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TREATING ADULT FEMALE ACNE

Adult female acne (AFA) is a common and challenging condition to treat, often resistant to conventional acne treatments. AFA is a type of hormonal acne that affects women, typically peaking in the 20s and slowly declining with age. A 2015 survey documenting the self-reported prevalence of acne in 540 adult females showed that 50.9% of women in their 20s, 35.2% of women in their 30s, 26.3% of women in their 40s and 15.3% of women in their 50s are affected.[1] A 1997 article in the *British Journal of Dermatology* elucidated the increasingly common phenomenon of acne in adults older than 25 years of age and reported that approximately 75% of women (mean age = 35.5 years) report acne as being continuous or intermittent from adolescence while 18.4% report no history of adolescent acne.[2]

While AFA can affect any area on the face and upper body, it typically occurs in a u-shaped pattern on the lower cheeks, jawline and neck. It is characterized by inflammatory papules and cysts as well as comedones. Patients often complain of facial cysts that fail to come to a head, are painful, last for months and resolve with longstanding dyspigmentation. Sequelae are similar to adolescent acne and can involve scarring (20%), post-inflammatory pigmentary change and even depression (10%).[1]

Although the diagnosis of AFA is usually quite straightforward for the dermatologist, the management can be challenging. These patients are characterized by failure with standard topical therapies and disease recurrence after repeat courses of antibiotics and isotretinoin. As well, hormonal intrauterine devices (IUDs) and certain birth control pills can exacerbate or trigger the acne.

Of the four pathogenic factors causing acne: abnormal follicular keratinization, *cutibacterum acnes* colonization (previously known as *proprionibacterium acnes*), inflammatory events, and hormones; the hormonal element is the predominant causative factor in AFA. The sebaceous glands are androgen dependent. Androgens and end organ receptor sensitivity are responsible for gland activity and the resultant acne. Progesterones have varying degrees of androgenicity, and the degree of androgenicity plays a significant role in AFA.[3]

Successful disease management of AFA centers on the targeting of hormones. This includes using combined oral contraceptive pills (COC) and/or spironolactone. Topical agents should be used for optimization of therapy. Topical retinoids are often used for treating the comedomal aspect of AFA, and have been shown to help with post-inflammatory pigmentation and scarring, in addition to the anti-aging benefit many women in this age group seek. Efficacy in AFA has also been demonstrated for clindamycin-retinoid and benzoyl peroxide-retinoid combination gels. Additionally, dapsone 5% gel has shown efficacy in women with AFA, as has azelaic acid 15% gel, which has the added benefit in this patient population of being safe for women of child-bearing age and/or those who are pregnant.[2]

All COC pills have a net antiandrogen effect; however, they do not all have the same efficacy with respect to the treatment of acne. COCs contain the estrogen ethinyl estradiol (EE) which increases levels of sex hormone-binding globulin, resulting in lower levels of free testosterone.

Progesterones, which vary significantly in content by COC, are divided into 4 generations based on their androgenicity (**Figure 1**).[4] The first generation progesterones, such as norethindrone, have a marked intrinsic androgen effect, which worsens acne. This type of progesterone is found in many commonly-prescribed COCs and is also found in the 'minipill' which is progesterone-only, without the added anti-androgen benefit of estrogen. All of these first generation treatment options tend to worsen or trigger acne in women. Clinicians may be interested to learn that some commonly used treatments to abate menopausal symptoms, such as patches and tablets, contain estrogen in combination with norethindrone and can trigger or exacerbate acne in this older population of women.

Second generation progesterones such as levonorgestrel and norgestrel have varying androgenic effects and variable effects on acne. These progesterones are found in commonly prescribed COCs. While these commonly prescribed COCs (and their generic equivalents) are approved for both contraception and acne, they are not as effective at treating acne as COCs containing more anti-androgenic progesterones.[5]

Levonorgestrel is also the progesterone found in all currently available hormonal IUDs. These IUDs do not contain estrogen. The rates of acne demonstrated with these agents ranges from 1-10% and, in some instances, greater than 10% based on the data found in their Health Canada approved product monographs.[6] Retrospective studies have shown increased acne exacerbation with levonorgestrel containing IUDs than with COCs.[7,8] Additionally, a small survey of 51 respondents on levonorgestrel containing IUDs showed that there was significant

Generations of Progesterone and Treatment of Acne	
1st Generation-marked intrinsic androgenic effect • metabolize to norethindrone (such as Lolo, Ortho, Demulen) • Micronor, Depo-provera • Menopausal treatments (such as Estralis, Activella)	Worsen/cause acne
2nd Generation- varying androgenic effect • Norgestrel/levonorgestrel (Ovral, Triphasil, Seasonalle, Alesse, Alysena, Triquilar) • Also IUD's Mirena, Kylena	May or may not worsen/cause acne
3rd Generation - Least androgenic • Desogestrel, norgestimate, gestodene (Marvelon, Tricyclen, Linessa, Cyclen) • Etonogestrel in Nuvaring (related to desogetrel) • Norelgestromin in Evra Patch	Effectively treat acne

Synthetic Progestins- Antiandrogenic
• Cyproterone acetate: inhibit 5 alpha reductase and block androgen
  • Diane 35 and generics
• Drospirenone: inhibits ovarian production of androgen and blocks androgen R in skin
  • Yaz, Yasmin and generics
  • Synthetic spironolactone analogue equivalent to ~25 mg spironolactone
	Most effective for treating acne

Figure 1. Generations of progesterone and treatment of acne; adapted from Apgar et al, 2000

(P = .0005) change in acne severity upon IUD placement with 35% of women reporting worsening of acne.[9]

Third generation progesterones such as desogestrel, norgestimate and gestodene are the least androgenic of the first three generations and can be very effective at treating acne and are the progesterones found in commonly prescribed pills and their generic equivalents. In addition, the Evra™ Patch (norelgestromin) and the NuvaRing® (etonogestrel) contain third generation progesterones with estrogen and can be good alternatives for contraception and acne control in those who do not want to take COC.[3,4]

Finally, the fourth generation 'synthetic progesterones' are anti-androgenic and are the most effective for treating acne.[3] These include drospirenone and cyproterone acetate. Drospirenone is a synthetic analogue of spironolactone which is equivalent to about 25 mg of spironolactone[10] and works by blocking both the androgen receptor and inhibiting ovarian androgen production.[10] It is found in combination with EE in commonly-prescribed COCs and their generic equivalents, which are approved for both contraception and acne.

Cyproterone acetate blocks the androgen receptor and inhibits 5 alpha-reductase.[10] This is found in combination with EE in some COCs and their generic equivalents, which are approved for treatment of acne but not for contraception.

The use of COCs is not without risk, including the risk of venous thromboembolic (VTE) events. The risk of VTE in women of reproductive age who are COC non-users is estimated at 4- 5/10,000 women per year (WPY). Women on COCs have been estimated to have an increased risk of 9-10/ 10,000 WPY.[11,12] This risk is felt to be associated with the estrogen more than the progesterone. Additionally, the risk of VTE is higher with COCs containing a higher dose of EE (> 30 mcg). There has been controversy regarding whether there is a slightly increased risk of VTE with COCs using third and fourth (synthetic) generation progesterones.[11,12] Epidemiological studies demonstrate a slight increase in the risk of VTE, but these observational studies do not fully control for confounding in their methodology. Prospective studies, conversely, do not show an increased risk of VTE. The Society of Obstetricians and Gynecologists of Canada (SOGC) states that for cyproterone acetate/ estrogen COC users, the risk of VTE is very low and comparable to that of other combined hormonal contraceptives and that for the majority of women, the benefits outweigh the risks. Similarly, for drospirenone the SOGC suggests that users of COCs should be advised that the highest quality evidence available at this time does not suggest any difference in VTE risk based on the type of progestin in the COC.[11] Additionally, the risk of VTE from COCs is low relative to the risk of VTE in pregnancy (29/10,000 WPY) and post partum (up to 300-400/10,000 WPY).[10-12] When counseling women about the risk of VTE with COCs, it is important to consider relative risks, as well as other risk factors for VTE such as age, polycystic ovary syndrome, obesity, smoking, air travel, surgery, and personal and family history of VTE.[10-12]

Spironolactone is an anti-androgen therapy that acts at the androgen receptor and is also an

Spironolactone drug interactions

- **Amiloride (X - avoid combination)**
- **Bromperidol (X)**
- **Cyclosporine (X)**
- **Triamterene (X)**
- Amifostine, ammonium chloride, cosyntropin, eplerenone, mitotane, obinutuzumab, potassium salts, sodium phosphates (all D- modify regimen)
- Abiraterone, alfuzosin, Alpha/beta agonists, **amphetamines, ACE inhibitors, ARBs, atypical anti-psychotics, ASA, atorvastatin, barbituates**, benperidol, **brimonidine (topical)**, cardiac glycosides, **ciprofloxacin**, cholestyramine, diacerein, diazoxide, **digoxin**, **drospirenone**, duloxetine, **heparin**, some herbs, levodopa, **lithium**, lormetazepam, molsidomine, naftopidil, non-depolarizing neuromuscular blocking agents, nicergoline, nicarandil, **nitrofurantoin**, nitroprusside, **NSAIDs**, **opioids**, **pentoxifylline**, pholcodine, PDE5 inhibitors, prostacyclin, quinagolide, quinidine, tacrolimus (systemic), tolvaptan, trimethoprim, yohimbine, canagliflozin, mianserin, mirabegron, oxymetazoline (topical), protirelin, Vitamin K antagonists (category C- monitor therapy)

Figure 2. Spironolactone drug interactions; adapted from Plavanich et al and Azarchi et al.

antagonist of aldosterone which is used as a potassium-sparing diuretic. While it is approved by Health Canada for the treatment of essential hypertension, edematous conditions, primary hyperaldosteronism and hypokalemia, it is commonly used off-label to treat AFA at doses of 25-200 mg daily (the typical starting dose is 100 mg).[13] New evidence shows that in healthy women less than 50 years of age taking spironolactone for acne, routine potassium monitoring is not necessary as rates of hyperkalemia in the spironolactone-treated population are equivalent to those found in the general population. Potassium monitoring is recommended if there are other risk factors for hyperkalemia such as renal impairment or use of other medications which cause hyperkalemia (**Figure 2**).[14,15] Additionally, while contraindicated in pregnancy, spironolactone is safe in lactation. Intense diuresis can suppress lactation, but this is unlikely to occur with acne dosing.[16] Additionally, large registries have failed to show increased risk of breast cancer previously suggested by early animal studies, supporting the safety of this therapy.[14,15]

The future treatment horizon for AFA includes a new topical androgen receptor inhibitor, clascoterone 1% cream, which will soon be available for clinicians. This topical agent reduces oil in the skin and has demonstrated efficacy in treating both inflammatory and comedomal lesions in patients with moderate-to-severe acne in phase III clinical trials.[17]

Adult female acne is a common entity and a challenging condition to treat, often failing conventional acne treatments. Topical agents alone are rarely effective for AFA but have a role as adjunctive therapy. Anti-androgen COCs, specifically those containing a synthetic progesterone (drospirenone or cyproterone acetate), are the most effective COCs for treating acne, followed by those containing third generation progesterones. First and second generation COCs may not help and can even exacerbate or cause hormonal acne. Hormonal IUDs are also known to induce and worsen acne. Spironolactone is a safe and effective therapy for AFA and can be used with an anti-androgen oral contraceptive pill in a complementary fashion to further improve results.[10]

References:

1. B, Drena. Treatment of adult female acne: a new challenge. JEADV. 2015; 29(supplement 5): 14-19

2. Bagatin, E. et al. Adult female acne: a guide to clinical practice. An Bras Dermatol. 2019;94(1):62-75.

3. Bosanac, S. et al. Progestins and acne vulgaris: a review. Dermatology online journal. 2018; 24(5): 1-6.

4. Apgar, B. et al. Using progestins in clinical practice. Am Fam Physician. 2000; 62(8):1839-1846.

5. Arowojolu, A. et al. Combined oral contraceptive pills for treatment of acne. Cochrane Database of Systematic reviews. July 2012.

6. Mirena and Kylena Drug monographs

7. Lortscher, D. et al. Hormonal contraceptives and Acne. A retrospective analysis of 2147 patients. J Drugs Dermatol. 2016;15(6):670-674

8. Barbieri, JS. Et al. Influence of contraception class on incidence and severity of acne vulgaris. Obstet Gynecol. 2020;135(6):1306-1312

9. Lullo, JJ et al. Incidence of androgenic dermatologic side effects following placement of a levonorgestrel intrauterine device for menorrhagia: A survey-based study. J Am Acad Dermatol. 2018;79(2):364-365.

10. Buzney, E. et al. Polycystic ovarian syndrome, a review for dermatologists. J Am Acad Dermatol. 2014; 71(5):859

11. Reid, R. Et al. Oral Contraceptives and the Risk of Venous Thromboembolism: An Update. SOGC Clinical Practice Guideline. JOGC. 252: 1192-1197

12. Kimball, A. et al. Acne and oral contraceptives. Update on women's health screening guidelines. J Am Acad Dermatol. 2008:58(5); 781-786

13. Garg, V et al. Long term use of sprinolactone for acne in women: a case series of 403 patients. J Am Acad Dermatol. 2021; 84(5):1348-1353

14. Plovanich, M. et al. Low usefulness of potassium monitoring among healthy young women on spironolactone for acne. JAMA Derm. 2015;151(9):941-944

15. Azarchi, S. et al. Androgens in women: Hormone modulating therapies for skin disease. J Am Acad Dermatol. 2018. 80(6); 1509-1520

16. Butler, D. et al. Safety of dermatologic medications in pregnancy and lactation. Part II Lactation. J Am Acad Dermatol. 2014;70(3):417. e2-e10.

17. Herbert, A. et al. Efficacy and safety of topical clascoterone cream, 1%, for treatment of patients with facial acne. Two randomized controlled phase 3 studies. JAMA Derm. 2020:156(6);621-630