J. Adv. Res. in Information Technology, Systems and Management
Volume 8 Issue 1 - 2024, Pg. No. 12-18
Peer Reviewed Journal

Research Article

# Breaking New Ground: A Comprehensive Review of Advanced Intravaginal Rings in the Management of Hormonal Imbalances in Polycystic Ovarian Syndrome

Tamanna Sharma

Pcte Group Of Institues, Baddowal, Ludhiana.

## I N F O

**E-mail Id:**
tamanna@pcte.edu.in
**Orcid ID:**
https://orcid.org/0009-0000-2989-590X

**How to cite this article:**
Sharma T, Breaking New Ground: A Comprehensive Review of Advanced Intravaginal Rings in the Management of Hormonal Imbalances in Polycystic Ovarian Syndrome. *J Adv Res Info Tech Sys Mgmt* 2024; 8(1):12-18.

Date of Submission: 2024-02-03
Date of Acceptance: 2024-03-07

## A B S T R A C T

This review aims to shed light on the potential of advanced IVRs as a transformative therapeutic tool, paving the way for future research and clinical applications in the tailored management of hormonal imbalances in Polycystic Ovarian Syndrome. Polycystic Ovarian Syndrome (PCOS) is a prevalent endocrine disorder affecting reproductive-aged women, characterized by hormonal imbalances and ovarian dysfunction. This comprehensive review explores the innovative approach of utilizing advanced intravaginal rings (IVRs) as a novel therapeutic strategy for managing hormonal imbalances in PCOS.The paper highlights the Importance of hormones such as estrogen, progesterone, and androgens, which contribute to the syndrome's multifaceted symptomatology. Traditional treatment modalities often fall short in addressing the complex hormonal dysregulation observed in PCOS, prompting the exploration of alternative delivery methods. Intravaginal rings, known for their sustained and controlled release of medications, offer a promising avenue for targeted hormone delivery. The review provides an in-depth analysis of recent advancements in IVR technology, discussing the design, pharmacokinetics, and safety profiles of various prototypes specifically tailored for PCOS management. Furthermore, the paper evaluates the efficacy of IVRs in regulating menstrual cycles, mitigating hyperandrogenism, and improving metabolic parameters in PCOS patients. Insights from preclinical and clinical studies are synthesized, offering a comprehensive overview of the evolving landscape of IVRs in the context of PCOS treatment.

**Keywords:** PCOS, Hormonal Imbalance, IVR Technology, Intra-Vaginal Rings, Therapeutic Efficacy

## Introduction

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder in gynecology, with incidence rates ranging from 6 to 10% in women and 9 to 18% in women of childbearing age[1, 2] PCOS is identified by elevated androgen levels, persistent anovulation, and ovarian changes marked by the presence of multiple cysts.

While Stein and Leventhal are commonly acknowledged as

the first investigators of polycystic ovary syndrome (PCOS), the initial historical account can be attributed to Vallisneri, an Italian medical scientist, physician, and naturalist. In 1721, Vallisneri described a married, infertile woman with ovaries exhibiting a shiny appearance, a white surface, and a size comparable to pigeon eggs.[1] Another early report dates back to 1844 when Chereau and Rokitansky documented fibrous and sclerotic lesions in ovaries of a degenerative nature, accompanied by hydrops follicle[2,3] The term "hyperthecosis" was introduced by Bulius and Kretschmar in their description[4] In 1879, Lawson Tait advocated for bilateral oophorectomy as a treatment for symptomatic cystic degeneration of the ovaries[5] Shortly after, partial resection of the ovaries was proposed[6] In 1902, von Kahlden provided a comprehensive review on the pathology and clinical implications associated with these ovarian conditions.

## Traditional Therapies

Traditional pharmaceutical management faces limitations in the treatment of women with PCOS, including contraindications, ineffectiveness in certain cases, and side effects. Additionally, some women with PCOS prefer alternative treatments over pharmaceutical options[3] This review explores the potential of herbal medicine as an alternative treatment, examining the mechanisms of effect.[7] Six herbal medicines with both pre-clinical and clinical data supporting their reproductive endocrinological effects in PCOS, along with associated oligo/amenorrhea and hyperandrogenism, are identified. The use of complementary medicine (CM) has seen a notable increase among women over the past decade, with usage rates ranging from 26% to 91%. Herbal medicine, a popular type of CM, contains pharmacologically active constituents with physiological effects on female endocrinology. Moreover, herbal medicines have been positively associated with reduced incidences of breast cancer, osteoporosis, and cardiovascular disease[8,]

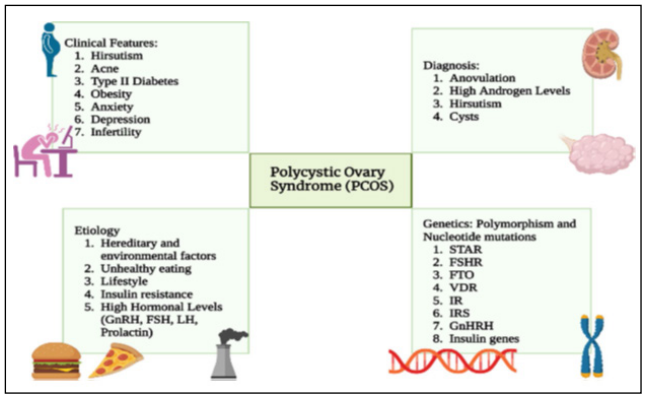


**Figure 1.Schematic Diagram of Pcos**

## Current Treatment Strategies

This comprehensive review thoroughly examines the existing evidence on lifestyle strategies employed for optimizing the management of Polycystic Ovary Syndrome (PCOS). Embracing a holistic approach to patient care, the review encompasses traditional aspects of lifestyle modification, including dietary adjustments, physical activity, and behavioral changes.[9.10] Furthermore, it explores psychological interventions, sleep management, and approaches from Traditional, Complementary, and Integrative Medicine (TCIM), such as supplements, herbal medicine, and yoga. The PCOS guideline underscores the importance of promoting healthy lifestyle behaviors for all women with PCOS, with the overarching goals of achieving and maintaining a healthy weight and optimizing overall health.[18] Specifically, for women with excess weight, the guideline recommends a weight loss target of 5-10%, with an emphasis on creating an energy deficit of 30% or 500-750 kcal/day (1200-1500 kcal/day). While weight management is considered a central element of lifestyle interventions, the guideline acknowledges that the benefits of a healthy lifestyle extend beyond weight change, emphasizing the broader positive impacts on health.

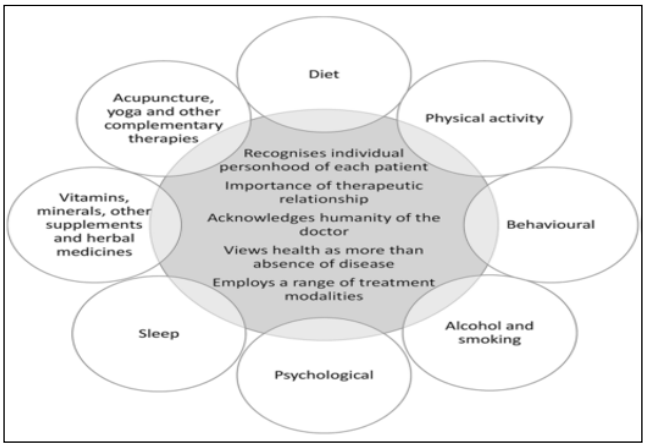


**Figure 2.Schematic Representation of Lifestyle**

## Oral Contraceptive Therapy

Oral contraceptive (OC) pills represent a primary treatment for the long-term management of Polycystic Ovary Syndrome (PCOS)[20] Typically composed of estrogen and progesterone, OCs exert their effects through various mechanisms. Estrogen impedes the formation and maturation of ovarian follicles by inhibiting follicle-stimulating hormone (FSH), while progesterone suppresses ovulation by inhibiting luteinizing hormone (LH). Additionally, progesterone enhances the viscosity of cervical mucus, impeding sperm penetration and fertilization of the egg [21]

Simultaneously, OCs elevate the concentration of sex hormone-binding globulin (SHBG), leading to a reduction in free testosterone levels. This diminishes the peripheral

effects of androgens, facilitating androgen deprivation. OC therapy contributes to the restoration of the menstrual cycle, improvement of hyperandrogenism, provision of contraception, and protection of the endometrium, thereby aiding in cancer prevention.[20] Commonly prescribed OCs in clinical practice include desogestrel/ethinylestradiol (Marvelon), cyproterone acetate/ethinylestradiol (Diane-35), and drospirenone/ethinylestradiol (Yasmin).

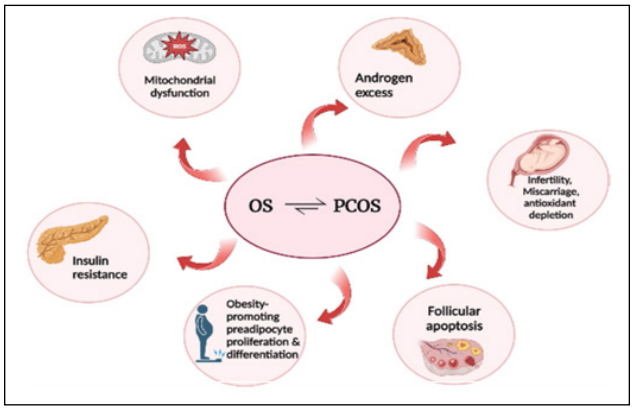


**Figure 3.Os System**

## High Testosterone Therapy

Elevated androgen levels in individuals with Polycystic Ovary Syndrome (PCOS) are linked to the biological synthesis of theca cells and the excessive secretion of androgens from adrenal zona reticularis cells, specifically testosterone[35–39] Women with PCOS, particularly those with insulin resistance or hyperinsulinemia, exhibit heightened androgen secretion from both the ovaries and adrenal glands[10,11] However, while androgen therapy can be effective, it is not without potential side effects, particularly in PCOS patients who face an increased risk of cardiovascular disease when left untreated[23,22]

Regardless of whether individuals with PCOS are obese or not, elevated testosterone levels are directly associated with dysglycemia[18], hypotension[19,20], and subclinical arteriosclerosis. These findings underscore the importance of addressing and managing androgen levels in PCOS patients, especially in the context of potential cardiovascular implications and metabolic disturbances.

## Ovulation Induction

One of the diagnostic criteria for individuals with Polycystic Ovary Syndrome (PCOS) involves non-ovulation or ovulatory disorders. Ovulation induction serves as an effective treatment for PCOS patients with fertility requirements, utilizing medications such as clomiphene citrate (CC), a selective estrogen receptor modulator; letrozole (LE), an aromatase inhibitor; and gonadotropin.

Clomiphene citrate (CC) is typically initiated at a daily dose of 50 mg, starting on day 2–5 of the menstrual cycle for five days. Ovulation typically occurs 5–10 days after the completion of the treatment. If ovulation is not achieved, the dosage can be gradually increased, with a maximum dose of 250 mg/day.

Letrozole, a third-generation aromatase inhibitor, blocks the conversion of androgens to estrogens in ovarian follicles, peripheral tissues, and the brain. This action creates a positive feedback loop with estrogen in the Hypothalamic-Pituitary-Ovarian (HPO) axis, leading to the endogenous release of GnRH, the promotion of FSH secretion, and follicular growth. Letrozole is administered at doses ranging from 2.5 to 5 mg/day for five days, starting on day 3–7 of the menstrual cycle.[26] Emerging research suggests that letrozole aromatase inhibitors may replace the selective estrogen receptor modulator clomiphene as a first-line treatment option for inducing ovulation.[27] Letrozole is believed to have a unique advantage in promoting ovulation, particularly in obese patients with PCOS.[27] Additionally, letrozole has a minimal impact on the uterine lining and offers certain safety advantages, such as preventing ovarian hyperstimulation or adverse outcomes like multiple pregnancies.

## Inositol Treatment Theory

Nestler et al. observed that women diagnosed with polycystic ovary syndrome (PCOS) exhibit heightened ovarian activity due to specific phenotypes. This increased activity results in greater conversion of Myo-inositol (MI) to D-chiro-inositol (DCI), leading to decreased MI levels in the follicles. However, their study revealed a noteworthy finding: the presence of a higher number of normal mature follicles and increased follicular fluid in fertilized oocytes with MI compared to the lower count of immature or infertile follicles. Consequently, inositol treatment is anticipated to enhance the quality of ovarian follicles, promote regular menstrual cycles, and alleviate insulin resistance in PCOS-afflicted women. This therapeutic approach holds promise for improving outcomes in PCOS patients in the future.

## Insulin sensitizer

In the clinical context, a substantial majority (60–80%) of individuals with polycystic ovary syndrome (PCOS) experience varying levels of insulin resistance.[28,29] The insulin sensitizer metformin plays a crucial role in alleviating symptoms associated with elevated testosterone by reducing glycogen production, thereby enhancing sugar metabolism and inhibiting follicular membrane cells. Research indicates that metformin can restore ovulation in approximately 30–50% of women with PCOS. Treatment for the initial six months typically involves progesterone cycles until establishing a regular menstrual cycle. However, its efficacy in terms of pregnancy rates and productivity is lower compared to clomiphene .[28,32]

It's noteworthy that metformin, classified as a class B drug by the U.S. Food and Drug Administration, should be used cautiously despite a meta-analysis suggesting no increased risk of birth defects with early use in PCOS patients .[33] Other drugs such as thiazolidinediones (TZDS) and incretin, lacking sufficient clinical data, pose uncertainties regarding their specific interventions and long-term treatment outcomes. Further clinical trials and follow-up studies are necessary to elucidate the prognosis of these interventions and the safety of extended drug usage.

### Leptin Theory

Vazquez et al. have comprehensively reviewed the mechanisms and roles of leptin over the last two decades, highlighting its impact on gonadotropin levels through central regulation in the brain. Leptin exerts its influence by modulating the hypothalamus-pituitary gonad (HPG) axis, thereby contributing to follicle maturation and ovulation.[34] Additionally, leptin plays a role in ameliorating insulin resistance and hyperinsulinemia.[36] The study observed a significant elevation in leptin levels and increased expression of leptin mRNA in PCOS patients, suggesting a potential association with early morbid obesity or an event affecting the brain's KISS neurons, possibly leading to future inhibition of leptin expression.

This insight into leptin's involvement opens up new avenues for scientific advancements in the treatment of PCOS. Future research in therapy is anticipated to explore novel directions based on the understanding of leptin's intricate role. Beyond leptin-focused interventions, various treatments for PCOS patients targeting lipid metabolism have been identified. These include spironolactone, which enhances high-density lipoprotein and reduces triglycerides[21]; flutamide, known for decreasing total cholesterol, low-density lipoproteins, and triglycerides[31]; acarbose, which mitigates the digestion and absorption of polysaccharides[31]; and orlistat, recognized for reducing factors such as dietary fat absorption.[31]

### Surgical Treatment

- Ovarian Drilling
- Assisted reproductive technology (ART) therapy
- Bariatric surgery

## Combined Oral Contraceptives

Beyond contraception, healthcare providers prescribe COCs for various medical conditions, including irregular menstrual cycles, dysmenorrhea (painful menstruation), premenstrual syndrome (PMS), and polycystic ovary syndrome (PCOS). Combined oral contraceptives (COCs) incorporate two types of hormones – estrogen and progestin. Ethinyl estradiol serves as a common synthetic estrogen, and various progestins, such as levonorgestrel, norethindrone, and drospirenone, are employed.

The primary mechanism of action for COCs involves the suppression of ovulation, preventing the release of an egg from the ovary. Additionally, they induce changes in cervical mucus, making it more challenging for sperm to reach the egg, and modify the uterine lining, reducing its receptivity to a fertilized egg. When used correctly, COCs demonstrate high efficacy in preventing pregnancy. The typical use failure rate is higher than the perfect use failure rate, underscoring the significance of consistent and proper use.

COCs are available in different formulations, including monophasic (maintaining a fixed dose of estrogen and progestin throughout the cycle) and multiphasic (featuring varying hormone levels during the menstrual cycle). The choice of formulation depends on individual patient needs. Typically taken once a day at the same time, COCs are administered for 21 or 28 days, depending on the specific formulation.[36,37] The 21-day packs consist of active hormonal pills, while the 28-day packs include placebo or reminder pills. Common side effects of COCs may include nausea, breast tenderness, and breakthrough bleeding. Serious risks, notably blood clots, are carefully considered, particularly in individuals who smoke and are over 35 years old. COCs offer non-contraceptive benefits, such as the regulation of menstrual cycles, reduction in menstrual cramps, and improvement in acne. They may also provide protection against certain gynecological cancers.[38,39]

However, COCs are not suitable for everyone, with contraindications including a history of blood clots, specific cardiovascular conditions, liver disease, and a history of certain cancers. Smoking is generally discouraged, especially in individuals over 35.

## Intravaginal Rings

Intravaginal rings (IVRs) serve as drug delivery systems (DDS) for the systemic or topical administration of one or more drugs. Shaped like doughnuts, these polymeric devices can remain in the vagina for durations ranging from 1 to 12 months.[40] This method of drug delivery addresses challenges associated with conventional approaches, such as oral administration leading to gastrointestinal side effects or the hepatic first-pass effect. A key advantage of IVRs lies in their capacity to deliver drugs consistently.[41] Utilizing IVRs as DDS eliminates the need for minor surgical procedures associated with other implantable drug delivery methods, rendering IVRs less invasive and more appealing to patients. Therefore, reducing costs and expanding the availability of contraceptive vaginal rings is important, as is development of those with longer durations that do not need refrigeration, which would increase the contraceptive options for women globally.

By delivering steroid hormones through the female reproductive tract, IVRs circumvent the initial hepatic metabolism, ensuring constant steroid levels and thereby enhancing the bioavailability of these hormones. Osmotic pressure, reservoir systems (employing a rate-controlling membrane [RCM]), and matrix systems are common DDSs providing sustained and controlled release. IVRs are designed in various forms, including matrix (homogeneous dispersion), reservoir, or hybrid (a combination of matrix and reservoir). Additionally, IVRs can serve as casings for vaginal tablets or rods.[42]

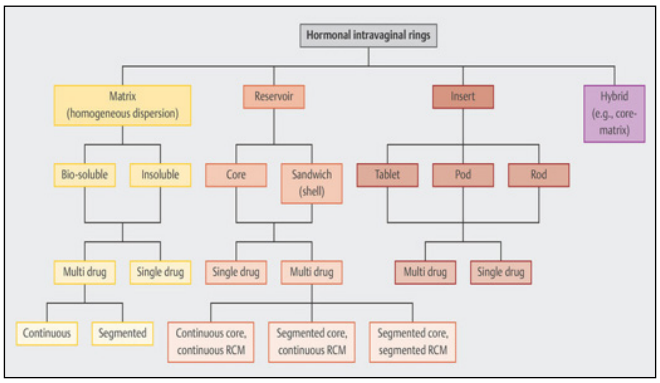


**Figure 4.Comprehensive classification of these four types of IVR design which are commercially available**

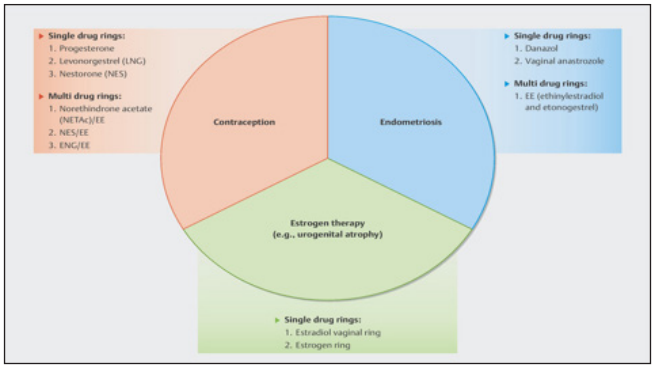


**Figure 5.Schematic diagram of hormonal IVR applications**

**Table1.List of commercially available hormonal IVRs.**

| IVR NAME | COMPANY | HORMONE | APLLICATION |
|---|---|---|---|
| Annovera® | Therapeutics MD | Nestorone (segesterone acetate) and ethinylestradiol[45] | Contraception |
| Estring | Pfizer | Estradiol[44] | Urogenital atrophy |
| Fertiring ® | Silesia Laboratories | Progesterone[47] | Contraception |
| NuvaRing | Netherlands/Merck & Co., USA | etonogestrel and ethinylestradiol[44] | Contraception |
| Ornibel | Exeltis Healthcare | etonogestrel and ethinylestradiol[46] | Contraception |
| Progering | Silesia Laboratories | Progesterone | Contraception |

## Discussion

Intravaginal rings hold promise as methods for the extended delivery of hormones for various applications. While currently employed predominantly for contraception, their utility extends to treating conditions like endometriosis, urogenital atrophy, and estrogen therapy. Anticipated future applications include combining intravaginal rings with other therapies, such as HIV prevention and contraception, positioning them as highly effective treatments for women alongside implants. Beyond hormones, intravaginal rings offer the potential for systemic delivery of other drugs via the vaginal tract. Despite the existence of numerous commercially available intravaginal rings, there are persistent challenges that need addressing for enhanced efficiency. A major hurdle involves developing intravaginal rings capable of delivering different types of drugs over extended durations. Additional challenges include the creation of cost-effective intravaginal rings, ensuring broader accessibility for larger female populations. Overcoming these challenges could establish intravaginal rings as the most efficient drug delivery system, catering not only to female-specific ailments but also to drugs requiring systemic absorption

## Conclusion

In delivering hormones, intravaginal rings (IVRs) prove to be highly efficient systems. Their advantages encompass effective drug delivery, the capability to bypass the hepatic first-pass effect, prolonged release of drugs, simple administration, and a reduction in the frequency of necessary physician appointments. Despite these benefits, obtaining a prescription and guidance on IVR usage requires women to consult a physician. The sustained release of hormones and the potential for simultaneous use of multiple hormones and drugs make IVRs highly efficient for numerous patients. Silicone elastomer stands out as a widely utilized polymer due to its high biocompatibility, making it possibly the most effective material for IVRs. Various IVR manufacturing designs, including pod, sandwich, and core configurations, are employed for diverse therapeutic purposes, aiming to maximize the efficiency of these drug delivery systems.

Hormonal IVRs emerge as one of the most efficient and effective approaches for treating a diverse array of diseases. These innovative drug delivery systems have the potential to significantly enhance women's lives and contribute to an overall improvement in their quality of life.

## References

1. Orvieto R, Ben-Rafael Z. Polycystic ovary syndrome: a simplified approach based on the evolving set of symptoms. Human Reproduction. 2003 Apr 1;18(4):896-7.
2. Warren-Ulanch J, Arslanian S. Treatment of PCOS in adolescence. Best practice & research Clinical endocrinology & metabolism. 2006 Jun 1;20(2):311-30.
3. Azziz R, Dumesic DA, Goodarzi MO. Polycystic ovary syndrome: an ancient disorder? Fertility and sterility. 2011Apr 1; 95(5): 1544-8.
4. Goodarzi MO, Dumesic DA, Chazenbalk G, Azziz R.Polycystic ovary syndrome: etiology, pathogenesis and diagnosis. Nature reviews endocrinology. 2011 Apr; 7(4):219-31.
5. Sadeghi HM, Adeli I, Calina D, Docea AO, Mousavi T, Daniali M, Nikfar S,Tsatsakis A, Abdollahi M (2022) Polycystic ovary syndrome: a comprehensive review of pathogenesis, management, and drug repurposing. Int J Mol Sci 23(2):583
6. Siddiqui S, Mateen S, Ahmad R, Moin S (2022) A brief insight into the etiology, genetics, and immunology of polycystic ovarian syndrome(PCOS). J Assist Reprod Genet 39(11):2439–2473.
7. Palomba S, Falbo A, La Sala GB: Metformin and gonadotropins for ovulation induction in patients with polycystic ovary syndrome: a systematic review with meta-analysis of randomized controlled trials. Reprod Biol Endocrinol. 2014, 12:3. 10.1186/1477-7827-12-3
8. Jia LY, Feng JX, Li JL, Liu FY, Xie LZ, Luo SJ, Han FJ: The complementary and alternative medicine for polycystic ovary syndrome: a review of clinical application and mechanism. Evid Based Complement Alternat Med. 2021, 2021:5555315. 10.1155/2021/5555315
9. Pasquali R: Contemporary approaches to the management of polycystic ovary syndrome. Ther AdvEndocrinol Metab. 2018, 9:123-34. 10.1177/2042018818756790de Melo AS, Dos Reis RM, Ferriani RA, Vieira CS: Hormonal contraception in women with polycystic ovary syndrome: choices, challenges, and noncontraceptive benefits. Open Access J Contracept. 2017, 8:13-23.10.2147/OAJC.S85543.
10. Vause TD, Cheung AP: Ovulation induction in polycystic ovary syndrome. J Obstet Gynaecol Can. 2010,32:495-502. 10.1016/S1701-2163(16)34504-2.
11. Ndefo UA, Eaton A, Green MR: Polycystic ovary syndrome: a review of treatment options with a focus on pharmacological approaches. P T. 2013, 38:336-55.
12. Panda SR, Jain M, Jain S, Saxena R, Hota S: Effect of orlistat versus metformin in various aspects of polycystic ovarian syndrome: a systematic review of randomized control trials. J Obstet Gynaecol India.2018, 68:336-43. 10.1007/s13224-018-1140-6
13. Durmus U, Duran C, Ecirli S: Visceral adiposity index levels in overweight and/or obese, and non-obese patients with polycystic ovary syndrome and its relationship with metabolic and inflammatory parameters. J Endocrinol Invest. 2017, 40:487-97. 10.1007/s40618-016-0582-x
14. Teede HJ, Misso ML, Costello MF, et al.: Erratum. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Hum Reprod. 2019, 34:388.10.1093/humrep/dey363
15. De Leo V, Musacchio MC, Cappelli V, Massaro MG, Morgante G, Petraglia F: Genetic, hormonal and metabolic aspects of PCOS: an update. Reprod Biol Endocrinol. 2016, 14:38. 10.1186/s12958-016-0173-x
16. Cunha A, Póvoa AM: Infertility management in women with polycystic ovary syndrome: a review . Porto Biomed J. 2021, 6:e116. 10.1097/j.pbj.0000000000000116
17. Bulsara J, Patel P, Soni A, et al.: A review: Brief insight into polycystic ovarian syndrome. Endocr Metab Sci.2021, 3:100085. 10.1016/j.endmts.2021.100085
18. Barry JA, Azizia MM, Hardiman PJ: Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2014, 20:748-58.10.1093/humupd/dmu012
19. McCartney CR, Marshall JC: Clinical practice. Polycystic ovary syndrome. N Engl J Med. 2016, 375:54-64.10.1056/NEJMcp1514916
20. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, Abbasi-Kangevari M, Abbastabar H, Abd-Allah F, Abdelalim A. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020 Oct 17;396(10258):1204-22.
21. Farrell-Turner KA. polycystic Ovary syndrome: Update on Treatment Options and Treatment considerations for the Future. Clinical Medicine Insights: Women's Health. 2011 Jan; 4: CMWH-S6715.
22. Ajmal N, Khan SZ, Shaikh R (2019) Polycystic ovary syndrome (PCOS) and genetic predisposition: a review article. Eur J Obstet Gynecol Reprod Biol X 8(3):100060
23. Dong XC, Liu C, Zhuo GC, Ding Y (2023) Potential Roles of mtDNA mutations in PCOS-IR: a review. Diabetes Metab Syndr Obes 25(16):139–149
24. Papaleo, E.; Unfer, V.; Baillargeon, J.-P.; De Santis, L.;

Fusi, F.; Brigante, C.; Marelli, G.; Cino, I.; Redaelli, A.; Ferrari, A. Myo-inositol in patients with polycystic ovary syndrome: A novel method for ovulation induction. Gynecol. Endocrinol. 2007, 23, 700–703.[CrossRef]
25. Artini, P.G.; Di Berardino, O.M.; Papini, F.; Genazzani, A.D.; Simi, G.; Ruggiero, M.; Cela, V. Endocrine and clinical effects of myo-inositol administration in polycystic ovary syndrome. A randomized study. Gynecol. Endocrinol. Off. J. Int. Soc. Gynecol.Endocrinol. 2013, 29, 375–379. [CrossRef]
26. Piomboni, P.; Focarelli, R.; Capaldo, A.; Stendardi, A.; Cappelli, V.; Cianci, A.; La Marca, A.; Luddi, A.; De Leo, V. Protein modification as oxidative stress marker in follicular fluid from women with polycystic ovary syndrome: The effect of inositol and metformin. J. Assist. Reprod. Genet. 2014, 31, 1269–1276. [CrossRef] [PubMed]
27. Genazzani, A.D.; Santagni, S.; Rattighieri, E.; Chierchia, E.; Despini, G.; Marini, G.; Prati, A.; Simoncini, T. Modulatory role of D-chiro-inositol (DCI) on LH and insulin secretion in obese PCOS patients. Gynecol. Endocrinol. 2014, 30, 438–443. [CrossRef][PubMed]
28. Nestler, J.E.; Jakubowicz, D.J.; Reamer, P.; Gunn, R.D.; Allan, G. Ovulatory and metabolic effects of D-chiro-inositol in the polycystic ovary syndrome. N. Engl. J. Med. 1999, 340, 1314–1320. [CrossRef]
29. Iuorno, M.J.; Jakubowicz, D.J.; Baillargeon, J.-P.;Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Casson P, Christman GM, Huang H, Yan Q, Alvero R,Haisenleder DJ. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. N Engl J Med. 2014 Jul10; 371: 119-29
30. Azziz, R.; Marin, C.; Hoq, L.; Badamgarav, E.; Song, P. Health care-related economic burden of the polycystic ovary syndrome during the reproductive life span. J. Clin. Endocrinol. Metab. 2005, 90, 4650–4658. [CrossRef]
31. Bremer, A.A. Polycystic ovary syndrome in the pediatric population. Metab. Syndr. Relat. Disorders 2010, 8, 375–394. [CrossRef]
32. Liu, J.; Wu, Q.; Hao, Y.; Jiao, M.; Wang, X.; Jiang, S.; Han, L. Measuring the global disease burden of polycystic ovary syndrome in 194 countries: Global Burden of Disease Study 2017. Hum. Reprod. 2021, 36, 1108–1119. [CrossRef]
33. Hashemipour, M.; Amini, M.; Iranpour, R.; Sadri, G.H.; Javaheri, N.; Haghighi, S.; Hovsepian, S.; Javadi, A.A.; Nematbakhsh, M.;Sattari, G. Prevalence of congenital hypothyroidism in Isfahan, Iran: Results of a survey on 20,000 neonates. Horm. Res. 2004,62, 79–83. [CrossRef]
34. Lujan, M.E.; Chizen, D.R.; Pierson, R.A. Diagnostic criteria for polycystic ovary syndrome: Pitfalls and controversies. J. Obstet.Gynaecol. Can. 2008, 30, 671–679. [CrossRef] [PubMed]
35. Merkin, S.S.; Phy, J.L.; Sites, C.K.; Yang, D. Environmental determinants of polycystic ovary syndrome. Fertil. Steril. 2016, 106,16–24. [CrossRef]
36. Batra, M.; Bhatnager, R.; Kumar, A.; Suneja, P. Interplay between PCOS and microbiome: The road less travelled. Am. J. Reprod.Immunol. 2022, 88, e13580. [CrossRef] [PubMed]
37. Mumusoglu, S.; Yildiz, B.O. Polycystic ovary syndrome phenotypes and prevalence: Differential impact of diagnostic criteria and clinical versus unselected population. Curr. Opin. Endocr. Metab. Res. 2020, 12, 66–71. [CrossRef]
38. Witchel, S.F.; Oberfield, S.E.; Peña, A.S. Polycystic Ovary Syndrome: Pathophysiology, Presentation, and TreatmentWith Emphasis on Adolescent Girls. J. Endocr. Soc. 2019, 3, 1545–1573.
39. Brache V, Payán LJ, Faundes A. Current status of contraceptive vaginal rings. Contraception 2013; 87: 264–72.
40. Van der Straten A, Agot K, Ahmed K, Weinrib R, Browne EN, Manenzhe K, et al. The Tablets, Ring, Injections as Options (TRIO) study: what young African women chose and used for future HIV and pregnancy prevention. J Int AIDS Soc 2018;21(3):e25094. doi: 10.1002/jia2.25094.
41. Malcolm RK, Edwards KL, Kiser P, Romano J, Smith TJ. Advances in microbicide vaginal rings. Antiviral Res 2010;88(1):S30–9 Suppl. doi: 10.1016/j.antiviral.2010.09.003.
42. Roumen FJ, Apter D, Mulders TM, Dieben TO. Efficacy, tolerability and accept- ability of a novel contraceptive vaginal ring releasing etonogestrel and ethinyl estradiol. Hum Reprod 2001;16(3):469–75. doi: 10.1093/humrep/16.3.469.
43. SperoffL.Efficacy and tolerability of an estradiol vaginal ring for relief of menopausal symptoms. Obstet Gynecol 2003;102(4):823–34. doi: 10.1016/ s0 029-7844(03)0 0764-6.
44. IPM's Dapivirine Ring for Women's HIV Prevention Receives WHO Pre- qualification [press release], Silver Spring, MD, USA: IPM 2020; November 30 2020.
45. Palmeira-de-Oliveira R, Duarte P, Palmeira-de-Oliveira A, das Neves J, Ama- ral MH, Breitenfeld L, et al. Women's experiences, preferences and perceptions regarding vaginal products: Results from a cross-sectional web-based survey in Portugal. Eur J Contracept Reprod Health Care 2015;20(4):259–71. doi: 10.3109/13625187.2014.980501.
46. Mishell DR Jr, Lumkin ME. Contraceptive effect of varying dosages of progestogen in silastic vaginal rings. Fertil Steril 1970; 21: 99–103.