

Medical Sciences

Kayupova Nina

Kazakh Research Institute of Obstetrics and Gynecology;

Republican Center for Maternal and Child Health

Kazakh National Medical University

DYSMENORRHEA AND POLYCYSTIC OVARY SYNDROME: Indications for Referral to Cycle-Oriented Physical Rehabilitation

Summary. *Relevance. Dysmenorrhea and polycystic ovary syndrome (PCOS) remain among the most common gynecological conditions in women of reproductive age, substantially reducing quality of life and frequently proving resistant to standard pharmacological therapy. In recent years, non-pharmacological methods of correction based on the phases of the menstrual cycle have been actively introduced into clinical practice. Of particular interest to the obstetrician-gynecologist is the concept of cyclically oriented physical rehabilitation proposed by Vasiltsova (2023), which systematizes non-pharmacological interventions in accordance with the hormonal profile of each phase of the cycle.*

Objective. To determine the clinical indications and contraindications for referring patients with dysmenorrhea and PCOS to cycle-oriented physical rehabilitation, and to substantiate the need for medical supervision of this method from the standpoint of obstetrics and gynecology.

Materials and methods. Analysis of the current literature on the non-pharmacological correction of dysmenorrhea and PCOS, together with a detailed clinical analysis of the Cyclical Core Balance concept presented by Vasiltsova (2023) from the standpoint of obstetric and gynecological practice.

Results. It is shown that the cyclically oriented rehabilitation protocol, provided that patients are correctly stratified by diagnosis and that mandatory medical supervision is maintained, may serve as an effective adjunct to the standard therapy of dysmenorrhea and of selected PCOS phenotypes. Clinical criteria for patient selection, absolute and relative contraindications, and an algorithm for cooperation between the obstetrician-gynecologist and the physical rehabilitation specialist are defined.

Conclusion. Integrating gynecological expertise into cycle-oriented physical rehabilitation protocols appears to be a clinically justified direction for the development of multidisciplinary care for women with dysmenorrhea and PCOS. The concept proposed by Vasiltsova merits further study and may be recommended for inclusion in continuing professional education programs in obstetrics and gynecology.

Key words: dysmenorrhea, polycystic ovary syndrome, menstrual cycle, physical rehabilitation, non-pharmacological therapy, multidisciplinary approach, obstetrics and gynecology.

Introduction. Dysmenorrhea — painful menstruation accompanied by spastic pain in the lower abdomen — occurs in 45–95% of women of reproductive age and is one of the leading causes of temporary disability in young women [1, 2]. Polycystic ovary syndrome (PCOS), in turn, is the most common endocrinopathy of reproductive age, affecting 8 to 13% of women and characterized by ovarian dysfunction, hyperandrogenism, and metabolic disturbances [3, 4].

Standard therapy for both conditions includes hormonal correction, non-steroidal anti-inflammatory drugs and, in PCOS, insulin sensitizers and lifestyle modification [3, 5]. However, a substantial proportion of patients show an incomplete response to pharmacological therapy, resistance to first-line agents, or a

preference for non-pharmacological approaches on personal grounds — which accounts for the growing clinical interest in structured physical rehabilitation programs as a component of comprehensive therapy [6, 7].

Of particular note in this context is the 2023 work by Vasiltsova, “Cyclically oriented rehabilitation and functional training for women of reproductive age: concept and practical protocol” [8]. The author proposes the original concept of Cyclical Core Balance — a systematized physical rehabilitation protocol differentiated across the four phases of the menstrual cycle and built upon seven basic methodological principles. Notably, Vasiltsova explicitly names dysmenorrhea and PCOS among the clinical conditions for which this protocol may be applied, while at the same time emphasizing that the proposed method is not a medical treatment protocol and, in the presence of verified gynecological pathology, requires mandatory agreement with the treating physician [8].

This methodologically important thesis — the need for medical supervision when applying cycle-oriented rehabilitation in gynecological patients — nevertheless remains unexplored from a clinical standpoint in the original work, which is entirely understandable: the author presents the concept from the standpoint of physical therapy rather than obstetrics and gynecology. It is precisely this gap that the present work seeks to fill.

The aim of this article is to determine the clinical indications and contraindications for referring patients with dysmenorrhea and PCOS to cycle-oriented physical rehabilitation under the Cyclical Core Balance protocol [8], and to develop an algorithm for cooperation between the obstetrician-gynecologist and the physical rehabilitation specialist that ensures the safety and clinical validity of this method.

Dysmenorrhea: pathophysiological basis and the potential of non-pharmacological correction

2.1 Pathophysiology of primary dysmenorrhea

Primary dysmenorrhea is pathogenetically linked to the overproduction of prostaglandins F2 α and E2 by the endometrium during the secretory phase of the cycle, leading to excessive uterine contractions, local myometrial ischemia, and activation of pain receptors [1, 9]. The severity of the pain syndrome correlates with the concentration of prostaglandins in menstrual blood, which explains the effectiveness of non-steroidal anti-inflammatory drugs as first-line therapy [1].

It is important to note that the pro-inflammatory background underlying dysmenorrhea is not an isolated local process — it is accompanied by systemic changes in the pain threshold, pelvic floor muscle tone, and autonomic regulation [9, 10]. It is precisely this that provides the theoretical rationale for applying non-pharmacological methods directed at these systemic components rather than at the local inflammatory process alone.

2.2 Evidence base for non-pharmacological methods in dysmenorrhea

Systematic reviews demonstrate a moderate but clinically significant effectiveness of physical exercise in reducing the intensity of dysmenorrhea [2, 11]. The mechanisms of this effect include raising the pain sensitivity threshold via the endogenous opioid system, improving pelvic circulation, and reducing the local inflammatory background [11]. The effectiveness of thermal procedures and pelvic floor relaxation techniques in reducing the spastic component of pain has been shown separately [10].

In this context, the section of the Cyclical Core Balance protocol devoted to working with dysmenorrhea — including breathing techniques, thermal procedures, and deactivation of pelvic floor muscle trigger points during the menstrual phase [8] — appears pathophysiologically justified and consistent with the existing evidence base. A fundamental methodological merit of Vasiltsova’s concept is that these interventions are not applied in isolation but are integrated into a coherent system

synchronized with the phases of the cycle, which may potentially enhance their clinical effectiveness compared with fragmentary application.

Additional confirmation of the clinical significance of this direction has been obtained in studies of myofascial trigger points of the pelvic floor muscles, the detection rate of which is significantly increased in patients with primary dysmenorrhea, especially during the menstrual phase of the cycle [18, 19]. Manual therapy and pelvic floor muscle exercises have demonstrated a significant reduction in the intensity of the pain syndrome in primary dysmenorrhea in prospective observational studies [20], which supports the validity of including the corresponding techniques in Vasiltsova’s protocol [8]. A pelvic physical therapy specialist working as part of a multidisciplinary team is able to further enhance the effectiveness of this rehabilitation component [17, 21].

2.3 Clinical stratification of patients with dysmenorrhea for referral to rehabilitation

From an obstetric and gynecological standpoint, referring a patient with dysmenorrhea to cycle-oriented physical rehabilitation requires prior diagnostic verification. It is fundamentally important to differentiate primary dysmenorrhea from secondary dysmenorrhea caused by organic pathology — endometriosis, adenomyosis, uterine fibroids, or pelvic inflammatory disease [12, 13].

Indications for referral to rehabilitation:

- Verified primary dysmenorrhea without organic pathology
- Secondary dysmenorrhea associated with compensated, pharmacologically controlled mild-to-moderate endometriosis — as an adjunct to the primary therapy
- Insufficient response to standard analgesic therapy in the absence of indications for changing the pharmacological regimen

- The patient’s wish to reduce her pharmacological burden with a stable clinical course

Contraindications and conditions requiring particular caution:

- An unverified pain syndrome without gynecological examination
- Acute pelvic inflammatory disease
- Suspected rupture or torsion of an ovarian cyst
- Severe endometriosis with a pronounced pain syndrome not controlled pharmacologically — priority is given to surgical or intensified pharmacological treatment

This stratification appears to be a necessary complement to Vasiltsova’s protocol [8], which correctly points to the need for medical agreement but does not detail specific diagnostic criteria — a task that lies within the competence of the obstetrician-gynecologist rather than the physical rehabilitation specialist.

Polycystic ovary syndrome: phenotypic heterogeneity and differentiated indications

Phenotypic classification of PCOS and its clinical significance

PCOS is a heterogeneous condition classified, in accordance with the Rotterdam criteria, into four phenotypes depending on the combination of ovulatory dysfunction, hyperandrogenism, and polycystic ovarian morphology [3, 14]. This heterogeneity is of fundamental importance in determining the indications for non-pharmacological interventions: the metabolic profile and clinical picture differ substantially between phenotype A (classic, with pronounced hyperandrogenism and insulin resistance) and phenotype D (ovulatory dysfunction and polycystic morphology without hyperandrogenism) [14, 15].

The pathophysiological basis of the insulin-resistant phenotypes of PCOS is the vicious cycle of mutual reinforcement between hyperinsulinemia and

hyperandrogenism: compensatory hyperinsulinemia stimulates ovarian androgen synthesis and reduces the production of sex hormone-binding globulin, which in turn aggravates insulin resistance [22, 23]. This mechanism explains why it is precisely in the hyperandrogenic phenotypes (A and B) that physical activity aimed at improving tissue insulin sensitivity constitutes a pathogenetically justified therapeutic intervention [24, 25], whereas in the non-insulin-resistant phenotypes (predominantly D) the main therapeutic effect of physical exercise is realized through other, predominantly neuroendocrine, mechanisms [16].

Physical exercise and lifestyle modification are recognized as first-line therapy for PCOS regardless of phenotype; however, the mechanisms of their effectiveness differ: in the insulin-resistant phenotypes, improving insulin sensitivity and reducing visceral fat are of key importance, whereas in the non-insulin-resistant phenotypes the main effect is associated with normalization of the neuroendocrine regulation of the ovulatory cycle [5, 15].

Applicability of the cycle-oriented approach in an irregular cycle

Here it is necessary to note a methodologically significant limitation to which Vasiltsova herself [8] explicitly points: the Cyclical Core Balance protocol was developed for women with a regular ovulatory cycle, and its application in patients with anovulation and an irregular cycle requires adaptation to individual symptomatology rather than to fixed calendar phases. This observation appears clinically fundamental, since irregularity of the cycle is itself one of the diagnostic criteria of PCOS — which creates an obvious methodological contradiction when attempting to apply the four-phase protocol directly.

From an obstetric and gynecological standpoint, this contradiction is resolved as follows: in patients with PCOS and preserved, at least relatively regular, ovulatory function (predominantly phenotype D and, in part, phenotype C), application of the phase protocol is possible with orientation toward symptomatic rather than calendar

criteria — which is precisely what the author of the concept proposes [8]. In patients with pronounced anovulation and amenorrhea, the cycle-oriented approach in its original form is inapplicable, and rehabilitation measures should be built on other principles that lie beyond the scope of the present work.

Clinical indications and contraindications in PCOS

Indications for referral to cycle-oriented rehabilitation:

- PCOS with preserved, relatively regular ovulatory function (phenotype D, partly C)
- Metabolically uncomplicated forms of PCOS, as an adjunct to lifestyle modification
- Patients already receiving pharmacological therapy (metformin, combined oral contraceptives) with the aim of enhancing the effectiveness of comprehensive treatment

Contraindications and limitations:

- Pronounced anovulation, amenorrhea — the protocol in its original form is inapplicable
- Severe insulin resistance and metabolic syndrome without prior pharmacological correction — priority is given to endocrinological treatment
- Uncompensated carbohydrate metabolism disorders

Establishing this differentiated stratification appears to be a significant clinical contribution that complements Vasiltsova's original concept [8] and broadens the possibilities for its safe and justified application in real obstetric and gynecological practice.

Algorithm for cooperation between the obstetrician-gynecologist and the physical rehabilitation specialist

Stages of multidisciplinary cooperation

Safe and clinically justified application of the Cyclical Core Balance protocol [8] in patients with dysmenorrhea and PCOS requires clearly structured cooperation between the physician and the physical rehabilitation specialist. On the basis of the analysis presented, the following algorithm is proposed.

Stage 1. Initial medical verification. Before referral to rehabilitation, the obstetrician-gynecologist performs a complete clinical examination in order to exclude organic pathology requiring treatment in its own right: pelvic ultrasound, hormonal profile in cases of suspected PCOS, and exclusion of acute inflammatory processes [12, 14]. Only after this verification may the patient be referred to the physical rehabilitation specialist.

Stage 2. Formulation of a medical report for the rehabilitation specialist. The report should contain: the diagnosis, indicating the phenotype in cases of PCOS; the degree of regularity of the ovulatory cycle; a list of contraindications and limitations on exercise intensity; and the recommended duration of the course until the follow-up examination.

Stage 3. Application of the protocol by the rehabilitation specialist. The physical rehabilitation specialist implements the phase-specific protocol [8] in accordance with the medical report received, maintains the patient's cycle diary, and documents the dynamics of symptoms in line with the principles set out in the original concept.

Stage 4. Follow-up medical monitoring. A repeat examination after 2–3 cycles of applying the protocol — the interval recommended by Vasiltsova herself [8] for assessing effectiveness — with analysis of the cycle diary data, the dynamics of the pain syndrome on the VAS, and, in cases of PCOS, monitoring of ovulatory function. Based on the results of the examination, a decision is made on continuing the program, modifying it, or the need to intensify pharmacological therapy.

Criteria for discontinuing rehabilitation and escalating medical care

The obstetrician-gynecologist must clearly identify for the rehabilitation specialist the clinical “red flags” that require immediate discontinuation of the program and referral of the patient for a repeat medical consultation: an increase in the intensity of the pain syndrome despite rehabilitation measures; the appearance of new symptoms — irregular bleeding or signs of an acute abdomen; or the absence of clinical improvement after 3 complete cycles of applying the protocol.

Establishing such criteria appears to be a necessary medical complement to the original protocol which, having been developed by a physical rehabilitation specialist, justifiably focuses on rehabilitation rather than diagnostic aspects [8].

Discussion

The scientific and clinical value of the Cyclical Core Balance concept

Vasiltsova’s work [8] merits particular attention from the obstetric and gynecological community for several reasons. First, it represents one of the few attempts to systematize non-pharmacological interventions in strict accordance with the physiology of the menstrual cycle, drawing on a solid evidence base of 20 sources spanning the period from 2003 to 2021 [8]. Second, the seven basic principles of the method — in particular the principle of “recovery priority” in phases with reduced neuromuscular readiness and the principle of “continuity of monitoring” through cycle diaries — are methodologically consistent with contemporary conceptions of personalized medicine and the patient-centered approach [4].

From a clinical standpoint, particular attention is warranted by the fact that the author of the concept has independently and explicitly delineated the limits of applicability of her method — pointing to the need for medical supervision in gynecological pathology and to the limitations of its application in patients with an irregular cycle [8]. This methodological honesty substantially facilitates the

integration of the concept into real clinical practice and distinguishes this work from a number of popular non-pharmacological methods that are often presented without a clear indication of contraindications.

The significance of differentiated diagnostic stratification

The present work, developing Vasiltsova's concept [8], proposes a differentiated clinical stratification of patients with dysmenorrhea and PCOS that resolves the contradiction identified by the author between the phase structure of the protocol and the irregularity of the cycle characteristic of a substantial proportion of patients with PCOS. The criteria of indications and contraindications presented, together with the algorithm of medical supervision, substantially broaden the possibilities for the safe clinical application of the original concept, translating it from the plane of a general methodology of physical rehabilitation into the plane of a specific obstetric and gynecological protocol for patient routing.

Prospects for introduction into the educational process

In the opinion of the author of the present article, the analysis of the Cyclical Core Balance concept [8] presented here and the differentiated patient stratification proposed possess considerable educational potential. Integrating non-pharmacological, physiologically justified methods into the clinical reasoning of future obstetrician-gynecologists appears to be an important task of contemporary medical education, especially in the context of the growing demand from patients for personalized and minimally invasive approaches to the correction of dysmenorrhea and PCOS [6, 7].

In this connection, it appears expedient to consider including a review of the Cyclical Core Balance concept and the principles of cycle-oriented physical rehabilitation in continuing professional education programs and thematic advanced-training courses for obstetrician-gynecologists — as an illustrative example of the successful integration of non-pharmacological methods into a

specialist's clinical reasoning, and as material for seminars devoted to multidisciplinary cooperation in the treatment of dysmenorrhea and PCOS.

Limitations of the work

The present work has the character of an analytical review and clinical systematization based on the analysis of the literature and the logical development of the original concept [8]; it does not include the author's own empirical data on the clinical effectiveness of the proposed stratification. The indications and contraindications presented are based on pathophysiological reasoning and the author's clinical experience but require prospective validation in controlled clinical trials involving patients with dysmenorrhea and various PCOS phenotypes.

Conclusion. Dysmenorrhea and polycystic ovary syndrome remain clinically significant conditions in which non-pharmacological methods based on the physiology of the menstrual cycle may serve as an effective adjunct to standard therapy. The Cyclical Core Balance concept proposed by Vasiltsova [8] represents a methodologically justified and clinically valuable contribution to the development of this field, systematizing physical rehabilitation in accordance with the phases of the cycle on the basis of a solid evidence base.

The present work, developing this concept from an obstetric and gynecological standpoint, proposes a differentiated diagnostic stratification of patients with dysmenorrhea and PCOS, clear criteria of indications and contraindications, and an algorithm for multidisciplinary cooperation between the physician and the physical rehabilitation specialist. Together, these two works — Vasiltsova's original concept [8] and the clinical systematization presented here — form a coherent methodological foundation: one describes a physiologically justified rehabilitation protocol, while the other translates it into the plane of a specific, safe, and clinically applicable algorithm for routing gynecological patients. Such a combination of physical therapy methodology and medical expertise appears to be a

model of the productive multidisciplinary cooperation necessary for the safe introduction of non-pharmacological approaches into real clinical practice.

The author of the present article holds that both works — the Cyclical Core Balance concept [8] and the differentiated patient stratification proposed in this article — merit inclusion in continuing professional education programs in obstetrics and gynecology as an illustrative example of the effective integration of non-pharmacological, physiologically justified methods into the comprehensive therapy of gynecological disorders of the menstrual cycle. Further study of the clinical effectiveness of the proposed approach within the framework of prospective controlled trials appears to be a promising direction for the development of multidisciplinary care for women with dysmenorrhea and PCOS.

References

1. Itani R, Soubra L, Karout S, Rahme D, Karout L, Khojah HMJ. Primary dysmenorrhea: pathophysiology, diagnosis, and treatment updates. *Korean Journal of Family Medicine*. 2022;43(2):101–108. doi:10.4082/kjfm.21.0103.
2. Armour M, Parry K, Manohar N, Holmes K, Ferfolja T, Curry C, et al. The prevalence and academic impact of dysmenorrhea in 21,573 young women: a systematic review and meta-analysis. *Journal of Women's Health*. 2019;28(8):1161–1171. doi:10.1089/jwh.2018.7615.
3. Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. *Fertility and Sterility*. 2016;106(1):6–15. doi:10.1016/j.fertnstert.2016.05.003.
4. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Fertility and Sterility*. 2018;110(3):364–379. doi:10.1016/j.fertnstert.2018.05.004.

5. Lim SS, Hutchison SK, Van Ryswyk E, Norman RJ, Teede HJ, Moran LJ. Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database of Systematic Reviews*. 2019;3:CD007506. doi:10.1002/14651858.CD007506.pub4.
6. Chen CX, Carpenter JS, LaPradd M, Ofner S, Fortenberry JD. Perceived ineffectiveness of pharmacological treatments for dysmenorrhea. *Journal of Women's Health*. 2021;30(9):1334–1343. doi:10.1089/jwh.2020.8581.
7. Armour M, Parry K, Al-Dabbas MA, Curry C, Holmes K, MacMillan F, et al. Self-care strategies and sources of knowledge on menstruation in 12,526 young women with dysmenorrhea: a systematic review and meta-analysis. *PLoS One*. 2019;14(7):e0220103. doi:10.1371/journal.pone.0220103.
8. Vasylytsova V. Phase-dependent physical recovery and functional training of women of fertile age: a conceptual model and clinical protocol. *Colloquium-journal*. 2023;1(31(190)). ISSN 2520-6990 (print), 2520-2480 (online). Available from: <https://journals.indexcopernicus.com/search/article?articleId=4953088>
9. Hudson AN, Pearson MJ. Pathophysiology of primary dysmenorrhea. *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2023.
10. Proctor M, Farquhar C. Diagnosis and management of dysmenorrhoea. *BMJ*. 2006;332(7550):1134–1138. doi:10.1136/bmj.332.7550.1134.
11. Armour M, Smith CA, Steel KA, Macmillan F. The effectiveness of self-care and lifestyle interventions for primary dysmenorrhea: a systematic review and meta-analysis. *BMC Complementary and Alternative Medicine*. 2019;19(1):22. doi:10.1186/s12906-019-2433-8.
12. Bulun SE. Endometriosis. *New England Journal of Medicine*. 2009;360(3):268–279. doi:10.1056/NEJMra0804690.
13. American College of Obstetricians and Gynecologists. Dysmenorrhea and endometriosis in the adolescent. Committee Opinion No. 760. *Obstetrics & Gynecology*. 2018;132(6):e249–e258. doi:10.1097/AOG.0000000000002978.

14. Broekmans FJ, Knauff EA, Valkenburg O, Laven JS, Eijkemans MJ, Fauser BC. PCOS according to the Rotterdam consensus criteria: change in prevalence among WHO-II anovulation and association with metabolic factors. *BJOG*. 2006;113(10):1210–1217. doi:10.1111/j.1471-0528.2006.01008.x.

15. Lizneva D, Gavrilova-Jordan L, Walker W, Azziz R. Phenotypes and body mass in women with polycystic ovary syndrome identified in referral versus unselected populations: systematic review and meta-analysis. *Frontiers in Bioscience*. 2015;7:511–519. doi:10.2741/e750.

16. Teede HJ, Tay CT, Laven J, Dokras A, Moran LJ, Piltonen TT, et al. Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Journal of Clinical Endocrinology & Metabolism*. 2023;108(10):2447–2469. doi:10.1210/clinem/dgad463.

17. Naderpoor N, Shorakae S, de Courten B, Misso ML, Moran LJ, Teede HJ. Metformin and lifestyle modification in polycystic ovary syndrome: systematic review and meta-analysis. *Human Reproduction Update*. 2015;21(5):560–574. doi:10.1093/humupd/dmv025.

18. Wallace SL, Miller LD, Mishra K. Pelvic floor physical therapy in the treatment of pelvic floor dysfunction in women. *Current Opinion in Obstetrics and Gynecology*. 2019;31(6):485–493. doi:10.1097/GCO.0000000000000584.

19. Morin M, Carroll MS, Bergeron S. Systematic review of the effectiveness of physical therapy modalities in women with provoked vestibulodynia. *Sexual Medicine Reviews*. 2017;5(3):295–322. doi:10.1016/j.sxmr.2017.02.003.

20. Barassi G, Bellomo RG, Frondaroli F, et al. Manual therapy and active exercise for the relief of primary dysmenorrhea symptoms: a pilot study. *Journal of Bodywork and Movement Therapies*. 2021;28:1–6. doi:10.1016/j.jbmt.2021.07.011.

21. Diaz-Mohedo E, Barón-López FJ, Pineda-Galán C, et al. Prevalence and risk of myofascial pain syndrome in women with chronic pelvic pain. *Actas Urológicas Españolas*. 2014;38(4):248–253. doi:10.1016/j.acuro.2013.09.011.
22. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. *Endocrine Reviews*. 2012;33(6):981–1030. doi:10.1210/er.2011-1034.
23. Rosenfield RL, Ehrmann DA. The pathogenesis of polycystic ovary syndrome (PCOS): the hypothesis of PCOS as functional ovarian hyperandrogenism revisited. *Endocrine Reviews*. 2016;37(5):467–520. doi:10.1210/er.2015-1104.
24. Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database of Systematic Reviews*. 2011;2:CD007506. doi:10.1002/14651858.CD007506.pub3.
25. Dapas M, Dunaif A. Deconstructing a syndrome: genomic insights into PCOS causal mechanisms and classification. *Endocrine Reviews*. 2022;43(6):927–965. doi:10.1210/endrev/bnac001.