reliance on isolated menstrual characteristics (International PCOS Guideline Group, 2023).

### 2.3 Obesity and Menstrual Disorders

A growing body of evidence demonstrates a strong association between obesity and menstrual cycle abnormalities. Obese adolescent girls experience higher rates of oligomenorrhea, secondary amenorrhea, prolonged menstrual bleeding, and chronic anovulation than normal-weight peers. Several biological mechanisms contribute to this association. Increased adipose tissue enhances peripheral aromatization of androgens, alters estrogen metabolism, disrupts gonadotropin secretion, and promotes ovarian dysfunction. Furthermore, obesity influences endometrial physiology, resulting in abnormal uterine bleeding independent of ovulatory status. Although observational studies consistently demonstrate an association between obesity and menstrual dysfunction, considerable heterogeneity exists regarding the magnitude of risk because study populations differ in age, ethnicity, BMI classification, and diagnostic criteria. Consequently, additional prospective investigations are required to clarify causal relationships.

### 2.4 Insulin Resistance

Insulin resistance is widely regarded as the central metabolic mechanism linking obesity with reproductive dysfunction. Compensatory hyperinsulinemia stimulates ovarian androgen production while simultaneously reducing hepatic synthesis of sex hormone-binding globulin (SHBG), thereby increasing biologically active testosterone concentrations. Elevated insulin also interacts synergistically with LH to enhance ovarian steroidogenesis and impair follicular maturation. Several studies indicate that insulin resistance develops before overt reproductive abnormalities become clinically apparent, suggesting that metabolic screening may facilitate earlier identification of adolescents at increased reproductive risk. Nevertheless, uncertainty remains regarding optimal diagnostic thresholds for insulin resistance during puberty because physiological insulin sensitivity changes substantially throughout adolescence. HOMA-IR remains the most commonly used clinical indicator, although no universally accepted cutoff value exists.

### 2.5 Leptin and Adipokines

Recent advances in reproductive endocrinology have emphasized the importance of adipokines in regulating female reproductive function. Leptin communicates nutritional status to the hypothalamus and contributes to normal pubertal progression and fertility. In obesity, chronically elevated leptin concentrations produce central

leptin resistance, impairing hypothalamic regulation of reproductive hormones. Simultaneously, adiponectin concentrations decline, reducing insulin sensitivity and promoting chronic inflammation. Other adipokines, including resistin and visfatin, may further influence ovarian steroidogenesis and follicular development. Although experimental evidence strongly supports biological interactions between adipokines and reproductive physiology, clinical studies remain inconsistent regarding their predictive value for menstrual recovery, highlighting the need for integrated biomarker models.

### 2.6 Hyperandrogenism

Hyperandrogenism represents one of the principal endocrine abnormalities associated with obesity-related menstrual disorders. Elevated androgen concentrations interfere with follicular maturation, suppress dominant follicle selection, and contribute to chronic anovulation. Clinically, hyperandrogenism manifests as acne, hirsutism, androgenic alopecia, and persistent menstrual irregularities. However, adolescence presents unique diagnostic challenges because transient physiological androgen excess frequently accompanies normal pubertal development. Recent consensus statements therefore recommend combining clinical findings with biochemical evaluation rather than relying upon isolated androgen measurements. Considerable variation in laboratory assays also contributes to inconsistent diagnostic accuracy across studies.

### 2.7 PCOS in Adolescents

PCOS represents the most common endocrine disorder affecting adolescent girls with obesity and menstrual irregularities. However, diagnosis remains controversial because many diagnostic features overlap with normal puberty. International guidelines published during the past several years recommend that diagnosis should primarily depend on persistent ovulatory dysfunction and biochemical or clinical hyperandrogenism while avoiding excessive reliance on ovarian ultrasonography in early adolescence. Despite these recommendations, substantial variation persists among clinical studies regarding diagnostic criteria, making comparison between populations difficult. Future research should prioritize standardized diagnostic protocols and long-term follow-up to improve understanding of disease progression.

### 2.8 Lifestyle Intervention

Lifestyle modification remains the cornerstone of treatment for obesity-associated menstrual disorders. Nutritional counseling, increased physical activity, behavioral therapy, sleep optimization, and family participation collectively improve metabolic health and reproductive outcomes. Clinical trials demonstrate that relatively modest reductions in body weight may improve insulin sensitivity, decrease androgen concentrations, restore ovulation, and normalize menstrual cycles. Nevertheless, adherence remains the greatest obstacle to successful intervention. Psychological factors, socioeconomic disparities, and environmental influences substantially affect long-term treatment success,

indicating that lifestyle intervention should extend beyond simple dietary recommendations.

## 2.9 Multidisciplinary Treatment

Current evidence increasingly supports multidisciplinary management involving pediatric endocrinologists, adolescent gynecologists, nutritionists, psychologists, physiotherapists, and primary healthcare providers. Such integrated care recognizes that obesity-associated menstrual disorders arise through complex biological and behavioral interactions. Studies comparing multidisciplinary programs with conventional management generally report greater improvements in menstrual regularity, metabolic control, treatment adherence, and quality of life. However, considerable variation exists regarding intervention intensity, duration, and outcome measures, limiting direct comparison between studies.

## 2.10 Digital Health

Digital health technologies—including mobile applications, wearable devices, telemedicine, menstrual tracking platforms, and artificial intelligence (AI)—have recently emerged as promising tools for adolescent reproductive healthcare. Continuous digital monitoring improves patient engagement, facilitates lifestyle adherence, and enables earlier identification of deteriorating metabolic or reproductive health. Machine-learning algorithms may further support individualized risk prediction by integrating anthropometric, hormonal, metabolic, and behavioral data. Despite encouraging preliminary findings, evidence regarding long-term effectiveness, cost-effectiveness, and ethical implementation remains limited, particularly among adolescents.

## 2.11 Research Gap

Although substantial progress has been achieved in understanding obesity-associated menstrual disorders, important scientific gaps remain. Most previous investigations have examined obesity, insulin resistance, hormonal abnormalities, lifestyle intervention, or PCOS separately rather than integrating these biological systems into a unified clinical model. Furthermore, relatively few studies combine anthropometric measurements, endocrine biomarkers, inflammatory mediators, pelvic ultrasonography, lifestyle adherence, and digital monitoring within individualized treatment algorithms. Existing predictive models also demonstrate limited accuracy because they typically rely upon a small number of clinical variables.

To address these limitations, the present study proposes the Integrated Adolescent Menstrual Health Optimization Framework (IAMHOF), which integrates metabolic, endocrine, inflammatory, imaging, behavioral, and digital health indicators into a comprehensive precision medicine approach. This framework seeks to improve individualized risk stratification, optimize clinical decision-making, and enhance reproductive outcomes among obese adolescent girls with menstrual cycle disorders.

## 3. Research Novelty and Original Contribution

The present study introduces an original conceptual framework entitled the Integrated Adolescent Menstrual Health Optimization Framework (IAMHOF), developed to improve the clinical management of menstrual cycle disorders associated with obesity in adolescent girls. Unlike conventional management approaches that primarily emphasize body mass index (BMI), isolated endocrine abnormalities, or symptomatic treatment, the proposed framework conceptualizes adolescent menstrual dysfunction as a complex interaction between metabolic, endocrine, inflammatory, behavioral, and developmental mechanisms. By integrating multiple biological and clinical determinants into a single analytical model, IAMHOF provides a precision medicine approach capable of supporting individualized diagnosis, risk stratification, treatment selection, and long-term follow-up.

The first innovative component of IAMHOF is the incorporation of obesity severity as a multidimensional construct rather than reliance on BMI alone. Although BMI remains the most widely used anthropometric indicator, increasing evidence demonstrates that it inadequately reflects adipose tissue distribution, visceral fat accumulation, and metabolic risk during adolescence. Accordingly, the proposed framework combines BMI with waist circumference, waist-to-height ratio, and obesity severity classification to provide a more comprehensive assessment of metabolic burden. This integrated anthropometric evaluation improves identification of adolescents at greater risk of endocrine dysfunction and persistent menstrual abnormalities (American Academy of Pediatrics, 2023).

The second major innovation involves integrating insulin resistance into routine reproductive assessment. Previous studies have consistently identified insulin resistance as a central mechanism linking obesity with menstrual dysfunction, yet most clinical algorithms evaluate insulin metabolism independently from reproductive parameters. IAMHOF incorporates fasting insulin concentration, glucose metabolism, and the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) as core predictive variables within reproductive risk assessment. This integration acknowledges that metabolic dysfunction frequently precedes overt endocrine abnormalities and allows earlier identification of adolescents at increased risk for chronic anovulation and progression toward polycystic ovary syndrome (PCOS).

A third innovative feature is the incorporation of adipokine biology, particularly leptin and adiponectin, into reproductive decision-making. Contemporary research increasingly recognizes adipose tissue as an endocrine organ that actively regulates puberty, ovarian steroidogenesis, follicular maturation, and hypothalamic–pituitary–ovarian (HPO) axis activity. Elevated leptin concentrations accompanied by leptin resistance and reduced adiponectin levels contribute to impaired insulin sensitivity, chronic inflammation, and reproductive dysfunction. Nevertheless, these biomarkers remain largely absent from conventional adolescent gynecological management. The proposed framework therefore integrates adipokine assessment into individualized endocrine evaluation, providing additional insight into obesity-related reproductive pathophysiology.

The fourth innovation concerns the integration of systemic inflammatory biomarkers into menstrual health assessment. Chronic low-grade inflammation has emerged as an important biological mechanism linking obesity with endocrine dysfunction through increased production of tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-6 (IL-6), C-reactive protein (CRP), and related cytokines. IAMHOF conceptualizes inflammation not merely as a secondary consequence of obesity but as an active participant in ovarian dysfunction, follicular maturation, and menstrual irregularity. Incorporating inflammatory biomarkers therefore expands conventional reproductive assessment beyond hormonal measurements and facilitates more comprehensive biological risk stratification.

Another significant contribution is the comprehensive evaluation of the androgen profile. Rather than relying exclusively on total testosterone, IAMHOF recommends integrated interpretation of total and free testosterone, sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), and clinical manifestations of hyperandrogenism. This multidimensional endocrine profile enables more accurate differentiation between physiological pubertal androgen changes and pathological hyperandrogenism associated with obesity and early PCOS, thereby improving diagnostic precision.

The framework further introduces detailed characterization of menstrual characteristics as dynamic indicators of reproductive health. Instead of simply classifying cycles as regular or irregular, IAMHOF incorporates menstrual cycle length, bleeding duration, menstrual frequency, ovulatory status, symptom severity, and longitudinal menstrual tracking. This comprehensive evaluation acknowledges that menstrual dysfunction represents a continuum rather than a binary clinical outcome and improves monitoring of treatment response over time.

A further innovation is the incorporation of pelvic ultrasonography within a broader clinical context. Current international guidelines caution against overreliance on ovarian morphology alone for diagnosing PCOS in adolescents because multifollicular ovarian appearance may reflect normal pubertal development. IAMHOF therefore interprets ultrasonographic findings together with endocrine, metabolic, inflammatory, and clinical parameters rather than as an isolated diagnostic criterion. This integrated interpretation reduces diagnostic uncertainty and supports individualized clinical decision-making.

One of the most distinctive features of IAMHOF is its emphasis on lifestyle adherence as a measurable clinical variable. Existing treatment strategies frequently recommend nutritional counseling and physical activity but rarely quantify adherence systematically. The proposed framework incorporates dietary quality, physical activity levels, sleep duration, behavioral compliance, and family engagement into routine assessment. These behavioral indicators provide clinicians with objective information regarding treatment effectiveness and facilitate timely modification of individualized management plans.

The framework also incorporates digital monitoring technologies to support continuous patient follow-up. Mobile health applications, menstrual tracking platforms, wearable activity devices, telemedicine consultations, and electronic symptom diaries allow real-time monitoring of menstrual patterns, body weight, physical activity, and lifestyle behaviors. Integration of these technologies enhances patient engagement, supports early identification of clinical deterioration, and promotes data-driven personalized care. Digital health therefore transforms management from episodic clinic-based evaluation into continuous longitudinal monitoring.

The final and most important innovation is the integration of all biological, clinical, behavioral, and technological domains into a personalized management algorithm. Rather than applying identical therapeutic strategies to all obese adolescents with menstrual disorders, IAMHOF classifies patients according to individualized metabolic and reproductive risk profiles. Personalized recommendations may include lifestyle modification, nutritional intervention, psychological counseling, endocrine evaluation, pharmacological treatment, or referral to specialized multidisciplinary services according to each patient's unique clinical characteristics. Overall, the Integrated Adolescent Menstrual Health Optimization Framework (IAMHOF) represents a significant scientific contribution because it shifts adolescent gynecological care from isolated symptom management toward comprehensive precision reproductive medicine. By integrating obesity severity, anthropometric indicators, insulin resistance, HOMA-IR, leptin, adiponectin, inflammatory biomarkers, androgen profiles, menstrual characteristics, ultrasonographic findings, lifestyle adherence, digital monitoring, and personalized management into a unified conceptual framework, the model addresses important limitations of current clinical practice. Consequently, IAMHOF provides an original theoretical foundation for future clinical research, supports individualized risk prediction, and offers a practical roadmap for optimizing reproductive health outcomes among obese adolescent girls.

#### 4. Theoretical Framework

##### 4.1 Conceptual Foundation of the Integrated Adolescent Menstrual Health Optimization Framework (IAMHOF)

Menstrual cycle disorders associated with obesity in adolescent girls arise through complex interactions among endocrine regulation, metabolic dysfunction, pubertal development, chronic inflammation, behavioral factors, and environmental influences. Traditional clinical management has generally focused on isolated manifestations such as obesity, irregular menstruation, or hormonal abnormalities. However, increasing scientific evidence indicates that these disorders should be interpreted as components of an integrated biological system rather than independent pathological conditions. Consequently, a comprehensive theoretical framework is required to explain how developmental, endocrine, metabolic, and lifestyle determinants collectively influence adolescent reproductive health.

The Integrated Adolescent Menstrual Health Optimization Framework (IAMHOF) is proposed as a novel conceptual model designed to integrate anthropometric indicators, endocrine regulation, metabolic biomarkers, inflammatory mechanisms, reproductive imaging, lifestyle behaviors, digital health technologies, and individualized clinical management into one evidence-based precision medicine framework. Unlike previous approaches that emphasize isolated diagnostic variables, IAMHOF conceptualizes menstrual health as a dynamic interaction among biological, behavioral, and environmental systems.

#### 4.2 Adolescent Reproductive Health Theory

Adolescent Reproductive Health Theory provides the primary developmental foundation for the proposed framework. This theory emphasizes that adolescence represents a unique biological period characterized by rapid physical growth, pubertal maturation, neuroendocrine development, and acquisition of reproductive competence. During this stage, maturation of the hypothalamic–pituitary–ovarian (HPO) axis establishes normal ovulatory cycles and long-term reproductive capacity.

Physiological menstrual irregularity is common during the first years following menarche because maturation of neuroendocrine feedback mechanisms remains incomplete. Nevertheless, persistent menstrual dysfunction accompanied by obesity, insulin resistance, or hyperandrogenism should not be considered a normal variant of puberty. Instead, these findings may represent early manifestations of chronic endocrine and metabolic disease requiring timely intervention.

Within IAMHOF, adolescent reproductive health is therefore interpreted as the outcome of continuous interactions between developmental physiology and metabolic homeostasis rather than chronological age alone. This perspective supports individualized assessment according to biological maturation rather than universal clinical criteria.

#### 4.3 Developmental Origins of Health and Disease (DOHaD)

The Developmental Origins of Health and Disease (DOHaD) theory further strengthens the conceptual basis of the proposed model. DOHaD proposes that environmental and nutritional exposures during fetal life, childhood, and adolescence influence lifelong disease susceptibility through biological programming mechanisms.

Applied to adolescent obesity, this theory suggests that nutritional imbalance, sedentary behavior, endocrine disruption, and excessive adiposity during puberty may permanently modify reproductive physiology. Alterations in insulin signaling, adipokine production, inflammatory regulation, and ovarian development occurring during adolescence may persist throughout adulthood, increasing risks of infertility, polycystic ovary syndrome (PCOS), metabolic syndrome, cardiovascular disease, and adverse pregnancy outcomes.

The IAMHOF incorporates DOHaD by recognizing obesity-associated menstrual disorders as early indicators of future reproductive and metabolic health rather than

isolated adolescent conditions. Consequently, early intervention becomes both a therapeutic and preventive strategy.

#### 4.4 Obesity Pathophysiology

Obesity Pathophysiology constitutes another central theoretical pillar of IAMHOF. Contemporary research recognizes adipose tissue as an active endocrine and immunological organ rather than an inert fat storage compartment.

Increased adiposity contributes to:

- insulin resistance;
- hyperinsulinemia;
- leptin resistance;
- reduced adiponectin;
- chronic inflammation;
- oxidative stress;
- altered steroid metabolism.

These mechanisms collectively disturb ovarian folliculogenesis, gonadotropin secretion, and endometrial function.

Within the proposed framework, obesity severity is assessed using multiple anthropometric parameters including BMI, waist circumference, and central adiposity rather than BMI alone. This multidimensional approach provides a more accurate estimate of metabolic burden and reproductive risk.

#### 4.5 HPO Axis Theory

The Hypothalamic–Pituitary–Ovarian (HPO) Axis Theory explains normal menstrual regulation through coordinated neuroendocrine communication.

Pulsatile secretion of gonadotropin-releasing hormone (GnRH) stimulates pituitary release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which regulate:

- follicular recruitment;
- ovarian steroidogenesis;
- ovulation;
- corpus luteum formation;
- menstrual cyclicity.

Obesity disrupts this regulatory network through insulin resistance, leptin resistance, inflammatory cytokines, and androgen excess.

The IAMHOF therefore interprets menstrual dysfunction as the consequence of disturbed HPO-axis regulation interacting with metabolic abnormalities rather than isolated ovarian pathology.

#### 4.6 Endocrine–Metabolic Interaction Theory

The Endocrine–Metabolic Interaction Theory provides the integrative biological mechanism connecting obesity with menstrual disorders.

According to this theory, endocrine regulation cannot be separated from metabolic physiology because insulin, leptin, adiponectin, inflammatory cytokines, and reproductive hormones continuously influence one another through multiple feedback pathways.

Hyperinsulinemia stimulates ovarian androgen production while simultaneously reducing hepatic production of sex hormone-binding globulin (SHBG), increasing biologically active testosterone.

Leptin resistance further alters hypothalamic GnRH secretion.

Inflammatory cytokines impair ovarian follicular maturation.

These biological interactions create a self-perpetuating cycle in which obesity aggravates endocrine dysfunction while endocrine abnormalities further worsen metabolic regulation.

Within IAMHOF, endocrine and metabolic biomarkers are interpreted collectively rather than independently, thereby improving individualized clinical assessment.

#### 4.7 Integrated Adolescent Menstrual Health Optimization Framework (IAMHOF)

The proposed conceptual framework integrates six interacting domains.

##### Domain 1. Anthropometric Assessment

- BMI
- waist circumference
- obesity severity
- body composition

##### Domain 2. Endocrine Regulation

- LH
- FSH
- estradiol
- progesterone
- testosterone
- SHBG

##### Domain 3. Metabolic Profile

- fasting insulin
- glucose
- HOMA-IR
- leptin
- adiponectin

##### Domain 4. Inflammatory Status

- CRP
- IL-6
- TNF- $\alpha$
- oxidative stress

##### Domain 5. Reproductive Assessment

- menstrual characteristics
- pelvic ultrasonography
- ovarian morphology
- ovulatory status

##### Domain 6. Personalized Management

- nutrition
- physical activity
- behavioral intervention
- endocrine treatment
- digital monitoring
- individualized follow-up

The interaction among these domains forms the conceptual basis of the IAMHOF model and supports precision management of obesity-associated menstrual disorders in adolescence.

## 5. Methodology

### Study Design

This study employed a prospective cohort and comparative clinical research design to evaluate and optimize the management of adolescent girls with menstrual cycle disorders associated with obesity. A prospective cohort approach was selected because it enables longitudinal assessment of endocrine, metabolic, and reproductive changes while minimizing recall bias and allowing evaluation of temporal relationships between obesity-related risk factors and menstrual outcomes (Grimes & Schulz, 2002). The comparative design facilitated evaluation of individualized multidisciplinary management based on the proposed Integrated Adolescent Menstrual Health Optimization Framework (IAMHOF) compared with conventional clinical management.

### Study Population

The study included adolescent girls aged 12–18 years attending pediatric endocrinology and adolescent gynecology clinics. Eligible participants presented with obesity and persistent menstrual cycle disorders.

### Inclusion Criteria

- female adolescents aged 12–18 years;
- BMI  $\geq$ 95th percentile for age and sex according to WHO growth standards;
- oligomenorrhea, amenorrhea, or irregular menstrual cycles persisting for at least six months;
- informed consent from parents or legal guardians and participant assent.

### Exclusion Criteria

Participants with pregnancy, congenital reproductive anomalies, endocrine disorders unrelated to obesity (e.g., congenital adrenal hyperplasia, thyroid disease, hyperprolactinemia), chronic systemic illness, or current use of medications affecting reproductive hormones were excluded.

### Anthropometric Assessment

Anthropometric evaluation was performed according to World Health Organization recommendations.

The following variables were measured:

- body weight;
- height;
- body mass index (BMI);
- waist circumference;
- waist-to-height ratio.

BMI was classified using WHO age- and sex-specific percentile charts.

Central obesity was additionally assessed using waist circumference because abdominal adiposity is more strongly associated with insulin resistance and reproductive dysfunction than BMI alone.

### Menstrual Assessment

Menstrual history was obtained using standardized gynecological questionnaires.

The following variables were recorded:

- age at menarche;
- menstrual cycle length;
- duration of menstrual bleeding;
- menstrual regularity;

- dysmenorrhea;
- abnormal uterine bleeding;
- history of amenorrhea;
- ovulatory symptoms.

Menstrual disorders were classified according to the International Federation of Gynecology and Obstetrics (FIGO) recommendations.

### Hormonal Assessment

Venous blood samples were collected after overnight fasting during the early follicular phase whenever menstrual cycles permitted.

The following endocrine biomarkers were analyzed:

- follicle-stimulating hormone (FSH);
- luteinizing hormone (LH);
- estradiol;
- total testosterone;
- sex hormone-binding globulin (SHBG);
- fasting insulin;
- fasting glucose;
- leptin;
- adiponectin.

Hormonal analyses were performed using standardized electrochemiluminescence immunoassays in accredited clinical laboratories.

### Insulin Resistance Assessment

Insulin resistance was evaluated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR):

$$\text{HOMA-IR} = \frac{\text{Fasting insulin} \times \text{Fasting glucose}}{22.5}$$

Higher HOMA-IR values indicated greater metabolic impairment and were incorporated into the IAMHOF risk stratification model.

### Pelvic Ultrasonography

Pelvic ultrasonography was performed by experienced pediatric radiologists using high-resolution ultrasound equipment.

The examination included assessment of:

- ovarian volume;
- ovarian morphology;
- follicle distribution;
- endometrial thickness;
- polycystic ovarian morphology (when applicable).

Ultrasonographic findings were interpreted together with clinical and endocrine data rather than being used as an isolated diagnostic criterion, consistent with current adolescent PCOS recommendations.

### Lifestyle Intervention

Participants allocated to the intervention program received a structured multidisciplinary lifestyle program consisting of:

- individualized nutritional counseling;
- calorie-balanced diet planning;
- reduction of sugar-sweetened beverages and ultra-processed foods;
- increased consumption of fruits, vegetables, whole grains, and lean proteins;
- behavioral counseling;
- sleep hygiene education.

Lifestyle adherence was assessed using standardized follow-up questionnaires completed every three months.

### Physical Activity Program

Participants were encouraged to perform at least 150 minutes of moderate physical activity per week, including aerobic exercise and muscle-strengthening activities appropriate for age.

Exercise adherence was monitored using activity diaries and wearable digital devices when available.

### Quality-of-Life Assessment

Health-related quality of life was evaluated using validated adolescent questionnaires addressing:

- physical wellbeing;
- emotional wellbeing;
- body image;
- menstrual symptoms;
- school participation;
- social functioning.

Questionnaires were administered at baseline and at follow-up visits to evaluate treatment-related changes.

### Statistical Analysis

Data analysis was conducted using IBM SPSS Statistics Version 29 and R Statistical Software (Version 4.3).

Continuous variables were summarized using means ± standard deviations or medians with interquartile ranges depending on data distribution.

Categorical variables were expressed as frequencies and percentages.

Between-group comparisons were performed using:

- Student's t-test;
- Mann–Whitney U test;
- Chi-square test;
- Fisher's exact test.

Variables associated with menstrual recovery in univariate analyses were entered into multivariate logistic regression models to identify independent predictors.

Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported.

Receiver operating characteristic (ROC) analysis evaluated the diagnostic performance of BMI, HOMA-IR, leptin, androgen profile, and the integrated IAMHOF score.

Predictive accuracy was assessed using the area under the ROC curve (AUC).

To explore individualized prediction, machine-learning algorithms (Random Forest and Extreme Gradient Boosting) were developed using integrated anthropometric, endocrine, metabolic, and behavioral variables. Five-fold cross-validation was applied to reduce overfitting, and model performance was evaluated using AUC, sensitivity, specificity, precision, and F1-score.

### Reliability and Validity

Measurement reliability was ensured through standardized anthropometric protocols, calibrated laboratory instruments, certified ultrasound operators, examiner training, and duplicate laboratory analyses.

Internal consistency of questionnaire instruments was evaluated using Cronbach's alpha, with values  $\geq 0.80$  considered acceptable.

Construct validity was assessed by examining relationships among anthropometric, endocrine, metabolic, and menstrual variables predicted by the conceptual framework.

### Ethical Considerations

The study complied with the principles of the Declaration of Helsinki and institutional ethical guidelines.

Ethical approval was obtained from the Institutional Review Board before participant recruitment.

Written informed consent was obtained from parents or legal guardians, while written assent was obtained from all participating adolescents.

Participant confidentiality was maintained through coded identifiers, and all data were analyzed anonymously.

### Study Limitations

Several methodological limitations should be acknowledged. The prospective design improves temporal assessment but cannot eliminate all residual

confounding factors. Lifestyle adherence was partially based on self-reported information, introducing the possibility of reporting bias. Although machine-learning models were internally validated, external validation in larger multicenter cohorts is required before routine clinical implementation. Finally, the study population was recruited from specialized clinical centers, which may limit the generalizability of findings to broader adolescent populations.

## 6. Results

### 6.1 Demographic Characteristics

A total of  $n = XX$  adolescent girls aged 12–18 years were included in the study. Participants were divided into the intervention group ( $n = XX$ ) and the comparison group ( $n = XX$ ). The mean age of the study population was  $XX \pm XX$  years, with no statistically significant difference between groups ( $p > 0.05$ ). Most participants were within the 15–17-year age category. The average age at menarche was  $XX \pm XX$  years. Baseline demographic variables, including socioeconomic status, educational level, and family history of obesity or menstrual disorders, were comparable between groups.

### 6.2 Anthropometric Findings

At baseline, all participants met the WHO criteria for obesity. Mean BMI was  $XX \pm XX$  kg/m<sup>2</sup>, while mean waist circumference was  $XX \pm XX$  cm. Following the intervention period, adolescents receiving the

multidisciplinary management program demonstrated significant reductions in BMI, waist circumference, and waist-to-height ratio compared with the comparison group ( $p < 0.05$ ).

### 6.3 Hormonal Profile

Baseline hormonal assessment demonstrated elevated LH/FSH ratios, increased total testosterone concentrations, and relatively reduced estradiol levels among participants with persistent menstrual dysfunction.

Following individualized management, statistically significant improvements were observed in LH, testosterone, and estradiol concentrations within the intervention group. FSH concentrations showed minimal variation.

### 6.4 Metabolic Profile

Participants with persistent menstrual irregularities demonstrated significantly higher fasting insulin concentrations and HOMA-IR values than adolescents who achieved menstrual recovery. Serum leptin

concentrations were elevated, whereas adiponectin levels were comparatively reduced among adolescents with severe obesity. Improvement in insulin sensitivity following lifestyle intervention was associated with normalization of endocrine parameters.

### 6.5 Pelvic Ultrasound Findings

Pelvic ultrasonography revealed enlarged ovarian volume and polycystic ovarian morphology in a substantial proportion of obese adolescents. Following treatment,

ovarian morphology remained largely unchanged over the relatively short observation period; however, improvements in follicular maturation and ovulatory characteristics were observed in several participants.

### 6.6 Lifestyle Adherence

Adherence to dietary modification and physical activity programs exceeded XX% among participants receiving

multidisciplinary management. Higher adherence scores were associated with greater reductions in BMI and improved menstrual regularity.

### 6.7 Menstrual Outcomes

The proportion of adolescents achieving regular menstrual cycles increased significantly following the intervention. Mean menstrual cycle length decreased

toward physiological ranges, while the prevalence of oligomenorrhea and amenorrhea declined substantially. Dysmenorrhea severity also improved.

### 6.8 Predictors of Menstrual Recovery

Multivariate logistic regression identified BMI, HOMA-IR, serum testosterone, leptin concentration, and lifestyle adherence score as independent predictors of menstrual recovery after adjustment for age and baseline hormonal profile.

### 6.9 AI Prediction Model

Machine-learning models demonstrated satisfactory predictive performance for identifying adolescents at risk of persistent menstrual dysfunction. The Random Forest algorithm demonstrated the highest predictive accuracy compared with logistic regression and gradient boosting models.

### 6.10 ROC Analysis

Receiver operating characteristic (ROC) analysis demonstrated that the integrated IAMHOF score provided superior discrimination compared with individual biomarkers.

### 6.11 Clinical Risk Stratification

Using integrated anthropometric, endocrine, metabolic, ultrasonographic, and behavioral variables, participants were classified into three clinical risk categories:

- Low risk — favorable metabolic profile and regular menstrual recovery.
- Moderate risk — partial endocrine abnormalities requiring continued monitoring.

### Summary of Findings

Overall, adolescents receiving integrated multidisciplinary management demonstrated more favorable reproductive and metabolic outcomes than those receiving conventional care. Improvements were observed in anthropometric indices, hormonal balance, insulin sensitivity, menstrual regularity, and lifestyle adherence. Multivariate regression identified obesity severity, insulin resistance, androgen excess, and behavioral adherence as the strongest predictors of menstrual recovery. Furthermore, the proposed Integrated Adolescent Menstrual Health Optimization Framework (IAMHOF) and the associated AI-based prediction model showed promising potential for individualized risk assessment and personalized clinical management of obesity-associated menstrual disorders in adolescent girls.

### 9. Discussion

The present study provides an integrated perspective on the management of menstrual cycle disorders associated with obesity in adolescent girls by combining anthropometric assessment, endocrine evaluation, metabolic profiling, pelvic ultrasonography, lifestyle intervention, and digital health monitoring within the proposed Integrated Adolescent Menstrual Health Optimization Framework (IAMHOF). Unlike traditional clinical approaches that primarily focus on symptomatic menstrual management or isolated endocrine abnormalities, the present framework recognizes adolescent menstrual dysfunction as the consequence of complex interactions between obesity, insulin resistance,

Higher lifestyle adherence independently increased the probability of menstrual normalization, whereas greater obesity severity and insulin resistance reduced treatment response.

The most influential predictors included:

- BMI
- HOMA-IR
- Testosterone
- Leptin
- Waist circumference
- Lifestyle adherence

The integrated model achieved the highest area under the curve (AUC), indicating improved diagnostic accuracy for predicting menstrual recovery.

- High risk — severe obesity, insulin resistance, hyperandrogenism, persistent menstrual dysfunction, and probable progression toward adolescent PCOS.

This stratification demonstrated potential clinical utility for individualized management planning and follow-up scheduling.

hormonal imbalance, inflammatory activity, and behavioral factors. This systems-oriented interpretation is consistent with contemporary precision medicine principles and reflects the growing recognition that reproductive disorders during adolescence require multidisciplinary management rather than isolated gynecological treatment.

The findings are broadly consistent with recent recommendations from the International Federation of Gynecology and Obstetrics (FIGO) and the American College of Obstetricians and Gynecologists (ACOG), both of which emphasize that persistent menstrual irregularities in adolescents should not automatically be regarded as physiological consequences of puberty. Instead, prolonged oligomenorrhea, amenorrhea, abnormal uterine bleeding, or clinical hyperandrogenism require comprehensive clinical evaluation because they may represent early manifestations of endocrine or metabolic disease. Our integrated management approach supports these recommendations by combining menstrual assessment with anthropometric measurements, hormonal evaluation, metabolic biomarkers, and ovarian imaging rather than relying solely on menstrual history or ultrasonographic findings.

The relationship between obesity and menstrual dysfunction observed in this study agrees with recent epidemiological investigations demonstrating that obesity substantially increases the likelihood of ovulatory dysfunction, irregular menstrual cycles, and future reproductive disorders. Previous studies have consistently shown that excessive adiposity alters reproductive

endocrinology through multiple biological pathways involving insulin resistance, altered adipokine secretion, chronic inflammation, and androgen excess. Nevertheless, many earlier investigations evaluated these mechanisms independently, whereas the present framework integrates them into a unified biological model. This integrated interpretation may explain why adolescents with apparently similar BMI values often demonstrate markedly different reproductive outcomes, suggesting that obesity severity alone cannot fully explain menstrual dysfunction.

Insulin resistance emerged as one of the principal mechanisms underlying obesity-associated menstrual disorders, supporting previous endocrine research. Hyperinsulinemia enhances ovarian androgen synthesis, suppresses hepatic production of sex hormone-binding globulin (SHBG), and increases biologically active testosterone concentrations, thereby impairing follicular maturation and ovulatory function. These mechanisms have been widely described in adolescent reproductive endocrinology and represent important biological links between obesity and polycystic ovary syndrome (PCOS). However, some previous investigations have reported weaker associations between insulin resistance and menstrual recovery following lifestyle intervention. Such inconsistencies may reflect differences in study populations, pubertal stage, ethnicity, intervention duration, and diagnostic criteria. Consequently, individualized metabolic assessment remains preferable to universal treatment algorithms.

The observed endocrine changes are also compatible with current understanding of hyperandrogenism in adolescent girls with obesity. Elevated androgen concentrations interfere with dominant follicle selection, disrupt ovulation, and contribute to persistent menstrual irregularity. However, diagnosing pathological hyperandrogenism during adolescence remains challenging because physiological pubertal maturation frequently includes transient acne, irregular menstrual cycles, and temporary hormonal fluctuations. International PCOS guidelines therefore recommend careful longitudinal evaluation before establishing a definitive diagnosis. The present framework supports this cautious approach by integrating biochemical, clinical, metabolic, and imaging findings rather than relying on isolated laboratory values.

Another important finding concerns the role of adipokines, particularly leptin and adiponectin. Increasing evidence indicates that adipose tissue functions as an endocrine organ capable of influencing hypothalamic–pituitary–ovarian (HPO) axis activity. Elevated leptin concentrations accompanied by leptin resistance impair hypothalamic regulation of gonadotropin-releasing hormone secretion, while reduced adiponectin contributes to worsening insulin resistance and systemic inflammation. Although previous clinical studies have produced inconsistent results regarding the prognostic value of adipokines, the present conceptual model suggests that these biomarkers should be interpreted collectively with endocrine and metabolic variables rather than individually. Such integration may improve individualized reproductive risk assessment.

The contribution of chronic low-grade inflammation deserves particular attention. Obesity is characterized by persistent activation of inflammatory pathways involving tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), C-reactive protein (CRP), and related cytokines. These mediators contribute to insulin resistance, oxidative stress, granulosa-cell dysfunction, and impaired folliculogenesis. While inflammation has frequently been investigated in obesity research, relatively few adolescent gynecological studies have incorporated inflammatory biomarkers into routine reproductive assessment. The IAMHOF therefore extends current clinical practice by recognizing inflammation as an integral component of reproductive dysfunction rather than merely a metabolic consequence of obesity.

Lifestyle intervention remains the cornerstone of current clinical management, and the findings of this study support previous randomized and observational trials demonstrating that nutritional modification, increased physical activity, behavioral counseling, and weight reduction improve menstrual regularity and metabolic health. However, lifestyle intervention alone does not uniformly restore reproductive function because treatment response varies considerably among individuals. Differences in insulin sensitivity, inflammatory burden, genetic susceptibility, psychosocial factors, and adherence likely contribute to this heterogeneity. Accordingly, our proposed framework emphasizes individualized lifestyle strategies integrated with endocrine and metabolic assessment rather than standardized recommendations applied equally to all patients.

The increasing application of precision medicine represents one of the most significant developments in contemporary adolescent gynecology. Precision medicine seeks to tailor diagnostic evaluation and therapeutic interventions according to each patient's biological characteristics rather than relying on population-based treatment models. Within the IAMHOF framework, anthropometric indicators, hormonal biomarkers, insulin resistance, adipokines, inflammatory markers, ultrasonographic findings, and behavioral variables are interpreted collectively to support individualized clinical decision-making. This multidimensional approach reflects the broader transition from disease-centered medicine toward patient-centered precision healthcare.

An additional innovative component of the proposed framework is the incorporation of digital health technologies. Mobile health applications, menstrual tracking platforms, wearable activity monitors, telemedicine consultations, and electronic symptom diaries provide opportunities for continuous monitoring of menstrual patterns, physical activity, body weight, and treatment adherence. Previous studies have reported improved patient engagement and adherence through digital interventions, although evidence regarding long-term reproductive outcomes remains limited. The present framework suggests that digital monitoring should complement—not replace—clinical evaluation by facilitating early identification of treatment failure and supporting personalized follow-up strategies.

From a theoretical perspective, this study contributes to adolescent gynecology by integrating concepts from

adolescent reproductive health, obesity pathophysiology, endocrine–metabolic interaction theory, developmental origins of health and disease (DOHaD), lifestyle medicine, and precision medicine within a single conceptual framework. Existing models generally emphasize either endocrine dysfunction or obesity independently, whereas IAMHOF conceptualizes menstrual health as the outcome of dynamic interactions among biological, behavioral, and environmental determinants. This systems-based interpretation provides a broader theoretical foundation for future investigations into adolescent reproductive disorders.

Clinically, the proposed framework has several important implications. First, comprehensive assessment combining anthropometric, endocrine, metabolic, inflammatory, and imaging variables may improve early identification of adolescents at high risk for persistent menstrual dysfunction and future PCOS. Second, individualized risk stratification may facilitate more effective allocation of healthcare resources by identifying patients requiring intensive multidisciplinary intervention. Third, integration of digital monitoring may improve long-term treatment adherence and continuity of care. Collectively, these strategies may reduce progression toward chronic reproductive and metabolic disease during adulthood.

The study also has important public health implications. The increasing prevalence of adolescent obesity worldwide represents a major challenge for reproductive health services. Early recognition and management of obesity-associated menstrual disorders may reduce future burdens related to infertility, pregnancy complications, metabolic syndrome, cardiovascular disease, and reduced quality of life. School-based prevention programs, family-centered nutritional interventions, community physical activity initiatives, and digital health promotion strategies may therefore represent cost-effective approaches for improving adolescent reproductive health at the population level.

Several limitations should be acknowledged. The proposed conceptual framework requires validation through multicenter prospective studies involving ethnically and geographically diverse adolescent populations. Standardization of metabolic biomarkers, inflammatory indicators, and digital monitoring protocols will be necessary before routine implementation. Furthermore, long-term reproductive outcomes, including fertility, pregnancy, and adult metabolic health, require continued longitudinal investigation.

In conclusion, the present study supports a transition from symptom-oriented management toward integrated precision reproductive healthcare for obese adolescent girls with menstrual disorders. The Integrated Adolescent Menstrual Health Optimization Framework (IAMHOF) provides a novel systems-based model that combines anthropometric assessment, endocrine evaluation, metabolic profiling, inflammatory biomarkers, pelvic ultrasonography, lifestyle medicine, and digital health technologies within a unified clinical strategy. By emphasizing individualized risk assessment and multidisciplinary management, the framework has the potential to improve reproductive outcomes, optimize clinical decision-making, and contribute substantially to

the future development of adolescent gynecology and precision women's health.

## 10. Conclusion

Menstrual cycle disorders associated with obesity represent one of the most significant reproductive health challenges affecting adolescent girls worldwide. The increasing prevalence of adolescent obesity has transformed menstrual dysfunction from an isolated gynecological concern into a complex metabolic and endocrine disorder with substantial implications for future reproductive, cardiovascular, and psychological health. Growing scientific evidence demonstrates that obesity disrupts normal reproductive physiology through multiple interconnected mechanisms involving insulin resistance, hyperinsulinemia, adipokine imbalance, chronic inflammation, hyperandrogenism, and hypothalamic–pituitary–ovarian (HPO) axis dysregulation. Consequently, conventional management strategies focusing solely on symptomatic treatment of menstrual irregularities are no longer sufficient. Instead, comprehensive multidisciplinary approaches capable of addressing the biological complexity of obesity-associated reproductive dysfunction are required. The present study was therefore designed to optimize the management of adolescent girls with menstrual cycle disorders by integrating endocrine, metabolic, anthropometric, behavioral, imaging, and digital health components into a unified precision medicine framework. The principal findings of this study support the concept that menstrual dysfunction in obese adolescents should be interpreted as a multifactorial condition resulting from interactions between metabolic abnormalities, endocrine dysregulation, inflammatory activation, lifestyle behaviors, and developmental physiology. Comprehensive assessment demonstrated that obesity severity, central adiposity, insulin resistance, androgen excess, and poor lifestyle adherence collectively influence menstrual regularity and reproductive outcomes. Anthropometric indicators, including body mass index (BMI) and waist circumference, provided valuable measures of obesity severity, while endocrine biomarkers such as luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, testosterone, leptin, adiponectin, and HOMA-IR contributed substantially to individualized reproductive risk assessment. Integration of pelvic ultrasonography with hormonal and metabolic findings further improved clinical evaluation by reducing diagnostic uncertainty associated with adolescent reproductive disorders. Collectively, these observations reinforce the importance of comprehensive rather than isolated clinical assessment.

The major originality of this research lies in the development of the Integrated Adolescent Menstrual Health Optimization Framework (IAMHOF). Unlike conventional management models that primarily evaluate obesity, hormonal abnormalities, or menstrual symptoms independently, IAMHOF integrates anthropometric assessment, endocrine regulation, metabolic profiling, inflammatory mechanisms, reproductive imaging, lifestyle adherence, digital monitoring, and personalized clinical management into a single conceptual framework. This multidimensional approach recognizes that

adolescent menstrual health reflects continuous interactions among biological, behavioral, and environmental determinants rather than isolated pathological processes. By combining these diverse clinical domains within one evidence-based model, IAMHOF offers an innovative strategy for individualized diagnosis, risk stratification, therapeutic decision-making, and long-term follow-up.

From a theoretical perspective, this study contributes to adolescent gynecology by integrating principles derived from Adolescent Reproductive Health Theory, Developmental Origins of Health and Disease (DOHaD), obesity pathophysiology, hypothalamic–pituitary–ovarian axis regulation, endocrine–metabolic interaction theory, precision medicine, lifestyle medicine, and digital health. Existing theoretical models generally explain menstrual disorders from either endocrine or metabolic perspectives. In contrast, IAMHOF conceptualizes reproductive health as the product of complex interactions among endocrine regulation, metabolic homeostasis, inflammatory activity, behavioral adaptation, and technological support. This systems-based interpretation provides a broader theoretical foundation for future investigations and advances understanding of adolescent reproductive physiology within the context of obesity.

The clinical implications of the proposed framework are considerable. First, individualized assessment integrating anthropometric, endocrine, metabolic, inflammatory, and imaging findings may facilitate earlier identification of adolescents at increased risk for persistent menstrual dysfunction, polycystic ovary syndrome, and future reproductive complications. Second, incorporation of lifestyle adherence into routine clinical assessment emphasizes the importance of behavioral factors as measurable determinants of therapeutic success rather than merely supportive recommendations. Third, multidisciplinary collaboration among adolescent gynecologists, pediatric endocrinologists, nutritionists, psychologists, physiotherapists, and primary healthcare providers may improve treatment adherence and optimize long-term reproductive outcomes. Finally, digital health technologies—including menstrual tracking applications, wearable activity monitors, telemedicine platforms, and electronic symptom diaries—may strengthen continuity of care by enabling continuous monitoring and personalized clinical follow-up.

Beyond individual patient care, the findings have important public health implications. Adolescent obesity continues to increase globally, creating substantial future burdens related to infertility, metabolic syndrome, cardiovascular disease, type 2 diabetes mellitus, pregnancy complications, and reduced quality of life. Early recognition and management of obesity-associated menstrual disorders may therefore contribute not only to improved reproductive health but also to prevention of chronic noncommunicable diseases across the lifespan. Integration of school-based health promotion, family-centered nutritional counseling, community physical activity programs, and digital health education may support sustainable public health strategies aimed at reducing obesity-related reproductive morbidity among adolescent girls.

Despite these strengths, several limitations should be acknowledged. The proposed conceptual framework requires validation in larger multicenter populations representing diverse ethnic, socioeconomic, and geographic backgrounds before widespread clinical implementation. Lifestyle adherence was evaluated using standardized behavioral assessment methods; however, self-reported information may introduce reporting bias. Although the proposed digital monitoring strategies demonstrate promising clinical potential, additional evidence regarding long-term effectiveness, patient acceptability, data security, and cost-effectiveness remains necessary. Furthermore, the predictive performance of the IAMHOF framework should be externally validated using independent prospective cohorts before routine integration into clinical practice.

Future research should focus on multicenter longitudinal studies evaluating long-term reproductive outcomes following individualized multidisciplinary management. Additional investigations integrating genomics, metabolomics, inflammatory biomarkers, microbiome analysis, and artificial intelligence–based prediction models may further improve personalized reproductive healthcare. Randomized controlled trials comparing integrated precision medicine approaches with conventional management will also be essential to establish clinical effectiveness and cost-efficiency. Moreover, future studies should investigate the long-term effects of early intervention on fertility, pregnancy outcomes, metabolic health, and psychological wellbeing during adulthood.

In conclusion, this study supports a transition from symptom-oriented treatment toward precision adolescent reproductive healthcare. The proposed Integrated Adolescent Menstrual Health Optimization Framework (IAMHOF) provides an original, evidence-based conceptual model that integrates obesity severity, endocrine regulation, metabolic biomarkers, inflammatory mechanisms, reproductive imaging, lifestyle medicine, digital monitoring, and personalized management into a unified clinical strategy. By addressing the multidimensional nature of obesity-associated menstrual disorders, the framework offers a scientifically grounded approach for improving diagnostic accuracy, optimizing individualized treatment, strengthening multidisciplinary collaboration, and enhancing long-term reproductive health outcomes. The findings of this study contribute both theoretically and clinically to the evolving field of adolescent gynecology and provide a practical foundation for future research and evidence-based clinical practice.

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