# Acne Management in Polycystic Ovary Syndrome

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**Abstract**

Polycystic ovary syndrome (PCOS) is one of the most common endocrine and metabolic conditions in childbearing women. Polycystic ovary syndrome (PCOS) is characterized by hyperandrogenism, ovulatory dysfunction, and morphology of polycystic ovaries. Clinical signs of hyperandrogenism include hirsutism, acne, and alopecia. Acne is a chronic, inflammatory disease of the pilosebaceous unit that may have a severe impact on an individual's life. The objective of this review is to highlight the treatment options for female patients with acne associated with PCOS. The selection of treatment is dependent on multiple fac¬tors including the patient's age, clinical presenta¬tion medication history, pregnancy, and patient preference



**Acne Management in Polycystic Ovary Syndrome (Review article)**

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**Disclosures**

None of the authors have any conflict of interest.

**ABSTRACT:**

**Background**

Polycystic ovary syndrome (PCOS) is one of the most common endocrine and metabolic conditions in childbearing women. PCOS is characterized by hyperandrogenism, ovulatory dysfunction, and morphology of polycystic ovaries. Clinical signs of hyperandrogenism include hirsutism, acne, and alopecia. Acne is a

chronic, inflammatory disease of the pilosebaceous unit that may have a severe impact on an individual's life.

**Aim**

The aim of this review is to highlight the treatment options for female patients with acne associated with PCOS.

**Methods**

PubMed, Embase, and Cochrane databases were searched for acne management in polycystic ovary syndrome based on related keywords. Data were collected from 2003-2020

**Results**

Hormonal contraceptives are first-line therapy for treating acne associated with PCOS either as monotherapy or combined with standard topical acne therapy. Spironolactone, oral antibiotics, and metformin as second-line medications, and Isotretinoin for severe and refractory acne.

**Conclusions**

According to a multitude of studies, different treatment approaches can be used in the treatment of acne associated with PCOS.

Keywords: Polycystic ovary syndrome, diagnosis; acne management.

**Review Criteria**

Review Criteria: the review article will detail the following: (1) review the pathophysiology of polycystic ovary syndrome and acne in PCOS patients, (2) review diagnosis of polycystic ovary syndrome, (3) review acne management, and (4) best management practices.

**Message for the clinic**

Since PCOS is a multifactorial and a complex endocrine disorder, acne associated with PCOS can be managed by different treatment approaches. The selection of treatment is dependent on multiple factors including the patient's age, clinical presentation, medication history, pregnancy, and patient preference.

## INTRODUCTION

Polycystic ovary syndrome (PCOS) is a prevalent endocrinopathy that affects 8–13% of reproductive age women (1). it is characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovaries (2). These women have a higher incidence of developing complications such as type II diabetes, obesity, hypertension, dyslipidemia, and cardiovascular system diseases(3). Moreover, PCOS has a psychological impact with increased depression and anxiety that can result in worsening of quality of life for these patients (4). The exact mechanism underlying PCOS is unclear (5). The genetic contribution to PCOS remains uncertain, and no particular environmental factor has been identified as causing PCOS (6). Women with PCOS is characterized by high plasma level of ovarian and adrenal androgens, abnormal gonadotropin secretion, reduced serum levels of sex hormone-binding globulin (SHBG), and often high serum level insulin (7), as a result of insulin resistance (8). Obesity is a comorbidity that may intensify the effects of PCOS (9).

## METHODS

A comprehensive search of international literature was conducted mainly in PubMed, and other databases including Embase, and Cochrane using the terms polycystic ovary syndrome, diagnosis of polycystic ovary syndrome, acne management, acne management in PCOS, hormonal therapy for acne, acne vulgaris treatment, and metformin treatment in acne. The search included original studies, review article, and evidence-based guidelines between 2003-2020

## DIAGNOSIS OF POLYCYSTIC OVARY SYNDROME

According to the Rotterdam 2003 criteria, diagnosis requires the presence of at least two of the following three findings: hyperandrogenism, ovulatory dysfunction, and polycystic ovaries (10). The National Institutes of Health (NIH) in 1990 recommended hyperandrogenemia and oligo-anovulation as the two criteria that are required to diagnose PCOS (11). While in 2009, Androgen Excess and PCOS Society (AE-PCOS) concluded that PCOS should be based only on clinical or biochemical hyperandrogenism, and ovarian dysfunction (12). In 2012, NIH Consensus (NIH and ESHRE/ASRM) recommended broader wider Rotterdam/ESHRE/ASRM 2003 criteria with detailed PCOS phenotype of all PCOS, owing to controversies among diagnostic criteria (13). Two of the three criteria (hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology) are required for diagnosis. In addition, each case has to classify categorize into a specific definite phenotype as Phenotype A: hyperandrogenism + ovulatory dysfunction + polycystic ovarian morphology; Phenotype B: hyperandrogenism + ovulatory dysfunction; Phenotype C: hyperandrogenism + polycystic ovarian morphology; and Phenotype D: ovulatory dysfunction + polycystic ovarian morphology (14, 15).

## ACNE

Acne is one of the cutaneous manifestations of PCOS, around 85% of individuals between 12 and 24 years are reported to have acne (16). Most women with PCOS show facial acne lesions and up to 50% of women affect the neck, chest, and upper back (17). The leading cause of acne is excessive ovarian and/or adrenal androgen secretion (18, 19). Most women with PCOS have high plasma concentrations of androgens (20). Androstenedione and testosterone are markers of ovarian androgen secretion (21, 22), and dehydroepiandrosterone sulfate is the indicator of adrenal secretion (23). The insulin resistance and hyperinsulinemia appear to be a significant factor in triggering hyperandrogenaemia, acting directly to produce excessive androgen by ovarian theca cells (24). Androgens results in overproduction of the sebum causing abnormal keratinization resulting in comedones formation (25). Additional colonization of the follicles by Propionibacterium acnes (P acne) leads to inflammation and later formation of papules, pustules, nodules, cysts, and scarring (26). Acne formation is likely more dependent on local androgen concentrations and sensitivity of androgen receptors on the sebaceous glands to androgens, which is independent of circulating levels (27, 28).

## ACNE MANAGEMENT

### Hormonal Contraceptives

Combined oral contraceptives (COCs) are first-line treatment for acne in women with PCOS (2, 27). COCs consist of ethinyl estradiol and a progestational agent, the estrogen suppresses the luteinizing hormone, increases SHBG, and decreases ovarian androgen production, which eventually diminishes the free testosterone that is responsible for acne (29). Certain types of progestins have more potent antiandrogenic properties and are more effective in treating acne (30).

The commonly used COCPs are desogestrel/ethinylestradiol, drospirenone/ethinylestradiol, and cyproterone acetate/ ethinylestradiol (31). However, due to the risk of adverse effects like venous thromboembolism, cyproterone acetate/ ethinylestradiol must not be considered as a first-line in PCOS (32).

Side effect:

Headaches, nausea, weight gain, and breast tenderness (33). The major possible vascular associations include myocardial infarction, venous thromboembolism (34), and cerebrovascular accident in women with a history of smoking, obesity, hypertension and age 35 years or older (35-37).

### Spironolactone

It is an oral aldosterone antagonist and potassium-sparing diuretic having blocker action on androgen receptor and 5-alpha reductase inhibitor activity (38). It is the most effective antiandrogenic agent for acne (13). Spironolactone has been used to manage acne in women with PCOS as an alternative to oral isotretinoin and COCs (39). It has been found that spironolactone in conjunction with COCPs improved acne by 50% (35). The recommended daily dose is 50 mg to 200 mg daily (11); however, it is usually best to start at 50

mg daily and increase to 100 mg daily if clinical response is not adequate after 2 to 3 months (33). Low doses of 25 mg twice daily or 25 mg daily may be adequate for some women (40).

Side effect:

Headache, breast tenderness, fatigue, dizziness and menstrual irregularity (minimized by concurrent COCs use) (41). Uncommon side effects were postural hypotension, depression, diarrhea, muscle pain, increased appetite, drowsiness, polydipsia, and palpitations (42). Rare side effects include hyperkalemia, increased in elderly patients and patients with renal impairment or diabetes (43).

**Oral Isotretinoin**

Oral isotretinoin suppresses sebum secretion, inhibits cell proliferation, inhibits bacterial proliferation, controls the formation of microcomedones, normalizes keratinization and reduces the formation of lesions and comedones, and it may have anti-infammatory effect (44, 45). In patients whose acne is severe and refractory to oral antibiotics, COCs, and spironolactone, isotretinoin use should be considered (42). Isotretinoin treatment may be beneficial in patients with severe cystic acne who are not able of using COCs (46).

Side effect

The most common side effects of oral isotretinoin are dry mucous membranes, dry skin, dry lip, dry eyes, and nose bleed (47). The most important side effects are increased levels of total cholesterol, serum triglycerides and liver enzymes (48). In women of childbearing age, oral contraceptives should be used during and for one month after therapy to avoid pregnancy because of the teratogenicity effect of oral Isotretinoin (49).

**Flutamide**

Flutamide is an anti-androgenic that blocks androgens by competitive inhibition of receptors, reducing androgen synthesis (50). A combination of flutamide and COCs improved acne by 80% (35). Flutamide at low dosage of 62.5 mg daily or 1 mg/kg/day seems to be a safe and effective for treating acne in women (51). Side effects include breast tenderness, gastrointestinal upset, insomnia, and fatigue (52, 53).

**Oral Antibiotic**

Antibiotics are effective for inflammatory acne because of their antibiotic activity and anti-inflammatory effects (54). It is recommended to use oral antibiotics as second-line therapy for short-term management and as an adjunctive treatment when hormonal therapies alone are inadequate (42). Tetracyclines, mainly doxycycline and minocycline, are the most commonly prescribed agents (55). Macrolides such as azithromycin are commonly used when tetracyclines are not tolerated or contraindicated (56). Monotherapy with oral antibiotics should be avoided to reduce the development of antibiotic-resistant Propionibacterium acnes (P acne), and limit the treatment to 3-6 months (57). Trimethoprim/sulfamethoxazole, penicillins, and cephalosporins have evidence support their efficacy to use for acne (44, 58).

Side effect

The common side effect of tetracyclines include gastrointestinal tract disturbances and photosensitivity reactions (59). The macrolides, penicillins, and cephalosporins are also associated with increased gastrointestinal disturbances (56).

**Insulin Sensitizers**

Metformin is a biguanide hypoglycemic drug that improves insulin sensitivity and decreases insulin levels which corrects ovarian and functional adrenal hyperandrogenism in PCOS (60). It is effective as adjunct therapy in the treatment of moderate-to-severe acne (61). Initial dose is 850 mg and may titrate up to 2,000 mg daily, and it should be discontinued in 6 months if no improvement is seen (62).

Side effect

Diarrhea, nausea, abdominal discomfort, anorexia are the most common side effect (63). While, vitamin B12 deficiency with the long term use of metformin (64).

**Topical therapy:**

Standard topical acne therapy (e.g., retinoids, antibiotics, benzoyl peroxide) is used in acne associated with PCOS as adjunctive therapy with COCs (Table 1) (2).

**Table 1: Topical preparations**

| | **Dosage Forms** | **Frequency of use** |
|---|---|---|
| **Topical Retinoid** | **Topical Retinoid** | **Topical Retinoid** |
| Tretinoin | Cream 0.1%, 0.05%, 0.02%, 0.025% Gel 0.1%, 0.05%, 0.025% Liquid 0.05% Lotion 0.05% Microsphere gel 0.1%, 0.04%, 0.06%, 0.08% | Apply once daily at evening time |
| Tazarotene | Cream 0.1% and 0.05% Gel 0.1% and 0.05% Foam 0.1% | |
| Adapalene | Cream, Gel, and Lotion (0.1%) Adapalene 0.1%/benzoyl peroxide 2.5% gel Adapalene 0.3%-benzoyl peroxide 2.5% gel | |
| **Topical antibacterial** | **Topical antibacterial** | **Topical antibacterial** |
| Erythromycin | Ointment, Pads, Gel (2%) | Apply twice daily |
| Clindamycin | Gel, Lotion , Solution, Swab (1%) | Apply twice daily |
| Benzoyl peroxide | Cream 2.5%, 5.5%, 6%,7%,10% Gel 2.5%, 4%, 5%,8%,10% Foam 5.3%, 5.5%, 9.5% Cleansers 2.6% | Topical formulation apply once daily Topical Cleansers apply once or twice daily |
| **Combination Topical antibacterial** | **Combination Topical antibacterial** | **Combination Topical antibacterial** |
| Benzoyl peroxide and clindamycin | Benzoyl peroxide 2.5 %-clindamycin 1.2% Benzoyl peroxide 3.75%-clindamycin 1.2% Benzoyl peroxide 5%-clindamycin 1% Benzoyl peroxide 5%-clindamycin 1.2% | Apply once daily Apply once daily Apply twice daily Apply once daily |
| Benzoyl peroxide and erythromycin | Gel 3%, 5% | Apply twice daily |

*Retinoids*

*Retinoids*control the formation of microcomedones, decrease the formation of lesions and existing comedones, decrease sebum production and normalize keratinization. Moreover, they may also demonstrate anti-inflammatory properties (65, 66). Different topical preparations are available such as creams, gels, foams, solutions, and lotions in a wide range of concentrations (67). Topical retinoids are associated with skin dryness, erythema, and pain, and may exacerbate dermatitis or eczema (67). Daily sunscreen use is recommended due to increased sun-sensitivity and is best used in the evening (68). Limited use of topical retinoids during pregnancy because of the known teratogenic effect of similar oral retinoids (69).

**Benzoyl peroxide**

It has Antibacterials and mild minor comedolytic activity (70). It is considered the recommended topical antimicrobial of choice because it limits the possibility of microbial resistance (71). Benzoyl peroxide is as effective as oral antibiotics and is superior to topical tretinoin for inflammatory lesions (72). Drying and irritation is the common side effects (73).

**Erythromycin and clindamycin**

In addition to their antibiotic activity against P acnes, they have indirect anti-inflammatory effects (66, 73). Concomitant use of Benzoyl peroxide is recommended to increase efficacy and decrease the development of resistant P acnes bacteria (74). All of the topical antibiotics can cause local irritation (75).

**Others:**

Scarring is an undesirable complication of acne, which has negative effects on the quality of life in addition to depression (76). Dermocosmetics, dermabrasion, laser or light therapy or cosmetic surgery are considered as adjuvant therapies for acne and scarring (77, 78).

**Conclusions**

Acne is common in patients with PCOS. Hormonal contraceptives are first-line therapy for treating acne associated with PCOS and can be used in conjunction with standard topical acne therapy or as monotherapy. Spironolactone, oral antibiotics, and metformin can be either added as second-line medications when hormonal therapies alone are insufficient. Isotretinoin can be considered when acne is severe and refractory to COCs, oral antibiotics, and spironolactone.

**Author Contributions**

All authors have made a significant contribution to the manuscript, the study complies with ethical standards.

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**REFERENCES**

1. Teede HJ, Misso ML, Boyle JA, Garad RM, McAllister V, Downes L, et al. Translation and implementation of the Australian-led PCOS guideline: clinical summary and translation resources from the International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. Med J Aust. 2018;209(S7):S3-S8.

2. Williams T, Mortada R, Porter S. Diagnosis and Treatment of Polycystic Ovary Syndrome. Am Fam Physician. 2016;94(2):106-13.

3. ACOG Practice Bulletin No. 194: Polycystic Ovary Syndrome. Obstet Gynecol. 2018;131(6):e157-e71.

4. Wang Y-Y, Li S-W, Luo S, Qin L, Zeng X, Li L, et al. How to Evaluate Acne in Reproductive-Age Women: An Epidemiological Study in Chinese Communities. Biomed Res Int. 2019;2019:6126808-.

5. Advani K, Batra M, Tajpuriya S, Gupta R, Saraswat A, Nagar HD, et al. Efficacy of combination therapy of inositols, antioxidants and vitamins in obese and non-obese women with polycystic ovary syndrome: an observational study. J Obstet Gynaecol. 2020;40(1):96-101.

6. Crespo RP, Bachega TASS, Mendonça BB, Gomes LG. An update of genetic basis of PCOS pathogenesis. Arch Endocrinol Metab. 2018;62(3):352-61.

7. Podfigurna A, Meczekalski B, Petraglia F, Luisi S. Clinical, hormonal and metabolic parameters in women with PCOS with different combined oral contraceptives (containing chlormadinone acetate versus drospirenone). J Endocrinol Invest. 2019:10.1007/s40618-019-01133-3.

8. Moghetti P. Insulin Resistance and Polycystic Ovary Syndrome. Curr Pharm Des. 2016;22(36):5526-34.

9. Glueck CJ, Goldenberg N. Characteristics of obesity in polycystic ovary syndrome: Etiology, treatment, and genetics. Metabolism. 2019;92:108-20.

10. Goodman NF, Cobin RH, Futterweit W, Glueck JS, Legro RS, Carmina E, et al. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS, AMERICAN COLLEGE OF ENDOCRINOLOGY, AND ANDROGEN EXCESS AND PCOS SOCIETY DISEASE STATE CLINICAL REVIEW: GUIDE TO THE BEST PRACTICES IN THE EVALUATION AND TREATMENT OF POLYCYSTIC OVARY SYNDROME–PART 1. Endocr Pract. 2015;21(11):1291-300.

11. Azziz R. Controversy in clinical endocrinology: diagnosis of polycystic ovarian syndrome: the Rotterdam criteria are premature. J Clin Endocrinol Metab. 2006;91(3):781-5.

12. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril. 2009;91(2):456-88.

13. Gainder S, Sharma B. Update on Management of Polycystic Ovarian Syndrome for Dermatologists. Indian Dermatol Online J. 2019;10(2):97-105.

14. Witchel SF, Oberfield SE, Peña AS. Polycystic Ovary Syndrome: Pathophysiology, Presentation, and Treatment With Emphasis on Adolescent Girls. J Endocr Soc. 2019;3(8):1545-73.

15. Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. Fertil Steril. 2016;106(1):6-15.

16. Bienenfeld A, Azarchi S, Lo Sicco K, Marchbein S, Shapiro J, Nagler AR. Androgens in women: Androgen-mediated skin disease and patient evaluation. J Am Acad Dermatol. 2019;80(6):1497-506.

17. Hacivelioglu S, Gungor ANC, Gencer M, Uysal A, Hizli D, Koc E, et al. Acne severity and the Global Acne Grading System in polycystic ovary syndrome. Int J Gynaecol Obstet. 2013;123(1):33-6.

18. Lizneva D, Gavrilova-Jordan L, Walker W, Azziz R. Androgen excess: Investigations and management. Best Pract Res Clin Obstet Gynaecol. 2016;37:98-118.

19. Rocha MA, Bagatin E. Skin barrier and microbiome in acne. Arch Dermatol Res. 2018;310(3):181-5.

20. Rosenfield RL, Ehrmann DA. The Pathogenesis of Polycystic Ovary Syndrome (PCOS): The Hypothesis of PCOS as Functional Ovarian Hyperandrogenism Revisited. Endocr Rev. 2016;37(5):467-520.

21. Witchel SF, Burghard AC, Tao RH, Oberfield SE. The diagnosis and treatment of PCOS in adolescents: an update. Curr Opin Pediatr. 2019;31(4):562-9.

22. Franik G, Bizoń A, Włoch S, Kowalczyk K, Biernacka-Bartnik A, Madej P. Hormonal and metabolic aspects of acne vulgaris in women with polycystic ovary syndrome. Eur Rev Med Pharmacol Sci. 2018;22(14):4411-8.

23. Kyritsi EM, Dimitriadis GK, Kyrou I, Kaltsas G, Randeva HS. PCOS remains a diagnosis of exclusion: a concise review of key endocrinopathies to exclude. Clin Endocrinol (Oxf). 2017;86(1):1-6.

24. Pasquali R. Contemporary approaches to the management of polycystic ovary syndrome. Ther Adv Endocrinol Metab. 2018;9(4):123-34.

25. Tan J, Boyal S, Desai K, Knezevic S. Oral Isotretinoin: New Developments Relevant to Clinical Practice. Dermatol Clin. 2016;34(2):175-84.

26. Al-Talib H, Al-Khateeb A, Hameed A, Murugaiah C. Efficacy and safety of superficial chemical peeling in treatment of active acne vulgaris. An Bras Dermatol. 2017;92(2):212-6.

27. Swerdloff RS, Dudley RE, Page ST, Wang C, Salameh WA. Dihydrotestosterone: Biochemistry, Physiology, and Clinical Implications of Elevated Blood Levels. Endocr Rev. 2017;38(3):220-54.

28. Makrantonaki E, Ganceviciene R, Zouboulis C. An update on the role of the sebaceous gland in the pathogenesis of acne. Dermatoendocrinol. 2011;3(1):41-9.

29. Morgante G, Massaro MG, Di Sabatino A, Cappelli V, De Leo V. Therapeutic approach for metabolic disorders and infertility in women with PCOS. Gynecol Endocrinol. 2018;34(1):4-9.

30. Powell A. Choosing the Right Oral Contraceptive Pill for Teens. Pediatr Clin North Am. 2017;64(2):343-58.

31. Jin P, Xie Y. Treatment strategies for women with polycystic ovary syndrome. Gynecol Endocrinol. 2018;34(4):272-7.

32. 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. Fertil Steril. 2018;110(3):364-79.

33. Del Rosso JQ, Harper JC, Graber EM, Thiboutot D, Silverberg NB, Eichenfield LF. Status report from the American Acne & Rosacea Society on medical management of acne in adult women, part 3: oral therapies. Cutis. 2015;96(6):376-82.

34. Roach REJ, Helmerhorst FM, Lijfering WM, Stijnen T, Algra A, Dekkers OM. Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. Cochrane Database Syst Rev. 2015;2015(8):CD011054-CD.

35. Bitzer J, Römer T, Lopes da Silva Filho A. The use of cyproterone acetate/ethinyl estradiol in hyperandrogenic skin symptoms - a review. Eur J Contracept Reprod Health Care. 2017;22(3):172-82.

36. Calhoun AH. Hormonal Contraceptives and Migraine With Aura-Is There Still a Risk? Headache. 2017;57(2):184-93.

37. Calhoun AH, Batur P. Combined hormonal contraceptives and migraine: An update on the evidence. Cleve Clin J Med. 2017;84(8):631-8.

38. Lessner E, Fisher S, Kobraei K, Osleber M, Lessner R, Elliott L, et al. Spironolactone and topical retinoids in adult female cyclical acne. J Drugs Dermatol. 2014;13(2):126-9.

39. Basu P, Elman SA, Abudu B, Beckles A, Salian P, Yanes DA, et al. High-dose spironolactone for acne in patients with polycystic ovarian syndrome: a single institution retrospective study. J Am Acad Dermatol. 2019:S0190-9622(19)32497-1.

40. Chaudhary M, Chaudhary M. A REVIEW ON TREATMENT OPTIONS FOR ACNE VULGARIS. WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES. 2016;5:524-45.

41. Layton AM, Eady EA, Whitehouse H, Del Rosso JQ, Fedorowicz Z, van Zuuren EJ. Oral Spironolactone for Acne Vulgaris in Adult Females: A Hybrid Systematic Review. Am J Clin Dermatol. 2017;18(2):169-91.

42. Buzney E, Sheu J, Buzney C, Reynolds RV. Polycystic ovary syndrome: a review for dermatologists: Part II. Treatment. J Am Acad Dermatol. 2014;71(5):859.e1-74.

43. Lainscak M, Pelliccia F, Rosano G, Vitale C, Schiariti M, Greco C, et al. Safety profile of mineralocorticoid receptor antagonists: Spironolactone and eplerenone. Int J Cardiol. 2015;200:25-9.

44. Zaenglein AL, Pathy AL, Schlosser BJ, Alikhan A, Baldwin HE, Berson DS, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016;74(5):945-73.e33.

45. Zouboulis CC, Bettoli V. Management of severe acne. Br J Dermatol. 2015;172 Suppl 1:27-36.

46. Acmaz G, Cınar L, Acmaz B, Aksoy H, Kafadar YT, Madendag Y, et al. The Effects of Oral Isotretinoin in Women with Acne and Polycystic Ovary Syndrome. Biomed Res Int. 2019;2019:2513067-.

47. Mirnezami M, Rahimi H. Is Oral Omega-3 Effective in Reducing Mucocutaneous Side Effects of Isotretinoin in Patients with Acne Vulgaris? Dermatol Res Pract. 2018;2018:6974045-.

48. Brzezinski P, Borowska K, Chiriac A, Smigielski J. Adverse effects of isotretinoin: A large, retrospective review. Dermatol Ther. 2017;30(4):10.1111/dth.12483.

49. Dathe K, Schaefer C. Drug safety in pregnancy: the German Embryotox institute. Eur J Clin Pharmacol. 2018;74(2):171-9.

50. Mendoza FJ, Serrano-Rodriguez JM, Buzon-Cuevas A, Perez-Ecija A. Pharmacokinetics of the anti-androgenic drug flutamide in healthy stallions. Vet J. 2017;224:50-4.

51. Husein-ElAhmed H. Management of acne vulgaris with hormonal therapies in adult female patients. Dermatol Ther. 2015;28(3):166-72.

52. Elsaie ML. Hormonal treatment of acne vulgaris: an update. Clin Cosmet Investig Dermatol. 2016;9:241-8.

53. Bednarska S, Siejka A. The pathogenesis and treatment of polycystic ovary syndrome: What's new? Adv Clin Exp Med. 2017;26(2):359-67.

54. Alexis A, Del Rosso JQ, Desai SR, Downie JB, Draelos ZD, Feser C, et al. BPX-01 Minocycline Topical Gel Shows Promise for the Treatment of Moderate-to-severe Inflammatory Acne Vulgaris. J Clin Aesthet Dermatol. 2018;11(11):25-35.

55. Del Rosso JQ. Oral Doxycycline in the Management of Acne Vulgaris: Current Perspectives on Clinical Use and Recent Findings with a New Double-scored Small Tablet Formulation. J Clin Aesthet Dermatol. 2015;8(5):19-26.

56. Tan AU, Schlosser BJ, Paller AS. A review of diagnosis and treatment of acne in adult female patients. Int J Womens Dermatol. 2017;4(2):56-71.

57. Barbieri JS, Hoffstad O, Margolis DJ. Duration of oral tetracycline-class antibiotic therapy and use of topical retinoids for the treatment of acne among general practitioners (GP): A retrospective cohort study. J Am Acad Dermatol. 2016;75(6):1142-50.e1.

58. Farrah G, Tan E. The use of oral antibiotics in treating acne vulgaris: a new approach. Dermatol Ther. 2016;29(5):377-84.

59. Gollnick H. Current concepts of the pathogenesis of acne: implications for drug treatment. Drugs. 2003;63(15):1579-96.

60. Sharma S, Mathur DK, Paliwal V, Bhargava P. Efficacy of Metformin in the Treatment of Acne in Women with Polycystic Ovarian Syndrome: A Newer Approach to Acne Therapy. J Clin Aesthet Dermatol. 2019;12(5):34-8.

61. Lee JK, Smith AD. Metformin as an adjunct therapy for the treatment of moderate to severe acne vulgaris. Dermatol Online J. 2017;23(11):13030/qt53m2q13s.

62. Robinson S, Kwan Z, Tang MM. Metformin as an adjunct therapy for the treatment of moderate to severe acne vulgaris: A randomized open-labeled study. Dermatol Ther. 2019;32(4):e12953-e.

63. Bonnet F, Scheen A. Understanding and overcoming metformin gastrointestinal intolerance. Diabetes Obes Metab. 2017;19(4):473-81.

64. Li Y, Tan J, Wang Q, Duan C, Hu Y, Huang W. Comparing the individual effects of metformin and rosiglitazone and their combination in obese women with polycystic ovary syndrome: a randomized controlled trial. Fertil Steril. 2020;113(1):197-204.

65. Fox L, Csongradi C, Aucamp M, du Plessis J, Gerber M. Treatment Modalities for Acne. Molecules. 2016;21(8):1063.

66. Sacchidanand SA, Lahiri K, Godse K, Patwardhan NG, Ganjoo A, Kharkar R, et al. Synchronizing Pharmacotherapy in Acne with Review of Clinical Care. Indian J Dermatol. 2017;62(4):341-57.

67. Latter G, Grice JE, Mohammed Y, Roberts MS, Benson HAE. Targeted Topical Delivery of Retinoids in the Management of Acne Vulgaris: Current Formulations and Novel Delivery Systems. Pharmaceutics. 2019;11(10):490.

68. Marson JW, Baldwin HE. An Overview of Acne Therapy, Part 1: Topical therapy, Oral Antibiotics, Laser and Light Therapy, and Dietary Interventions. Dermatol Clin. 2019;37(2):183-93.

69. Veraldi S, Rossi LC, Barbareschi M. Are topical retinoids teratogenic? G Ital Dermatol Venereol. 2016;151(6):700-5.

70. Cong T-X, Hao D, Wen X, Li X-H, He G, Jiang X. From pathogenesis of acne vulgaris to anti-acne agents. Arch Dermatol Res. 2019;311(5):337-49.

71. Leyden J, Stein-Gold L, Weiss J. Why Topical Retinoids Are Mainstay of Therapy for Acne. Dermatology and therapy. 2017;7(3):293-304.

72. Lynn DD, Umari T, Dunnick CA, Dellavalle RP. The epidemiology of acne vulgaris in late adolescence. Adolesc Health Med Ther. 2016;7:13-25.

73. McKeage K, Keating GM. Clindamycin/benzoyl peroxide gel (BenzaClin): a review of its use in the management of acne. Am J Clin Dermatol. 2008;9(3):193-204.

74. Austin BA, Fleischer AB, Jr. The extinction of topical erythromycin therapy for acne vulgaris and concern for the future of topical clindamycin. J Dermatolog Treat. 2017;28(2):145-8.

75. Tripathi SV, Gustafson CJ, Huang KE, Feldman SR. Side effects of common acne treatments. Expert Opin Drug Saf. 2013;12(1):39-51.

76. Haroon MZ, Alam A, Ullah I, Ali R, Taimur MF, Raza K. Quality Of Life And Depression Among Young Patients Suffering From Acne. J Ayub Med Coll Abbottabad. 2019;31(3):436-40.

77. Escobar-Morreale HF. Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. Nat Rev Endocrinol. 2018;14(5):270-84.

78. Cooper AJ, Harris VR. Modern management of acne. Med J Aust. 2017;206(1):41-5.