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 factors including the patient’s age, clinical presentation, 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-inflammatory 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**

<table>
<thead>
<tr>
<th>Topical Retinoid</th>
<th>Dosage Forms</th>
<th>Frequency of use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tretinoin</td>
<td>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%</td>
<td>Apply once daily at evening time</td>
</tr>
<tr>
<td>Tazarotene</td>
<td>Cream 0.1% and 0.05% Gel 0.1% and 0.05% Foam 0.1%</td>
<td></td>
</tr>
<tr>
<td>Adapalene</td>
<td>Cream, Gel, and Lotion (0.1%) Adapalene 0.1%/benzoyl peroxide 2.5% gel Adapalene 0.3%-benzoyl peroxide 2.5% gel</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Topical antibacterial</th>
<th>Dosage Forms</th>
<th>Frequency of use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin</td>
<td>Ointment, Pads, Gel (2%)</td>
<td>Apply twice daily</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Gel, Lotion, Solution, Swab (1%)</td>
<td>Apply twice daily</td>
</tr>
<tr>
<td>Benzoyl peroxide</td>
<td>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%</td>
<td>Topical formulation apply once daily Topical Cleansers apply once or twice daily</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Combination Topical antibacterial</th>
<th>Dosage Forms</th>
<th>Frequency of use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoyl peroxide and clindamycin</td>
<td>Benzoil peroxide 2.5 %-clindamycin 1.2% Benzoyl peroxide 3.75%-clindamycin 1.2% Benzoyl peroxide 5%-clindamycin 1% Benzoil peroxide 5%-clindamycin 1.2%</td>
<td>Apply once daily Apply once daily Apply twice daily Apply once daily</td>
</tr>
<tr>
<td>and erythromycin</td>
<td>Gel 3%, 5%</td>
<td>Apply twice daily</td>
</tr>
</tbody>
</table>

**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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