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BEST OF ACNE

2017 | TOP CONTENT ON TREATMENT AND PATIENT MANAGEMENT

INTRODUCTION

Acne is one of the top conditions treated by dermatologists and requires an in-depth understanding of pathophysiology, available therapies, and tools for managing patient concerns. *Cutis* serves to educate dermatologists on these areas of acne management through publishing original research, news from American Academy of Dermatology meetings, pearls from Editorial Board members, guideline reports from leading societies, and physician columns on specific topic areas such as Cosmetic Dermatology and Pediatric Dermatology.

This collection consists of our top-accessed content online this year in one convenient file. Topics include hormonal therapies such as oral contraceptives and spironolactone, oral therapies, alternative therapies for acne scarring, and patient management in populations such as children. I have provided an Editor's Commentary for each article, highlighting how we can apply this content to our management of patients with acne.

Save this collection, print it, and/or share it with your colleagues. Any suggestions for topics in the coming year can be sent to our Editorial Office (cutis@frontlinemedcom.com).

We hope this comprehensive collection will positively impact how you manage acne patients.

Gary Goldenberg, MD
Digital Editor, Cutis

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MARCH 2017
Cutis. 2017;99:195-201.

Oral Contraceptives for Acne Treatment: US Dermatologists' Knowledge, Comfort, and Prescribing Practices

Laura Fitzpatrick, MD; Elizabeth Mauer, MS; Cynthia L. Chen, MD

PRACTICE **POINTS**

- In prior reports, oral contraceptive pills (OCPs) were found to be as effective as systemic antibiotics in reducing acne lesion counts at 6 months of treatment.
- Most dermatologists have prescribed OCPs and most believed they were an effective treatment for acne in women.

The use of oral contraceptive pills (OCPs), which can be an effective treatment of acne in women, is poorly understood among many dermatologists. In this study, we surveyed 116 US dermatologists about their knowledge, comfort, and prescribing practices pertaining to the use of OCPs. The majority of respondents had previously prescribed OCPs and believed they were an effective treatment of acne in women. Despite adverse effects such as increased risk for venous thromboembolism (VTE) associated with OCPs, especially those containing drospirenone, our study indicated that many dermatologists believe the benefits of increased treatment efficacy may outweigh the risks.

Cutis. 2017;99:195-201.

AUDIO **ONLINE**

Dr. Cynthia Chen discusses oral contraceptives for acne treatment with *Cutis* Editor-in-Chief Vincent A. DeLeo, MD, in a "Peer to Peer" audiocast
>> **http://bit.ly/2AGyykW**

Dr. Fitzpatrick and Ms. Mauer are from and Dr. Chen was from Weill Cornell Medical College, New York, New York. Dr. Chen currently is from the Permanente Medical Group, Pleasanton, California.
The authors report no conflict of interest.
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The incidence of acne in adult females is rising,[1] and treatment with combined oral contraceptive pills (OCPs) is becoming an increasingly important therapy for women with acne. Prior reports have indicated that OCPs were as effective as systemic antibiotics in reducing inflammatory, noninflammatory, and total facial acne lesions after 6 months of treatment.[2,3] The acne management guidelines of the American Academy of Dermatology confer OCPs a grade A recommendation based on consistent and good-quality patient-oriented evidence.[4]

The US Food and Drug Administration (FDA) has approved 3 OCPs for the treatment of acne in adult women: norgestimate–ethinyl estradiol in 1997, norethindrone acetate–ethinyl estradiol in 2001, and drospirenone–ethinyl estradiol in 2007.[5] However, the use of these OCPs is poorly understood by many dermatologists. One study showed that dermatologists prescribed OCPs in only 2% of visits with female patients aged 12 to 55 years who presented for acne treatment, which is less often than obstetrician/gynecologists (36%) and internists (11%),[6] perhaps due to perceived risks or unfamiliarity with OCP formulations and guidelines among dermatologists.[7] Adverse effects of OCPs include venous thromboembolism (VTE), myocardial infarction, and hypertension,[8] but they generally are well tolerated.[9]

Even less is known about dermatologists' use of drospirenone-containing OCPs (DCOCPs), which

contain the only FDA-approved progestin that blocks androgen receptors. In prior studies, treatment with DCOCPs was associated with greater reductions in total lesion count and investigator-graded acne severity compared to early-generation OCPs.[10,11] However, DCOCPs have been associated with a greater risk for VTE (4.0–6.3 times higher than OCP nonuse; 1.0–3.3 times higher than levonorgestrel-containing OCPs),[12] which may explain the decline in DCOCP prescriptions among gynecologists in Germany from 23.8% of OCP prescriptions in 2007 to 11.4% in 2011.[13]

In this study, we surveyed US dermatologists about their knowledge, comfort, and prescribing practices pertaining to the use of OCPs. We compare OCP-prescribing to nonprescribing dermatologists, and those frequently prescribing DCOCPs to those who infrequently prescribe DCOCPs.

Methods

Survey Design—We performed a cross-sectional survey study using convenience sampling. The instrument was designed based on primary literature on OCPs in acne treatment and questionnaires assessing the use of OCPs in other specialties. Topics included prescribing practices, contraindications for OCPs defined by the Centers for Disease Control and Prevention (CDC),[14] VTE risk, patient selection for hormonal acne therapy, comfort with prescribing OCP therapy, and participant demographics.

Skip logic was employed (ie, subsequent questions depended on prior answers). A pilot study surveyed 9 board-certified dermatologists at our home institution (Weill Cornell Medical College, New York, New York).

Data Collection—Eligible participants were board-certified US dermatologists. Data were collected and managed using an electronic data capture tool through the Weill Cornell Medical College Clinical & Translational Science Center. Surveys were distributed electronically to dermatologic society members, university alumni networks, investigators' professional contacts, and dermatologists whose contact information was purchased from an email marketing company. Chain-referral sampling (ie, participants' recruitment among their colleagues) was used. Surveys were distributed at a regional dermatology meeting. Responses were collected from November 2014 to April 2015. This study was approved by the institutional review board.

Statistical Analysis—For the descriptive data, all responses including pilot study participants were analyzed regardless of survey completion and were summarized using frequency counts and percentages (N=130).

For the analysis of OCP prescription predictors, the sample included all respondents answering the demographic questions and indicating if they prescribe OCPs (N=116). One respondent was excluded for answering other for current practice setting. Demographic predictors of OCP prescription were physician characteristics, geographic region, practice location population density, practice attributes, time spent on medical versus pediatric dermatology, number of weekly acne patients, and percentage of total patients who are female. Medical school graduation year was a categorical variable and was categorized as prior to 1997 (when norgestimate–ethinyl estradiol was FDA approved for acne[5]) versus 1997 or later. Respondents' practice states were analyzed according to US regions—Northeast, Midwest, South, West/Pacific—and population density (persons per square mile) using US Census Bureau data.[15,16]

Univariate logistic regressions modeling OCP prescribing probability were performed for each demographic variable; a multivariable logistic model was constructed including all variables significant at α=.20 from univariate modeling.

To compare frequent prescribers versus infrequent prescribers of DCOCPs, we included all respondents answering whether they frequently prescribe DCOCPs and whether they believed the risk for VTE associated with DCOCPs differed from other OCPs (n=68). A univariate logistic regression was performed to model the probability of responding "Yes, they pose a greater risk" versus any of the other 3 responses by whether or not the respondent frequently prescribed DCOCPs for acne, and an unadjusted odds ratio was obtained. All *P* values were 2-tailed with statistical significance evaluated at α=.05. Ninety-five percent confidence intervals were calculated to assess precision of obtained estimates. Analyses were performed using SAS software version 9.4.

Results

Demographics—Participant demographics as predictors of OCP prescription practices are described in Table 1.

Knowledge—Oral contraceptive pills were endorsed as effective in the treatment of acne in women by 95.4% (124/130) of respondents. Among prescribers of OCPs for acne, 94.2% (65/69) believed OCPs were associated with an increased risk for VTE, no respondents thought OCPs were associated with a decreased VTE risk, 2.9% (2/69) believed OCPs did not affect VTE risk, and 2.9% (2/69) were unsure.

Among prescribers of OCPs for acne, 46.4% (32/69) believed DCOCPs posed a greater VTE risk than other OCPs. Odds of this response did not differ

Table 1.

Participant Demographics as Predictors of OCP Prescriptions Among Dermatologists (N=116)

Characteristic	Prescribers, n (%)	Nonprescribers, n (%)	Total, N (%)	Univariate OR (95% CI)	Univariate *P* Value	Multivariable OR (95% CI)	Multivariable *P* Value[a]
Gender							
Male	27 (50.0)	27 (50.0)	54 (100)	RV			
Female	36 (58.1)	26 (41.9)	62 (100)	1.385 (0.664-2.885)	.3850		
Year graduated from medical school							
Prior to 1997	26 (44.8)	32 (55.2)	58 (100)	RV		RV	
1997 or later	37 (63.8)	21 (36.2)	58 (100)	2.168 (1.030-4.566)	.0416	1.956 (0.884-4.329)	.0979
US region							
Northeast	17 (41.5)	24 (58.5)	41 (100)	RV			
Midwest	9 (64.3)	5 (35.7)	14 (100)	2.541 (0.723-8.936)	.5786		
South	26 (57.8)	19 (42.2)	45 (100)	1.932 (0.819-4.556)	.9417		
West/Pacific	11 (68.8)	5 (31.2)	16 (100)	3.105 (0.911-10.583)	.3060		
Population density[b]							
More than median	23 (40.4)	34 (59.6)	57 (100)	RV		RV	
Median or less	40 (67.8)	19 (32.2)	59 (100)	3.112 (1.455-6.656)	.0034	3.111 (1.408-6.871)	.0050
Practice setting							
Nonacademic	36 (46.2)	42 (53.8)	78 (100)	RV		RV	
Academic	27 (71.1)	11 (28.9)	38 (100)	2.864 (1.248-6.570)	.0130	2.635 (1.101-6.306)	.0295
Percentage of practice by time: medical dermatology							
>50%	42 (53.2)	37 (46.8)	79 (100)	RV			
≤50%	21 (56.8)	16 (43.2)	37 (100)	1.156 (0.527-2.538)	.7174		
Percentage of practice by time: pediatric dermatology							
>50%	7 (87.5)	1 (12.5)	8 (100)	RV			
≤50%	56 (51.9)	52 (48.1)	108 (100)	0.154 (0.018-1.293)	.0849		

CONTINUED ON NEXT PAGE

Table 1. (continued)

Characteristic	Prescribers, n (%)	Nonprescribers, n (%)	Total, N (%)	Univariate OR (95% CI)	Univariate *P* Value	Multivariable OR (95% CI)	Multivariable *P* Value[a]
Average no. of patients seen per week							
>99	27 (48.2)	29 (51.8)	56 (100)				
≤99	36 (60)	24 (40)	60 (100)				
Average no. of acne patients seen per week							
<25	36 (57.1)	27 (42.9)	63 (100)	RV			
≥25	27 (50.9)	26 (49.1)	53 (100)	0.779 (0.374-1.623)	.5046		
Percentage of female patients total							
<51%	10 (50)	10 (50)	20 (100)	RV			
≥51%	53 (55.2)	43 (44.8)	96 (100)	1.233 (0.470-3.233)	.6709		

Abbreviations: OCP, oral contraceptive pill; OR, odds ratio; CI, confidence interval; RV, reference variable.
[a]Multivariable logistic model was constructed including all variables significant at $\alpha = .20$ from univariate modeling.
[b]Persons per square mile (median, 239).

with frequent DCOCP prescribers versus infrequent prescribers (odds ratio, 0.731 [95% confidence interval, 0.272-1.964]; $P = .5342$). Participant responses on VTE risk and DCOCPs are provided in Table 2.

Dermatologists prescribing OCPs for acne endorsed greater likelihood of doing so in cases of cyclical flares with menstrual cycle (94.2% [65/69]), acne unresponsive to conventional therapy (87.0% [60/69]), acne on the lower half of the face (78.3% [54/69]), diagnosis of polycystic ovary syndrome (PCOS)(76.8% [53/69]), clinical suspicion of PCOS (71.0% [49/69]), concomitant hirsutism (71.0% [49/69]), late- or adult-onset acne (66.7% [46/69]), laboratory evidence of hyperandrogenism (60.9% [42/69]), and concomitant androgenetic alopecia (49.3% [34/69]).

Among dermatologists who prescribed OCPs for acne, CDC-defined absolute contraindications identified correctly were blood pressure of 160/100 mm Hg (59.4% [41/69]) and history of migraine with focal neurologic symptoms (49.3% [34/69]). The CDC-defined relative contraindications identified correctly were history of deep vein thrombosis or pulmonary embolism (1.4% [1/69]), breast cancer history with 5 years of no disease (15.9% [11/69]), hyperlipidemia (42.0% [29/69]), and 36 years or older smoking fewer than 15 cigarettes per day (21.7% [15/69]).

Comfort—Dermatologist self-reported comfort levels in prescribing OCPs for acne are shown in Table 3.

Prescribing Practices—Among all respondents, acne medications prescribed often included oral antibiotics (76.9% [100/130]), isotretinoin (41.5% [54/130]), and spironolactone (40.8% [53/130]).

Overall, 55.4% (72/130) of respondents prescribed OCPs for the following uses: acne (95.8% [69/72]), concomitant treatment with teratogenic medication (48.6% [35/72]), PCOS (34.7% [25/72]), hirsutism (26.4% [19/72]), androgenetic alopecia (19.4% [14/72]), SAHA (seborrhea, acne, hirsutism, alopecia) syndrome (12.5% [9/72]), and HAIR-AN (hyperandrogenism, insulin resistance, acanthosis nigricans) syndrome (11.1% [8/72]). For teratogenic medications, dermatologists prescribing OCPs did so with isotretinoin (77.8% [56/72]), spironolactone (73.6% [53/72]), tetracycline antibiotics (37.5% [27/72]), and other (34.7% [25/72]).

Of dermatologists prescribing OCPs for acne, frequency included often (19% [13/69]),

Table 2.

Responses on VTE Risk and DCOCPs

Question	All Respondents, n (%)	Frequent DCOCP Prescribers, n (%)	Infrequent DCOCP Prescribers, n (%)
Do you believe combined OCPs affect the risk of VTE?			
Yes, they increase the risk	65 (94.2)		
Yes, they decrease the risk	0 (0)		
No, they have no effect on the risk	2 (2.9)		
Not sure	2 (2.9)		
No response	0 (0)		
Total	69 (100)		
Do you believe DCOCPs have a different effect on the risk of VTE than other OCPs do?			
Yes, they pose a greater risk	32 (47.1)	19 (44.2)	13 (52)
Yes, they pose less of a risk	2 (2.9)	2 (4.6)	0 (0)
No, they pose the same risk	19 (27.9)	12 (27.9)	7 (28)
Not sure	15 (22.1)	10 (23.3)	5 (20)
Total	68 (100)	43 (100)	25 (100)
For participants selecting "Yes, they pose a greater risk" to the previous question (n=32)[a]: Has your knowledge of the increased risk of VTE posed by DCOCPs made you less likely to prescribe these medications for acne?			
Yes	24 (75)		
No	8 (25)		
Not sure	0 (0)		
No response	0 (0)		
Total	32 (100)		

Abbreviations: VTE, venous thromboembolism; DCOCP, drospirenone-containing oral contraceptive pill; OCP, oral contraceptive pill.
[a]The odds ratio calculated for "Yes, they pose a greater risk" versus any of the other 3 responses in frequent prescribers versus infrequent prescribers of DCOCPs was 0.731 (95% confidence interval, 0.272-1.964; *P*=.5342).

sometimes (45% [31/69]), and rarely (36% [25/69]). The most frequently prescribed OCPs included Ortho Tri-Cyclen (Janssen Pharmaceuticals, Inc) (80% [55/69]), Yaz (Bayer)(64% [44/69]), and Estrostep (Warner Chilcott)(19% [13/69]). Fill-in responses included Desogen (Merck & Co, Inc) (3/69 [4%]), Alesse (Wyeth Pharmaceuticals, Inc) (3/69 [4%]), Lutera (Watson Pharma, Inc)(1/69 [1%]), Loestrin (Warner Chilcott)(1/69 [1%]), and Yasmin (Bayer)(1/69 [1%]).

In univariate regressions, graduation from medical school in 1997 or later (*P*=.0416), academic practice setting (*P*=.0130), and low-density practice setting (*P*=.0034) were significant predictors of prescribing OCPs. In multivariable regression, only academic practice setting (*P*=.0295) and low-density practice setting (*P*=.0050) remained significant predictors. Demographic predictors are summarized in Table 1.

Comment

Our results suggest that most dermatologists (95.4%) believe OCPs effectively treat acne; however, only 54% of respondents reported prescribing them. Academic dermatologists were more likely to prescribe OCPs than nonacademic dermatologists, possibly indicating that academic dermatologists are more familiar with the literature on the efficacy and

Table 3.

Dermatologist Self-reported Comfort Levels Among Prescribers of OCPs for Acne (N=72)

	Comfort Level of Respondents, n (%)			
Parameter	**Not Comfortable**	**Somewhat Comfortable**	**Very Comfortable**	**No Response**
Determining whether a patient is a good candidate for acne therapy with OCPs	2 (2.8)	21 (29.2)	40 (55.5)	9 (12.5)
Counseling patients on how to begin taking OCPs	5 (6.9)	25 (34.7)	33 (45.8)	9 (12.5)
Counseling patients about side effects	5 (6.9)	23 (31.9)	35 (48.6)	9 (12.5)
Managing side effects	19 (26.4)	28 (38.9)	16 (22.2)	9 (12.5)

Abbreviation: OCP, oral contraceptive pill.

use of OCPs. Nearly half of respondents seeing 25 or more acne patients weekly did not prescribe OCPs, suggesting a notable practice gap. Dermatologists in less dense US regions were more likely to prescribe OCPs, perhaps because dermatologists may be more likely to prescribe OCPs than refer patients in health care access–limited areas, just as primary care providers treat a broader range of conditions in low-density rural areas than urban ones.[17] Exploring all dermatologists' referral patterns for OCPs is warranted.

A strong knowledge area revealed from this study was hormonal treatment of acne in women, a vital area because appropriate patient selection is key to treatment success.[8] Weaker knowledge areas included OCP contraindications and differences in VTE risk between formulations containing drospirenone and those not containing drospirenone. Only half the sample identified CDC-defined absolute contraindications, suggesting an education target for dermatologists to ensure patient safety. In contrast, respondents were conservative about relative contraindications, with most identifying deep vein thrombosis or pulmonary embolism, remote breast cancer history, and light smoking at 36 years or older as absolute contraindications. These results could reflect weighing the risk of relative contraindications against the benefit in acne, resulting in appropriately more conservative management than overall guidelines suggest. If so, it may suggest that dermatologists are adapting overall guidelines appropriately for use of OCPs in skin conditions.

Nearly all respondents knew that OCPs are associated with an increased risk for VTE. Approximately half understood that DCOCPs are associated with a greater VTE risk than other OCPs, with no difference between frequent and infrequent prescribers. Comparing these results to the findings on OCP prescribing overall, some dermatologists' risk-benefit calculation for VTE differs from other specialties because DCOCPs have superior efficacy in acne, whereas DCOCPs have similar contraceptive efficacy to other OCPs.[18] The fact that more dermatologists believed VTE to be an absolute contraindication than hypertension suggests dermatologists have a heightened awareness of VTE risk but prescribe DCOCPs for acne despite it.

Most OCP prescribers felt very comfortable selecting good candidates for OCPs (55.5%) and counseling on treatment initiation (45.8%) and side effects (48.6%). Only 22.2%, by contrast, were very comfortable managing side effects. This finding likely reflects the notion that VTEs are not most appropriately managed by a dermatologist. Exploring if a greater comfort level in managing side effects would make dermatologists more likely to prescribe OCPs is worthwhile. Additionally, exploring why many dermatologists do not prescribe OCPs despite believing they are effective for acne is warranted.

Study limitations included the use of convenience sampling. Additionally, our study did not investigate dermatologists' reasons for not prescribing OCPs.

Conclusion

This study demonstrates that dermatologists believe OCPs effectively treat acne in women and that most

dermatologists prescribing OCPs do so for acne treatment. Academic practice setting was associated with higher odds of prescribing OCPs than a nonacademic setting, but the number of weekly acne patients did not impact the likelihood of prescribing OCPs, which suggests a treatment gap warranting education efforts for dermatologists in nonacademic settings seeing many acne patients. Our study also suggests that awareness of the increased risk for VTE associated with DCOCPs is not associated with lower likelihood of prescribing DCOCPs, suggesting dermatologists may find greater treatment efficacy to be worth the higher risk.

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RELATED CONTENT **ONLINE**

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Birth Control Pills for Acne: Tips From Julie Harper at the Summer AAD

Acne treatment options now extend beyond antibiotics, and hormonal therapy, particularly birth control pills (BCPs), may provide clearance of acne in women who may not respond to other therapies. "Challenge [yourselves] to learn how to safely use BCPs," said Dr. Julie Harper, Clinical Associate Professor of Dermatology at the University of Alabama in Birmingham, in the presentation, "Use of Hormonal Therapy for Acne," at the Summer Meeting of the American Academy of Dermatology. The use of BCPs for acne has a strength-of-recommendation grade of A (consistent, good-quality patient-oriented evidence).

According to Dr. Harper, all combination BCPs should work for acne, except progestin-only BCPs, which will make acne worse. Currently, there are 4 BCPs approved by the US Food and Drug Administration for acne: norgestimate–ethinyl estradiol (Ortho Tri-Cyclen); norethindrone acetate–ethinyl estradiol (Estrostep Fe); drospirenone–ethinyl estradiol (Yaz); and drospirenone–ethinyl estradiol–levomefolate calcium (Beyaz). Birth control pills are known to carry risks for venous thromboembolism (VTE), stroke, hypertension, and myocardial infarction; however, they are generally well tolerated in acne patients. "The risk of venous thromboembolism in women who take BCPs is doubled or tripled compared to women who do not take these pills. This sounds scary until you put it into context," said Dr. Harper. She explains the risks to patients using the following 3-6-9-12 model: A woman's baseline risk of having a VTE if she is not on a BCP is approximately 3 in 10,000 women in one year. When she takes a BCP, her risk doubles to 6 per 10,000 women in one year. If she takes a BCP that contains drospirenone, her risk is 9 per 10,000 women in one year. If she gets pregnant, her risk is 12 per 10,000 women in one year.

Dermatologists may be apprehensive to prescribe BCPs, but Dr. Harper provided several important tips on managing patient expectations and monitoring patients. Dr. Harper emphasized that BCPs should be used patiently for acne. "It frequently takes at least 3 cycles of BCPs to see a meaningful change in acne reduction," she advised. She recommended obtaining a thorough medical history and blood pressure measurement prior to prescribing BCPs. However, a Papanicolaou test and bimanual pelvic examination are no longer deemed mandatory prior to initiating a BCP, according to the World Health Organization and the American Congress of Obstetricians and Gynecologists. "While these exams may help to detect cervical cancer and other pelvic diseases, BCPs help to prevent unwanted pregnancies and the risks that accompany those pregnancies," said Dr. Harper. "Remember that BCPs reduce the risk of ovarian, uterine and colorectal cancer and also lessen ovarian cysts and pelvic inflammatory disease." Dermatologists also should inform patients that rifampin and griseofulvin, both anti-infectives, will interact with BCPs, lessening their effectiveness.

A March 2017 study published in *Cutis* (2017;99:195-201) of US dermatologists' knowledge, comfort, and prescribing practices (N=116) revealed that most dermatologists (95.4%) believe BCPs effectively treat acne; however, only 54% reported prescribing them. The American Academy of Dermatology's guidelines of care for the management of acne vulgaris published in February 2016 (*J Am Acad Dermatol*. 2016;74:945-973) stated that "estrogen-containing combined oral contraceptives are effective and recommended in the treatment of inflammatory acne in females."

Overall, Dr. Harper's take-home message was that dermatologists should not be afraid to prescribe BCPs, even in teenaged girls (following the onset of menarche). "Birth control pills can be used in younger patients but it is not my first line of treatment," said Dr. Harper. "It is recommended that BCPs not be prescribed for acne until 2 years after the young woman has achieved menarche. When considering whether or not to use a BCP in the early teenage years, keep in mind that these are not short-term treatments. If a BCP does help acne, it will likely need to be maintained for many years." When discussing this treatment in front of parents/guardians, consider referring to it as *hormonal therapy* and use the term *birth control pills* only initially.

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Spironolactone for Adult Female Acne

Many cases of acne are hormonal in nature, meaning that they occur in adolescent girls and women and are aggravated by hormonal fluctuations such as those that occur during the menstrual cycle or in the setting of underlying hormonal imbalances as seen in polycystic ovary syndrome. For these patients, antihormonal therapy such as spironolactone is a valid and efficacious option. Herein, initiation and utilization of this medication is reviewed.

Adam J. Friedman, MD

What should you do during the first visit for a patient you may start on spironolactone?

Some women will come in asking about spironolactone for acne, so it is important to identify potential candidates for antihormonal therapy:

- Women with acne flares that cycle with menstruation
- Women with adult-onset acne or persistent-recurrent acne past teenaged years, even in the absence of clinical or laboratory signs of hyperandrogenism
- Women on oral contraceptives (OCs) who exhibit moderate to severe acne, especially with a hormonal pattern clinically
- Women not responding to conventional therapy and not wanting to use oral isotretinoin or who are not candidates for oral isotretinoin

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Evaluation of these women with acne for the possibility of hormonal imbalance may be necessary, with the 2 most common causes of hyperandrogenism being polycystic ovary syndrome and congenital adrenal hyperplasia. The presence of alopecia, hirsutism, acanthosis nigricans, or other signs of androgen excess, in combination with dysmenorrhea or amenorrhea, may be an indication that the patient has an underlying medical condition that needs to be addressed. Blood tests including testosterone, dehydroepiandrosterone, follicle-stimulating hormone, and luteinizing hormone would be appropriate screening tests and should be performed during the menstrual period or week prior; the patient should not be on an OC or have been on one within the last 6 weeks of testing.

Prior to initiating therapy with spironolactone, it is important to establish that there is no history of renal dysfunction; that the patient does not utilize salt substitutes, which may contain potassium in place of sodium; and that the patient is not taking potassium supplements, other potassium-sparing diuretics (ie, amiloride, triamterene), angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers.

Of note, the patient should not be currently or actively trying to become pregnant. Even though it has a category C rating, there is substantial theoretical risk for teratogenicity, especially in a male fetus (ie, feminization of a male fetus). However, there are no reports linking spironolactone with human congenital defects, and no well-controlled, prospective studies evaluating spironolactone exposure in pregnant women.

What does the patient need to know at the first visit?

Because patients have Dr. Internet on call within seconds on their smartphones and tablets, there are several points I review with patients as a semi-preemptive strike.

Spironolactone is not approved by the US Food and Drug Administration for the treatment of acne; however, it has been used for decades for acne and even longer for the management of high blood pressure (since 1957!). Because it is a potassium-sparing diuretic, patients need to be careful not to get too much of a good thing (ie, potassium). I counsel patients on potassium intake, including sources such as diet (ie, fruit/fruit drinks), coconut water (very popular right now), and over-the-counter nutritional supplements.

Spironolactone is used in varying doses depending on the situation (25–200 mg daily), but it is important to start with a lower dose and escalate in a stepwise fashion, if needed, depending on how the patient is doing. I usually tell the patient it requires at least one boost in the dosage (around 50 mg twice daily) to appreciate notable results; however, patients will often have some improvement even at the lowest dose of 25 mg twice daily within 4 weeks of treatment initiation, which is when I have them return for reevaluation.

Spironolactone will help with acne on the face, back, and chest.

The majority of sides effects associated with spironolactone are dose dependent; low-dose therapy (25–50 mg daily) generally is well tolerated, and even 100 mg daily is not problematic in most cases. Dose-dependent side effects include frequent urination, menstrual irregularities, breast tenderness and/or enlargement, low blood pressure, hyperkalemia, and reduced libido. Of note, a recent study (Plovanich et al) found that the incidence of hyperkalemia in healthy young women taking spironolactone for acne is equivalent to the baseline rate of hyperkalemia in this specific population. Therefore, routine potassium monitoring is unnecessary for healthy women taking spironolactone for acne. I tend not to check potassium in these patients unless I head to higher doses due to poor response or I am treating female pattern alopecia, which often requires higher dosing.

Spironolactone has sufficient data to suggest that long-term use appears to be safe overall. There was one long-term study with patients who received spironolactone for up to 8 years for the treatment of acne vulgaris (Shaw and White).

Spironolactone can be used as monotherapy or in combination with OCs safely. In fact, by prescribing spironolactone in combination with OCs you can kill 3 birds with 1 stone from efficacy (the synergy between the two often allows for lower dosing of spironolactone without compromising impact), contraception prevention, and dysmenorrhea perspectives. I do offer OCs to eligible patients who are starting on spironolactone. In general, spironolactone can be used safely in combination with oral antibiotics, though oral antibiotic use should be short-term to limit rising rates of antimicrobial resistance. Of note, there may be risk for hyperkalemia when spironolactone is combined with trimethoprim-sulfamethoxazole, so its use should be avoided in this setting.

How do you keep patients compliant with treatment?

If androgens are playing a notable role in the patient's acne, some response is usually noted by even the first return visit, which I always make for 4 weeks later, unlike with other acne treatment regimens, which I usually make for 7 to 8 weeks later. Even though most treatments require at least 8 weeks to show any sign of improvement, even spironolactone at times, close follow-up allows me to increase the dose, which is often needed, or change to another medication if the patient is not tolerating it. Given that I stress it will require taking the medication every day in a consistent fashion to allow me to effectively evaluate it, the short time frame between visits also enhances compliance, as it encourages the patient to actually take the medication and incorporate it into her routine.

What do you do if patients refuse treatment?

I always tell my patients they are the captains and I am helping them navigate through their disease. I will, however, discuss the chronicity of acne as well as the long-term sequelae of this inflammatory disease including scarring and postinflammatory pigment alteration for which there are no great treatments. I also tell them that if there is any issue with the medication, we simply stop, and the likelihood for severe adverse events is exceedingly low based on the evidence and anecdotal experience.

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Isotretinoin for Acne: Tips for Prescribing and Managing Patient Concerns

Stephen P. Stone, MD

Isotretinoin may be a useful treatment for patients with severe acne. The physician, the pharmacy, and the patient must be registered with the iPLEDGE program (https://www.ipledgeprogram.com). These pearls provide guidance on managing acne with isotretinoin, discussing side effects and false information with patients and/or parents/guardians, and providing reliable resources to them.

What does your patient need to know at the first visit?

Most important is what *you* need to know before the first visit. As the prescribing physician, you must be familiar with the iPLEDGE program. Because of the complexity of the program, consider identifying a physician in your area to refer patients if you are not going to be a regular prescriber of the medication.

If you are enrolled in iPLEDGE, let your patients (and/or their parents/guardians) know that there is a great deal of misinformation on the Internet. Reiterate that you and your staff are available to discuss their concerns. Also, give them reliable sources of information, such as the American Academy of Dermatology's patient information sheet (https://www.aad.org/public/diseases/acne-and-rosacea/isotretinoin-treatment-for-severe-acne) as well as the Mayo Clinic's acne information (http://www.mayoclinic.org/diseases-conditions/acne/basics/treatment/con-20020580). Drugs.com is another resource (https://www.drugs.com/cdi/isotretinoin.html).

All patients—males, females who cannot become pregnant, and females of childbearing potential (FCBPs)—must be aware that this medication can cause birth defects if taken during pregnancy. They must be informed that the medication is not to be shared with anyone and that they should not give blood while taking this medication.

What treatment course do you recommend?

My evidence-based approach is a course of isotretinoin totaling a minimum of 150 mg per kilogram body weight. Do not give a more abbreviated course unless the patient has cleared early; even then I tend to complete 150 mg when possible. There is published evidence that pushing the course to a total of 220 mg per kilogram body weight results in a longer remission.

Generally, I do few laboratory tests other than pretreatment lipid panels as well as 1 or 2 follow-up lipid panels at monthly intervals. To comply with the iPLEDGE program, FCBP patients must have a monthly pregnancy test, which is reported on the iPLEDGE website before the patient can be prescribed the drug and receive the drug from a pharmacist who is participating in the iPLEDGE program.

One of the defects of the iPLEDGE system is that although only a 30-day supply of pills can be prescribed, it is difficult to always bring a patient back in exactly 30 days; for example, we work on a 4-week cycle and 30 days brings us into the next week or uncommonly the weekend when we do not see patients. Our male patients or females not of childbearing potential are not affected, but for our FCBP patients, it means usually scheduling visits at 35-day intervals because the pregnancy tests must be performed at minimum 28-day intervals and the prescription cannot be written and the pregnancy test recorded until after at least 30 days.

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What are the side effects?

The common side effects are what you would expect from a medicine that is supposed to dry up the oil on your skin: dryness of the lips, mouth, and skin, as well as rashes due to the dryness. There also can be minor swelling of the eyelids or lips, nosebleeds, upset stomach, and thinning of the hair; dryness of the scalp may occur. I recommend using a little petroleum jelly inside the nostrils at night to counteract the dryness that leads to nosebleeds, and saline drops or gel for the eyes, especially for contact lens wearers.

Joint aches and pains have been reported, though I rarely see those effects in patients who are physically active such as those participating in competitive sports. Mood changes have been reported, including suicidal ideation.

What do you do if patients refuse treatment?

There is so much false information on the Internet about the dangers of isotretinoin, leaving some patients (and parents/guardians) too afraid to use it. I sympathize with this anxiety, but I do endeavor to point out that the birth defects occur *only* in women taking the drug while pregnant and have not been reported to occur after the drug is out of the patient's system.

Similarly, I point out that almost all of the evidence-based studies failed to confirm any association between the use of isotretinoin and depression, teenage suicide, and subsequent inflammatory bowel disease. Nonetheless, I mention these issues and recommend that the parents/guardians observe the teenager; in the case of adult patients, they themselves must be sensitive to symptoms.

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Effects of Oral Isotretinoin on Lipids and Liver Enzymes in Acne Patients

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Practice Points

- Isotretinoin is recommended for treatment of severe inflammatory acne and for cases resistant to prior treatment with antibiotics or topical agents; however, it may cause alterations in lipids and liver enzymes.
- In our study, liver enzymes were less affected than lipids in patients who were treated with isotretinoin.
- Use caution when administering isotretinoin in patients with a history of abnormal findings.

*Isotretinoin has been used to treat severe inflammatory acne that is resistant to antibiotics or topical agents; however, it also may cause alterations in lipids and liver enzymes. In this retrospective study, we evaluated changes in lipids and liver enzymes in 322 acne patients who had been treated with oral isotretinoin at our institution over a 3-year period. Each patient's medical records were evaluated to determine baseline triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels compared to levels recorded at 3 and 6 months following initiation of treatment with oral isotretinoin. Overall, statistically significant increases in TG and LDL levels were noted following treatment with isotretinoin (*P*<.001 and *P*<.001, respectively), while HDL levels were shown to decrease (*P*<.001). Statistically significant increases in AST levels also were noted (*P*=.016). Although ALT levels also increased, the changes were not statistically significant (*P*=.72). In our study, isotretinoin appeared to have a greater effect on lipids than liver enzymes. Dermatologists should not avoid isotretinoin use for appropriate indications, but close follow-up is important.*

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Acne is a chronic inflammatory condition of the pilosebaceous unit affecting approximately 79% to 95% of adolescents in the Western world.[1] Treatment of acne depends on its severity. Topical tretinoin, adapalene, benzoyl peroxide, azelaic acid, and topical antibiotics generally are used in cases of noninflammatory or mild inflammatory disease. Isotretinoin is recommended for treatment of severe inflammatory acne (eg, nodulocystic or conglobata acne) and for cases of acne that have proven to be resistant to prior treatment with antibiotics or topical agents. Dosages of isotretinoin range from 0.5 to 2 mg/kg daily for 16 to 24 weeks.[1] Isotretinoin reduces the activity and size of the sebaceous glands, normalizes keratinization of the sebaceous follicles, and decreases the number of *Propionibacterium acnes*. Isotretinoin also may cause clinical side effects and laboratory changes, the most important being teratogenicity. It also may cause mucocutaneous side effects including cracked lips, dryness of the skin and nasal mucosa, skin redness, eye dryness, and eye irritation.[1] It also may cause blepharoconjuctivitis, photosensitivity, asteatotic dermatitis, pruritus, telogen effluvium, secondary bacterial colonization, nail fragility, periungual pyogenic granuloma, paronychia, myalgia, intracranial hypertension, nausea, headache, vomiting, depression, psychosis, suicide, constipation, and allergic reactions.[2] Isotretinoin treatment may increase serum levels of liver enzymes, triglycerides (TGs), and low-density lipoprotein (LDL) cholesterol, and reduce the level of high-density lipoprotein (HDL) cholesterol.[1] This retrospective

study sought to evaluate the effect of isotretinoin on liver enzymes and lipids over 6 months.

Materials and Methods

Our retrospective study was conducted at the Hospital of Atatürk University in Erzurum, a city located in eastern Turkey. All patients who were treated in the department of dermatology and had received oral isotretinoin between June 2009 and June 2012 were included in the study. The study was based on an evaluation of the patients' medical records. All patients received oral isotretinoin 0.5 to 1 mg/kg daily; the majority of patients received 30 to 40 mg daily. Patient medical records included age; gender; white blood cell (WBC) count; red blood cell (RBC) count; hemoglobin count; and aspartate aminotransferase (AST), alanine aminotransferase (ALT), TG, LDL, and HDL levels at the beginning of treatment. Aspartate aminotransferase, ALT, TG, LDL, and HDL levels also were measured at 3- and 6-month follow-up. Analysis of AST, ALT, TG, LDL, and HDL levels was based on the National Cholesterol Education Program guidelines.[3] Aspartate aminotransferase and ALT levels were classified as normal (<40 U/L) and high (≥40 U/L). Triglyceride levels were classified as normal (<150 mg/dL), borderline high (150–199 mg/dL), high (200–499 mg/dL), and very high (≥500 mg/dL). Low-density lipoprotein levels were classified as optimal (<100 mg/dL), above optimal (100–129 mg/dL), borderline high (130–159 mg/dL), high (160–189 mg/dL), and very high (≥190 mg/dL). High-density lipoprotein levels were classified as low (<40 mg/dL), normal (40–59 mg/dL), and high (≥60 mg/dL). Normal WBC was defined as 3.5 to 12.5×10^3/mL. Normal hemoglobin count was defined as 11.5 to 15.0×10^6/mL for women and 13 to 17×10^6/mL for men. Normal RBC was defined as 4.0 to 5.2×10^6/mL for women and 4.5 to 5.9×10^6/mL for men. Statistical analysis was performed using SPSS version 17.0. Repeated measures analysis of variance was used to compare means between 3 groups (baseline, 3-month, and 6-month values). A paired sample *t* test was used to compare means between any 2 groups. Results with $P<.05$ were considered statistically significant.

Results

Treatment with oral isotretinoin was initiated in 349 patients at our institution from June 2009 to June 2012. Twenty-seven of these patients were excluded from the study because their medical records were not available. Medical records from 322 patients were obtained. The study population consisted of 226 (70.2%) women and 96 (29.8%) men. Patients ranged in age from 17 to 64 years, with a mean age of 23.9 years. The mean (standard deviation [SD]) age of the women was 23.9 (5.4) years and the mean (SD) age of the men was 23.8 (7.02) years. Most of the patients were on a regimen of 30 or 40 mg of isotretinoin daily. Differences between dosages and laboratory values were not analyzed because we assumed there would not be a significant difference, as most patients received the same dose. The mean (SD) WBC was 8.4 (3.5)$\times10^3$/mL. The mean (SD) RBC was 4.9 (0.5)$\times10^6$/mL. The mean (SD) hemoglobin count was 14.3 (1.7)$\times10^6$/mL (women, 13.6 [1.5]$\times10^6$/mL; men, 15.9 [1.1]$\times10^6$/mL).

The study evaluated the effects of isotretinoin on liver enzymes (AST and ALT) and lipids (TGs, LDL, and HDL). Nearly all of the patients (>95%) had normal AST and ALT levels at baseline. The results are outlined in the Table. Some values were not recorded for all patients at each follow-up.

Aspartate Aminotransferase Analysis—Aspartate aminotransferase levels were classified as normal and high. At baseline, mean (SD) AST levels were 20.2 (6.6) U/L, with normal levels in 311 (96.6%) patients and high in 7 (2.2%) patients. At 3-month follow-up, mean (SD) AST levels were 20.7 (5.2) U/L, with normal levels in 270 (83.9%) patients and high levels in 3 (0.9%) patients. At 6-month follow-up, mean (SD) AST levels were 21.3 (5.7) U/L, with normal levels in 209 (64.9%) patients and high levels in 4 (1.2%) patients. Aspartate aminotransferase levels increased at 3- and 6-month follow-up compared to baseline. Differences between AST levels were statistically significant ($F_{2,416}=4.2$, $P=.016$). Differences between AST levels at baseline and 3-month follow-up were not statistically significant ($P=.3$). Differences between AST levels at 3- and 6-month follow-up were not statistically significant ($P=.4$). Differences between AST levels at baseline and 6-month follow-up were statistically significant ($P=.07$). Differences between AST classifications at the 3 time points were not statistically significant ($F_{2,416}=0.44$, $P=.64$). Overall, the results indicated that AST levels increased over time in patients treated with isotretinoin, but the increase was not above the normal range and was not statistically significant.

Alanine Aminotransferase Analysis—Alanine aminotransferase levels were classified as normal or high. At baseline, mean (SD) ALT levels were 16.8 (11.2) U/L, with normal levels in 303 (94.1%) patients and high in 19 (5.9%) patients. At 3-month follow-up, mean (SD) ALT levels were 16.2 (9.3) U/L, with normal levels in 263 (81.7%) patients and high in 11 (3.4%) patients. At 6-month follow-up, mean (SD) ALT levels were 17.0 (11.3) U/L, with normal levels in 201 (62.4%) patients and high in 11 (3.4%) patients. Alanine

Summary of Results[a]

Laboratory Value	Patients, n (%)			*F* Score, *P* Value
	Baseline	3 Months	6 Months	
AST				$F_{2,416}$=0.44, *P*=.64
Normal (<40 U/L)	311 (96.6)	270 (83.9)	209 (64.9)	
High (≥40 U/L)	7 (2.2)	3 (0.9)	4 (1.2)	
ALT				$F_{2,418}$=0.21, *P*=.54
Normal (<40 U/L)	303 (94.1)	263 (81.7)	201 (62.4)	
High (≥40 U/L)	19 (5.9)	11 (3.4)	11 (3.4)	
TG				$F_{2,386}$=6.9, *P*=.001[b]
Normal (<150 mg/dL)	270 (83.9)	197 (61.2)	145 (45)	
Borderline high (150–199 mg/dL)	30 (9.3)	38 (11.8)	36 (11.2)	
High (200–499 mg/dL)	20 (6.2)	22 (6.8)	16 (5)	
Very high (≥500 mg/dL)	2 (0.6)	1 (0.3)	0 (0)	
LDL				$F_{2,382}$=51.2, *P*<.001[b]
Optimal (<100 mg/dL)	162 (50.3)	89 (27.6)	60 (18.6)	
Above optimal (100–129 mg/dL)	95 (29.5)	98 (30.4)	84 (26.1)	
Borderline high (130–159 mg/dL)	32 (9.9)	54 (16.8)	44 (13.7)	
High (160–189 mg/dL)	11 (3.4)	12 (3.7)	8 (2.5)	
Very high (≥190 mg/dL)	3 (0.9)	5 (1.6)	1 (0.3)	
HDL				$F_{2,384}$=5.2, *P*=.006[b]
Low (<40 mg/dL)	60 (18.6)	63 (19.6)	48 (14.9)	
Normal (40–59 mg/dL)	173 (53.7)	154 (47.8)	117 (36.3)	
High (≥60 mg/dL)	71 (22)	41 (12.7)	33 (10.2)	

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase, TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
[a]Some values were not recorded for all patients at each follow-up.
[b]Statistically significant.

aminotransferase levels at 3-month follow-up were lower than baseline but higher at 6-month follow-up compared to baseline and 3-month follow-up. Overall, ALT levels increased with time, but the differences between baseline and 3- and 6-month follow-up were not statistically significant ($F_{2,416}$=0.32, *P*=.72). Differences between ALT classifications at each time point were not statistically significant ($F_{2,418}$=0.21, *P*=.54). Overall, the results indicated that ALT levels increased over time in patients treated with isotretinoin, but the increase was not statistically significant.

Triglycerides Analysis—Triglyceride levels were classified as normal, borderline high, high, and very high. At baseline, mean (SD) TG levels were 107 (71) mg/dL, with normal levels in 270 (83.9%) patients, borderline high in 30 (9.3%) patients, high in 20 (6.2%) patients, and very high in 2 (0.6%) patients. At 3-month follow-up, mean (SD) TG levels were 117 (60) mg/dL, with normal levels in 197 (61.2%) patients, borderline high in 38 (11.8%) patients, high in 22 (6.8%) patients, and very high in 1 (0.3%) patient. At 6-month follow-up, mean (SD) TG levels were 122 (65) mg/dL, with normal levels in 145 (45%) patients, borderline high in 36 (11.2%) patients, high in 16 (5%) patients, and very high in 0 (0%) patients. Triglyceride levels increased and differences between TG levels at baseline and 3- and 6-month follow-up were statistically significant ($F_{2,384}$=17, *P*<.001). Baseline TG levels compared to 3-month follow-up were statistically significant (*P*<.001). Differences in TG levels at 6-month follow-up versus baseline were statistically significant (*P*<.001). However, changes in TG levels from

3- to 6-month follow-up were not statistically significant ($P=.21$). Differences between TG classifications at each time point were statistically significant ($F_{2,386}=6.9$, $P=.001$). Overall, TG levels increased from baseline during isotretinoin treatment at 3- and 6-month follow-up, and these increases were above normal range; however, there was no statistically significant increase from 3- to 6-month follow-up.

Low-Density Lipoprotein Analysis—Low-density lipoprotein levels were classified as optimal, above optimal, borderline high, high, and very high. At baseline, mean (SD) LDL levels were 102 (28) mg/dL, with optimal levels in 162 (50.3%) patients, above optimal in 95 (29.5%) patients, borderline high in 32 (9.9%) patients, high in 11 (3.4%) patients, and very high in 3 (0.9%) patients. At 3-month follow-up, mean (SD) LDL levels were 113 (30) mg/dL, with optimal levels in 89 (27.6%) patients, above optimal in 98 (30.4%) patients, borderline high in 54 (16.8%) patients, high in 12 (3.7%) patients, and very high in 5 (1.6%) patients. At 6-month follow-up, mean (SD) LDL levels were 113 (27) mg/dL, with optimal levels in 60 (18.6%) patients, above optimal in 84 (26.1%) patients, borderline high in 44 (13.7%) patients, high in 8 (2.5%) patients, and very high in 1 (0.3%) patient. Overall, there were statistically significant increases in LDL levels at 3- and 6-month follow-up ($F_{2,382}=75$, $P<.001$). Differences between baseline LDL levels and 3-month follow-up were statistically significant ($P<.001$). Differences between baseline LDL levels and 6-month follow-up were statistically significant ($P<.001$). However, differences in LDL levels at 3- and 6-month follow-up were not statistically significant ($P=.74$). Differences between LDL classifications at each time point were statistically significant ($F_{2,382}=51.2$, $P<.001$). Overall, statistically significant increases in LDL levels from baseline were noted during isotretinoin treatment and this increase was above normal range; however, LDL levels did not significantly increase from 3- to 6-month follow-up.

High-Density Lipoprotein Analysis—High-density lipoprotein levels were classified as low, normal, and high. At baseline, mean (SD) HDL levels were 52.4 (16) mg/dL, with low levels in 60 (18.6%) patients, normal in 173 (53.7%) patients, and high in 71 (22%) patients. At 3-month follow-up, mean (SD) HDL levels were 48 (12) mg/dL, with low levels in 63 (19.6%) patients, normal in 154 (47.8%) patients, and high in 41 (12.7%) patients. At 6-month follow-up, mean (SD) HDL levels were 47.6 (12) mg/dL, with low levels in 48 (14.9%) patients, normal in 117 (36.3%) patients, and high in 33 (10.2%) patients. Overall, statistically significant decreases were noted in HDL levels ($F_{2,384}=19$, $P<.001$). Differences between baseline HDL levels compared to 3-month follow-up were statistically significant ($P<.001$). Differences between baseline HDL levels compared to 6-month follow-up were statistically significant ($P<.001$). Differences in HDL levels at 3- and 6-month follow-up were statistically significant ($P<.001$). Differences between HDL classifications at each time point were statistically significant ($F_{2,384}=5.2$, $P=.006$). Overall, there were statistically significant decreases in HDL levels during isotretinoin treatment from baseline and this decrease was above normal range; however, HDL levels did not decrease at 3- and 6-month follow-up.

Comment

Studies in the literature evaluating the effects of isotretinoin on liver enzymes and lipids suggested that oral isotretinoin may cause alterations in liver aminotransferases (AST and ALT), TGs, HDL, and LDL in various degrees.[1] Zane et al[4] studied 13,772 patients with acne undergoing oral isotretinoin therapy between March 1995 and September 2002. The investigators found increased liver transaminase and serum lipid levels. They suggested that these abnormalities were generally transient and reversible.[4] Bershad et al[5] reported an increase in LDL and TG but a decrease in HDL during isotretinoin therapy. These changes in the lipid profile also appeared to be transient and returned to baseline level 2 months following the end of treatment.[5] In another study of 130 patients who were treated with isotretinoin, Vieira et al[1] noted an increase in AST, ALT, and TG levels. Most of the studies in the literature that reported effects of isotretinoin on liver enzymes and lipids suggested that the effects were reversible.

Although many studies reported alterations in serum transaminase and lipid levels, other studies reported no effect. In one study of 150 participants, Brito et al[2] found no statistically significant changes in liver transaminase, TG, HDL, or LDL levels following treatment with isotretinoin. In another study of 1292 participants by Alcalay et al,[6] serum levels of liver enzymes were not elevated to a degree necessitating discontinuation of isotretinoin treatment. In another study of 30 participants, Baxter et al[7] reported no significant changes in TG, LDL, or HDL levels measured at baseline or during treatment with isotretinoin.

Some studies suggest that routine laboratory tests are needed when treating patients with isotretinoin due to severe alterations in serum liver transaminase and lipid levels, while other studies conclude that the effects are minimal and laboratory tests are not needed. In the current study, we found that there

were statistically significant increases in TG and LDL levels in patients who underwent treatment with isotretinoin. We also found statistically significant decreases in HDL levels. In our study, liver enzymes were less affected than lipids in patients who underwent treatment with isotretinoin. There were statistically significant increases in AST levels, but the clinical classification was not affected. There also were increases in ALT levels, but the changes were not statistically significant.

Overall, we advise dermatologists that isotretinoin can be administered with minimal concern regarding changes in serum transaminase and lipid levels; however, although severe laboratory alterations were not noted in our study, we advise physicians to use caution when administering isotretinoin in patients with a history of abnormal findings.

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Status Report From the American Acne & Rosacea Society on Medical Management of Acne in Adult Women, Part 3: Oral Therapies

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PRACTICE **POINTS**

- Use of combination oral contraceptives to treat acne vulgaris (AV) in adult women who do not have measurable androgen excess is most rational in patients who also desire a method of contraception.
- Spironolactone is widely accepted as an oral agent that can be effective in treating adult women with AV and may be used in combination with other therapies.
- Monotherapy with oral antibiotics should be avoided in the treatment of adult women with AV, and concomitant use of benzoyl peroxide is suggested to reduce emergence of antibiotic-resistant *Propionibacterium acnes* strains.
- Oral isotretinoin use in adult women with AV warrants strict adherence to pregnancy prevention measures and requirements set forth by the federally mandated iPLEDGE™ risk management program.

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This article is the third of a 3-part series.
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Parts 1 and 2 of this 3-part series provided an overview of the epidemiology, visible patterns, and important considerations for clinical and laboratory evaluation of acne vulgaris (AV) in adult women and reviewed the role of proper skin care and topical therapies in this patient population. In Part 3, oral therapies including combination oral contraceptives, spironolactone, antibiotics, and isotretinoin are discussed along with important considerations that clinicians should keep in mind when selecting oral agents for management of AV in adult women.

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Selection of oral agents for treatment of AV in adult women is dependent on multiple factors including the patient's age, medication history, child-bearing potential, clinical presentation, and treatment preference following a discussion of the anticipated benefits versus potential risks.[1,2] In patients with the mixed inflammatory and comedonal clinical pattern of AV, oral antibiotics can be used concurrently with topical therapies when moderate to severe inflammatory lesions are noted.[3,4] However, many adult women who had AV as teenagers have already utilized oral antibiotic therapies in the past and often are interested in alternative options, express concerns regarding antibiotic resistance, report a history of antibiotic-associated yeast infections or other side effects, and/or encounter issues related to drug-drug interactions.[3,5-8] Oral hormonal therapies such as combination oral contraceptives (COCs) or spironolactone often are utilized to treat adult women with AV, sometimes in combination with each other or other agents. Combination oral contraceptives appear to be especially effective in the management of the *U*-shaped clinical pattern or predominantly inflammatory, late-onset AV.[1,5,9,10] Potential warnings, contraindications, adverse effects, and drug-drug interactions are important to keep in mind when considering the use of oral hormonal therapies.[8-10] Oral isotretinoin, which should be prescribed with strict adherence to the iPLEDGE™ program (https://www.ipledgeprogram.com/), remains a viable option for cases of severe nodular AV and selected cases of refractory inflammatory AV, especially when scarring and/or marked psychosocial distress are noted.[1,2,5,11] Although it is recognized that adult women with AV typically present with either a mixed inflammatory and comedonal or *U*-shaped clinical pattern predominantly involving the lower face and anterolateral neck, the available data do not adequately differentiate the relative responsiveness of these clinical patterns to specific therapeutic agents.

Combination Oral Contraceptives

Combination oral contraceptives are commonly used to treat AV in adult women, including those without and those with measurable androgen excess (eg, polycystic ovary syndrome [PCOS]). Combination oral contraceptives contain ethinyl estradiol and a progestational agent (eg, progestin); the latter varies in terms of its nonselective receptor interactions and the relative magnitude or absence of androgenic effects.[10,12,13] Although some COCs are approved by the US Food and Drug Administration (FDA) for AV, there is little data available to determine the comparative efficacy among these and other COCs.[10,14] When choosing a COC for treatment of AV, it is best to select an agent whose effectiveness is supported by evidence from clinical studies.[10,15]

Mechanisms of Action—The reported mechanisms of action for COCs include inhibition of ovarian androgen production and ovulation through gonadotropin suppression; upregulated synthesis of sex hormone–binding globulin, which decreases free testosterone levels through receptor binding; and inhibition of 5α-reductase (by some progestins), which reduces conversion of testosterone to dihydrotestosterone, the active derivative that induces androgenic effects at peripheral target tissues.[10,13,16,17]

Therapeutic Benefits—Use of COCs to treat AV in adult women who do not have measurable androgen excess is most rational in patients who also desire a method of contraception. Multiple monotherapy studies have demonstrated the efficacy of COCs in the treatment of AV on the face and trunk.[4,10,12,15,17,18] It may take a minimum of 3 monthly cycles of use before acne lesion counts begin to appreciably decrease.[12,15,19-21] Initiating COC therapy during menstruation ensures the absence of pregnancy. Combination oral contraceptives may be used with other topical and oral therapies for AV.[2,3,9,10] Potential ancillary benefits of COCs include normalization of the menstrual cycle; reduced premenstrual dysphoric disorder symptoms; and reduced risk of endometrial cancer (approximately 50%), ovarian cancer (approximately 40%), and colorectal cancer.[22-24]

Risks and Contraindications—It is important to consider the potential risks associated with the use of COCs, especially in women with AV who are not seeking a method of contraception. Side effects of COCs can include nausea, breast tenderness, breakthrough bleeding, and weight gain.[25,26] Potential adverse associations of COCs are described in the Table. The major potential vascular associations include venous thromboembolism, myocardial

Potential Adverse Associations With Combination Oral Contraceptive Use[10,22-39]

Association	Risk Factors
Breast cancer	Relative risk is 1.24 in current COC users; no increased risk after ≥10 y of use
Cerebrovascular accident	Risk factors for ischemic stroke include history of smoking, hypertension, migraines, taking COCs containing ≥50 mcg EE; risk factors for hemorrhagic stroke include age ≥35 y, history of smoking, hypertension
Cervical cancer	Increased risk with a greater likelihood of developing cervical cancer correlating with a longer duration of current COC use
Diminished bone mass	COCs containing ≥30 mcg EE do not adversely affect bone mass accrual during adolescence; COCs containing ≤20 mcg EE may not support adequate bone mass accrual, with greater risk if started within 3 y of menarche and used >2 y continuously
Myocardial infarction	Risk factors include history of smoking, age ≥35 y, hypertension; risk is increased up to 30-fold in smokers; no increased risk in current or prior healthy nonsmokers; smokers aged ≥35 y should avoid COCs
Venous thromboembolism	Associated with all COCs compared to nonusers; risk factors include smoking, age ≥35 y, <21 days postpartum, surgery with prolonged immobilization, history of DVT and/or PE, active/extensive IBD, hereditary thrombophilia, SLE, antiphospholipid antibody syndrome; risk dependent on dose of estrogen and type of progestin (lower rates reported with levonorgestrel; higher rates have been suggested with drospirenone)

Abbreviations: COC, combination oral contraceptive; EE, ethinyl estradiol; DVT, deep vein thrombosis; PE, pulmonary embolism; IBD, inflammatory bowel disease; SLE, systemic lupus erythematosus.

infarction, and cerebrovascular accident, all of which are influenced by concurrent factors such as a history of smoking, age (≥35 years), and hypertension.[27-32] It is recommended that blood pressure be measured before initiating COC therapy as part of the general examination.[33]

The potential increase in breast cancer risk appears to be low, while the cervical cancer risk is reported to increase relative to the duration of use.[34-37] This latter observation may be due to the greater likelihood of unprotected sex in women using a COC and exposure to multiple sexual partners in some cases, which may increase the likelihood of oncogenic human papillomavirus infection of the cervix. If a dermatologist elects to prescribe a COC to treat AV, it has been suggested that the patient also consult with her general practitioner or gynecologist to undergo pelvic and breast examinations and a Papanicolaou test.[33] The recommendation for initial screening for cervical cancer is within 3 years of initiation of sexual intercourse or by 21 years of age, whichever is first.[33,38,39]

Combination oral contraceptives are not ideal for all adult women with AV. Absolute contraindications are pregnancy and history of thromboembolic, cardiac, or hepatic disease; in women aged 35 years and older who smoke, relative contraindications include hypertension, diabetes, migraines, breastfeeding, and current breast or liver cancer.[33] In adult women with AV who have relative contraindications but are likely to benefit from the use of a COC when other options are limited or not viable, consultation with a gynecologist is prudent. Other than rifamycin antibiotics (eg, rifampin) and griseofulvin, there is no definitive evidence that oral antibiotics (eg, tetracycline) or oral antifungal agents reduce the contraceptive efficacy of COCs, although cautions remain in print within some approved package inserts.[8]

Spironolactone

Available since 1957, spironolactone is an oral aldosterone antagonist and potassium-sparing diuretic used to treat hypertension and congestive heart

failure.[9] Recognition of its antiandrogenic effects led to its use in dermatology to treat certain dermatologic disorders in women (eg, hirsutism, alopecia, AV).[1,4,5,9,10] Spironolactone is not approved for AV by the FDA; therefore, available data from multiple independent studies and retrospective analyses that have been collectively reviewed support its efficacy when used as both monotherapy or in combination with other agents in adult women with AV, especially those with a *U*-shaped pattern and/or late-onset AV.[9,40-43]

Mechanism of Action—Spironolactone inhibits sebaceous gland activity through peripheral androgen receptor blockade, inhibition of 5α-reductase, decrease in androgen production, and increase in sex hormone–binding globulin.[9,10,40]

Therapeutic Benefits—Good to excellent improvement of AV in women, many of whom are postadolescent, has ranged from 66% to 100% in published reports[9,40-43]; however, inclusion and exclusion criteria, dosing regimens, and concomitant therapies were not usually controlled. Spironolactone has been used to treat AV in adult women as monotherapy or in combination with topical agents, oral antibiotics, and COCs.[9,40-42] Additionally, dose-ranging studies have not been completed with spironolactone for AV.[9,40] The suggested dose range is 50 mg to 200 mg daily; however, it usually is best to start at 50 mg daily and increase to 100 mg daily if clinical response is not adequate after 2 to 3 months. The gastrointestinal (GI) absorption of spironolactone is increased when ingested with a high-fat meal.[9,10]

Once effective control of AV is achieved, it is optimal to use the lowest dose needed to continue reasonable suppression of new AV lesions. There is no defined end point for spironolactone use in AV, with or without concurrent PCOS, as many adult women usually continue treatment with low-dose therapy because they experience marked flaring shortly after the drug is stopped.[9]

Risks and Contraindications—Side effects associated with spironolactone are dose related and include increased diuresis, migraines, menstrual irregularities, breast tenderness, gynecomastia, fatigue, and dizziness.[9,10,40-44] Side effects (particularly menstrual irregularities and breast tenderness) are more common at doses higher than 100 mg daily, especially when used as monotherapy without concurrent use of a COC.[9,40]

Spironolactone-associated hyperkalemia is most clinically relevant in patients on higher doses (eg, 100–200 mg daily), in those with renal impairment and/or congestive heart failure, and when used concurrently with certain other medications. In any patient on spironolactone, the risk of clinically relevant hyperkalemia may be increased by coingestion of potassium supplements, potassium-based salt substitutes, potassium-sparing diuretics (eg, amiloride, triamterene); aldosterone antagonists and angiotensin-converting enzyme inhibitors (eg, lisinopril, benazepril); angiotensin II receptor blockers (eg, losartan, valsartan); and trimethoprim (with or without sulfamethoxazole).[8,9,40,45] Spironolactone may also increase serum levels of lithium or digoxin.[9,40,45,46] For management of AV, it is best that spironolactone be avoided in patients taking any of these medications.[9]

In healthy adult women with AV who are not on medications or supplements that interact adversely with spironolactone, there is no definitive recommendation regarding monitoring of serum potassium levels during treatment with spironolactone, and it has been suggested that monitoring serum potassium levels in this subgroup is not necessary.[47] However, each clinician is advised to choose whether or not they wish to obtain baseline and/or periodic serum potassium levels when prescribing spironolactone for AV based on their degree of comfort and the patient's history. Baseline and periodic blood testing to evaluate serum electrolytes and renal function are reasonable, especially as adult women with AV are usually treated with spironolactone over a prolonged period of time.[9]

The FDA black box warning for spironolactone states that it is tumorigenic in chronic toxicity studies in rats and refers to exposures 25- to 100-fold higher than those administered to humans.[9,48] Although continued vigilance is warranted, evaluation of large populations of women treated with spironolactone do not suggest an association with increased risk of breast cancer.[49,50]

Spironolactone is a category C drug and thus should be avoided during pregnancy, primarily due to animal data suggesting risks of hypospadias and feminization in male fetuses.[9] Importantly, there is an absence of reports linking exposure during pregnancy with congenital defects in humans, including in 2 known cases of high-dose exposures for maternal Bartter syndrome.[9]

The active metabolite, canrenone, is known to be present in breast milk at 0.2% of the maternal daily dose, but breastfeeding is generally believed to be safe with spironolactone based on evidence to date.[9]

Oral Antibiotics

Oral antibiotic therapy may be used in combination with a topical regimen to treat AV in adult women, keeping in mind some important caveats.[1-7] For instance, monotherapy with oral antibiotics

should be avoided, and concomitant use of benzoyl peroxide is suggested to reduce emergence of antibiotic-resistant *Propionibacterium acnes* strains.[3,4] A therapeutic exit plan also is suggested when prescribing oral antibiotics to limit treatment to 3 to 4 months, if possible, to help mitigate the emergence of antibiotic-resistant bacteria (eg, staphylococci and streptococci).[3-5,51]

Tetracyclines, especially doxycycline and minocycline, are the most commonly prescribed agents. Doxycycline use warrants patient education on measures to limit the risks of esophageal and GI side effects and phototoxicity; enteric-coated and small tablet formulations have been shown to reduce GI side effects, especially when administered with food.[3,52-55] In addition to vestibular side effects and hyperpigmentation, minocycline may be associated with rare but potentially severe adverse reactions such as drug hypersensitivity syndrome, autoimmune hepatitis, and lupus-like syndrome, which are reported more commonly in women.[5,52,54] Vestibular side effects have been shown to decrease with use of extended-release tablets with weight-based dosing.[53]

Oral Isotretinoin

Oral isotretinoin is well established as highly effective for treatment of severe, recalcitrant AV, including nodular acne on the face and trunk.[4,56] Currently available oral isotretinoins are branded generic formulations based on the pharmacokinetic profile of the original brand (Accutane [Roche Pharmaceuticals]) and with the use of Lidose Technology (Absorica [Cipher Pharmaceuticals]), which substantially increases GI absorption of isotretinoin in the absence of ingestion with a high-calorie, high-fat meal.[57] The short- and long-term efficacy, dosing regimens, safety considerations, and serious teratogenic risks for oral isotretinoin are well published.[4,56-58] Importantly, oral isotretinoin must be prescribed with strict adherence to the federally mandated iPLEDGE risk management program.

Low-dose oral isotretinoin therapy (<0.5 mg/kg–1 mg/kg daily) administered over several months longer than conventional regimens (ie, 16–20 weeks) has been suggested with demonstrated efficacy.[57] However, this approach is not optimal due to the lack of established sustained clearance of AV after discontinuation of therapy and the greater potential for exposure to isotretinoin during pregnancy. Recurrences of AV do occur after completion of isotretinoin therapy, especially if cumulative systemic exposure to the drug during the initial course of treatment was inadequate.[56,57]

Oral isotretinoin has been shown to be effective in AV in adult women with or without PCOS with 0.5 mg/kg to 1 mg/kg daily and a total cumulative exposure of 120 mg/kg to 150 mg/kg.[59] In one study, the presence of PCOS and greater number of nodules at baseline were predictive of a higher risk of relapse during the second year posttreatment.[59]

Conclusion

All oral therapies that are used to treat AV in adult women warrant individual consideration of possible benefits versus risks. Careful attention to possible side effects, patient-related risk factors, and potential drug-drug interactions is important. End points of therapy are not well established, with the exception of oral isotretinoin therapy. Clinicians must use their judgment in each case along with obtaining feedback from patients regarding the selection of therapy after a discussion of the available options.

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Acne Scarring: A Review of Cosmetic Therapies

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Practice Points

- Scarring is a common and undesirable outcome of acne vulgaris that can occur even in the setting of appropriate medical management.
- Acne scars can be classified into several different types based on scar quality and appearance. The choice of treatment with medical or surgical measures should be made with respect to the type of scar present.
- A combination of therapeutic modalities often is necessary to achieve optimal cosmetic outcomes in the treatment of both atrophic and hypertrophic acne scars.

Acne vulgaris is one of the most commonly encountered skin conditions and frequently is seen in both adolescent and adult populations. Scarring is a common result of acne and may take the form of atrophic or hypertrophic scars. Acne scarring often occurs in highly visible areas such as the face, thus resulting not only in an undesirable cosmetic appearance but also potential impairment of mental health, social functioning, and overall well-being. There is a wide variety of medical and surgical therapies available for treatment of acne scarring. In this article, we review some of the most commonly used cosmetic therapies for acne scarring, including dermabrasion, laser resurfacing, radiofrequency (RF), subcision, skin needling, punch techniques, chemical peels, soft-tissue augmentation, intralesional therapy, cryotherapy, and silicone dressings, with a focus on cosmetic outcomes.

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Acne vulgaris is one of the most common inflammatory dermatoses affecting nearly all adolescents and a large proportion of adults.[1] Incidence rates trend downward with age, but prevalence has been reported to be as high as 51% in individuals aged 20 to 29 years.[2] Notably, recent evidence suggests there is an increasing incidence rate of acne among postadolescent women, with the severity associated with the menstrual cycle.[3,4] Scarring is a common result of acne and may even occur in the setting of appropriate medical therapy. In particular, some form of facial scarring has been reported to occur in up to 95% of acne patients, with severe scarring in 30% of these patients.[5] The detrimental effects of acne scarring are not only limited to impaired cosmetic appearance, as it also has been associated with depression symptoms, suicidal ideation, mental health problems, and general social impairment.[6] Given the negative impact of acne scarring on overall health and well-being as

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well as its permanent nature, early and effective treatment is essential to maximize cosmetic outcomes and minimize long-term deleterious effects.

Acne scarring can be broadly divided into 2 major categories: atrophic and hypertrophic. Atrophic scarring is more common and is characterized by an overall localized reduction in collagen content. Clinically, atrophic scars present as depressions in the skin secondary to inflammatory fibrous contractions induced by acne. This type of scarring can be further divided into various subtypes based on morphologic criteria (eg, size, depth), such as boxcar, ice pick, and rolling scars.[7] Conversely, hypertrophic scarring is characterized by an overall increase in collagen content and presents as firm raised lesions. Hypertrophic scars should be distinguished from keloid scars, as the former will not outgrow the margins of the original wound while the latter will.[8] Treatment of acne scarring is based on scar type and can be accomplished through a variety of medical and surgical modalities (Table). In this article, we review some of the most commonly utilized therapies for both atrophic and hypertrophic acne scarring with a focus on cosmetic outcomes. It is important to keep in mind, however, that the best treatment is to prevent the occurrence of acne scarring through early and proactive treatment of acne.[9]

Dermabrasion

Dermabrasion is a decades-old technique that employs the use of a motorized device equipped with an abrasive material to physically remove the superficial layers of the skin, thus inducing the wound-healing process with subsequent formation of new collagen.[10] In the same vein, microdermabrasion utilizes aluminum oxide crystals ejected from a nozzle to induce superficial microlacerations.[11] This technique is most successful when used to soften scar edges in superficial atrophic scars of the rolling or boxcar subtypes.[12] Dermabrasion has been shown to be equally as effective as laser therapy in the treatment of facial scars but is reported to have a much greater risk for adverse effects (AEs) (eg, erythema, edema) that may last for several weeks posttherapy.[13,14] Dermabrasion is a particularly operator-dependent technique for which outcomes may vary depending on operator experience. As such, it is not generally recommended as a first-line therapy given its risks and relatively modest results; however, dermabrasion can be a useful adjunct when performed in the right setting. This technique,

Modalities for the Treatment of Acne Scars

Scar Type	Morphology	Treatment Modalities
Atrophic	Depressions in the skin, reduced collagen content	
Boxcar	Round to oval, sharply demarcated vertical edges with a wide base (1.5–4 mm), may be shallow (0.1–0.5 mm) or deep (≥0.5 mm)	Dermabrasion (shallow), dermal fillers (shallow), lasers (ablative, nonablative, fractional; shallow), punch techniques (deep), RF (shallow, deep), skin needling (shallow), subcision (shallow)
Ice pick	Narrow (<2 mm), deep, may extend into dermis or subcutaneous tissue, steep edges	Chemical peel (CROSS technique), punch techniques, RF
Rolling	Wide (4–5 mm), shallow, undulating appearance	Dermabrasion, dermal fillers, lasers (ablative, nonablative, fractional), RF, skin needling, subcision
Hypertrophic	Raised firm lesions, confined to area of original acne lesion, increased collagen content	Cryotherapy, intralesional therapy (corticosteroids, 5-fluorouracil, bleomycin, verapamil), PDL, silicone dressing

Abbreviations: RF, radiofrequency; CROSS, chemical reconstruction of skin scars; PDL, pulsed dye laser.

in addition to laser resurfacing, should be used with caution in patients who have recently taken or currently are taking isotretinoin, as several case series have reported postprocedural development of hypertrophic or keloid scars,[15-17] but these findings subsequently were questioned in the literature.[18]

Laser Therapy

Laser technology has advanced tremendously over the last few decades and there are now a multitude of available lasers that are capable of variable depth penetration and energy delivery patterns. Common to all, however, is the ability to induce localized thermal damage with eventual collagen remodeling. Lasers can be divided into 2 major categories: ablative and nonablative. Ablative lasers cause epidermal destruction, while nonablative lasers are able to selectively target dermal layers without disrupting the overlying epithelium. Generally speaking, ablative lasers are more effective than nonablative lasers in the treatment of atrophic scars, with reported mean improvements of up to 81%.[19] This increased efficacy comes with an increased risk for AEs such as postinflammatory hyperpigmentation, prolonged posttreatment erythema, and formation of additional scarring.[20] Both ablative and nonablative lasers can be applied in the more recently developed technology of fractional photothermolysis. With this method, noncontiguous microscopic columns of thermal injury surrounded by zones of viable tissue are created, which is in contrast to the traditional manner of inducing broad thermal injury. Fractional ablative lasers can achieve efficacy rates similar to traditional ablative lasers with a reduced risk for permanent scarring or dispigmentation.[21] Notably, recent studies have shown promising results for the use of fractional ablative lasers as a mechanism to enhance drug delivery of topically applied medications such as poly-L-lactic acid and triamcinolone acetonide in the treatment of atrophic and hypertrophic scars, respectively.[22,23]

Lasers also play a role in the treatment of hypertrophic acne scars with the use of nonablative pulsed dye lasers. These lasers cause selective thermolysis of dermal vasculature, and average clinical improvements in hypertrophic scars of 67.5% after a single treatment have been reported.[24] Temporary postoperative purpura and long-term hyperpigmentation are reported outcomes of this therapy.[20]

Radiofrequency

Nonablative radiofrequency (RF) is a relatively novel technique that creates an electric current in the dermis at preset depths to induce thermal damage and eventual collagen synthesis. There are a variety of modalities for which RF can be applied, but microneedle bipolar RF and fractional bipolar RF treatments offer the best results for atrophic acne scars. Improvements in scar appearance of 25% to 75% have been reported after several treatment sessions.[25] Better results have been reported in the treatment of ice pick scars as compared to more superficial scars,[26] but additional studies will be necessary to validate this claim. Adverse effects are largely limited to temporary erythema and posttreatment scabbing.[27]

Subcision

Subcision is a more physically intensive technique useful for treatment of superficial atrophic acne scars. This method involves the use of a small needle that is inserted into the periphery of a scar before being moved in a back-and-forth manner underneath the base of the scar to loosen the fibrotic adhesions that result in the depressed appearance of the scar. Additionally, loosening of the tissue and resultant bleeding creates a potential space for future collagen deposition during the subsequent wound-healing phase. Subcision has a reported success rate of 50% to 60% in the treatment of rolling scars, and prospective, randomized, split-face trials have indicated that the short-term outcomes of subcision are superior to dermal fillers while being equally effective long-term.[28,29] Of note, a small percentage of patients may develop a localized nodule at the site of treatment, which can be resolved with intralesional steroids.[11]

Skin Needling

Skin needling, also referred to as collagen induction therapy, utilizes vertical needle punctures rather than the horizontally directed punctures that are used in subcision and can be used to treat rolling and boxcar scars. Traditionally, a small roller equipped with rows of small needles typically ranging in size from 0.5 to 3.0 mm in length is passed over the skin using gentle pressure, puncturing the superficial layers of the skin to loosen fibrotic adhesions and induce collagen synthesis. This procedure may be repeated several times within a single session or over multiple sessions depending on the depth and quality of the scars. This technique has been reported to reduce scar depth up to 25% after 2 sessions.[30]

Punch Techniques

Punch techniques are useful for treatment of deeper atrophic acne scarring, for which most other treatment modalities are not particularly effective. A punch excision approximately equal to the scar size is first performed, which may then be followed by either

removal of the scar tissue with subsequent suturing, graft replacement of the removed tissue, or elevation of the already established scar tissue to the level of surrounding skin where it is then held in place by sutures or adhesive skin closure material. Success rates with this method are largely limited to case series, but punch techniques are reported to be efficacious, especially for treatment of ice pick scars. Risks for this method include graft failure, graft depression, and formation of sinus tracts.[31]

Chemical Peels

Chemicals peels traditionally employ the use of acidic compounds to strip away the outer layers of skin to variable depths depending on the concentration of the agent being applied. Chemical peels are not generally recommended for application in a nonspecific manner in the treatment of acne scars given the relatively mild cosmetic improvements seen and the high rate of AEs such as pigmentary alterations and additional scar formation.[12] Rather, clinicians should employ the CROSS (chemical reconstruction of skin scars) technique, in which peel agents such as trichloroacetic acid are applied in high concentrations only to areas of atrophic scarring. Use of this method can minimize AEs while simultaneously achieving high success rates, with excellent results in 100% (32/32) of patients after 5 to 6 treatment sessions.[32] This method has been successful for hard-to-treat ice pick scars.[33]

Soft-Tissue Augmentation

Soft-tissue augmentation is another effective treatment of superficial atrophic acne scarring that utilizes injections of collagen fillers such as hyaluronic acid, calcium hydroxylapatite, poly-L-lactic acid, silicone, and even autologous fat to replace lost tissue volume while simultaneously inducing collagen production via stretching of dermal fibroblasts.[34] These treatments may require multiple sessions for cosmetic improvement but have shown considerable efficacy in the treatment of atrophic acne scars. Hyaluronic acid has been reported to be particularly effective for rolling scars.[12] However, these compounds only provide temporary results, thus requiring repeated treatments to maintain cosmetic outcomes. Permanent options include the recently US Food and Drug Administration–approved polymethylmethacrylate microspheres suspended in bovine collagen as well as the novel technique of autologous fibroblast transfer. These options are relatively new, but initial double-blind, randomized, controlled trials have shown minimal AEs with substantial improvements in 64% to 100% of atrophic scars treated.[35,36]

Intralesional Therapy

Intralesional corticosteroid injections are a mainstay treatment of hypertrophic acne scarring and are believed to exert their effects by decreasing fibroblast proliferation and promoting collagen degradation.[37] Treatment with steroids generally is effective, with reported improvement in 75% (6/8) of patients and complete flattening in 50% (4/8) of lesions according to one study.[38] Development of hypopigmentation, dermal atrophy, and telangiectasia are potential sequelae of this treatment.[37]

5-Fluorouracil, bleomycin, and verapamil also have been used with good results as intralesional treatments of hypertrophic scars, but these agents typically are reserved for cases of corticosteroid failure. Such compounds are thought to mediate their effects through inhibition of dermal fibroblast proliferation.[39] Results with these therapies are varied, but greater than 75% improvement is seen in most cases. Adverse effects include injection-site ulceration and hyperpigmentation.[39]

Cryotherapy

Contact cryotherapy has been studied as treatment of hypertrophic acne scars. The exact mechanism through which scars are reduced is unclear, but it is hypothesized that the physical damage caused by freezing and thrombosis lead to collagen restructuring. According to one study, cryotherapy was reported to achieve good or excellent results in 76% (29/38) of cases.[40] Permanent pigmentary alterations are a possible AE.

Silicone Dressings

Silicone dressings are a reasonable treatment option for hypertrophic acne scarring given their proven efficacy and minimal risk for AEs. Thin sheets of silicone gels or membranes are applied daily in a topical manner to acne scars and are believed to be therapeutic through a combination of pressure and hydration, which subsequently inhibits fibroblast production of collagen. Notable reductions in scar appearance and size are seen in 60% to 80% of individuals using this method.[41] Adverse effects are limited to pruritus and local skin maceration. Patient noncompliance may be an issue, as the silicone dressings may be applied on highly visible areas such as the face. Patients may apply the dressings at night, but efficacy may be reduced.

Conclusion

When determining which treatment options to use in a patient with acne scarring, it is important to first determine the patient's treatment goals while simultaneously establishing realistic expectations. Important factors to

consider are the patient's preferences regarding treatment risk, duration, and permanence, as well as budget and social or work requirements. As such, treatment plans for each patient should be determined on a case-by-case basis. It also is important to note that a combination of different treatment modalities often is necessary and superior to monotherapy in achieving satisfactory cosmetic outcomes.

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Impact of Acne Vulgaris on Quality of Life and Self-esteem

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PRACTICE **POINTS**

- Grading of acne will help with appropriate treatment, thus reducing the adverse psychological effects of the condition.
- Acne severity has a negative impact on quality of life and self-esteem.
- A sympathetic approach and basic psychosomatic treatment are necessary in the management of acne.

The psychological impact of acne is determined by various factors including age, sex, personality, grade of disease, scarring, and environmental and ethnic background. Apart from managing the clinical manifestations of acne, clinicians also have to deal with the psychological aspects of the disease by assessing patients' quality of life (QOL) and self-esteem. These measures will aid in better management of acne patients. This study examined the relationship between acne and QOL and self-esteem. The results showed that acne severity may have a considerable adverse impact on QOL and self-esteem. Dermatologists need to emphasize the psychosocial sequelae of acne through awareness programs and encourage medical treatment along with basic psychosomatic remedies in the management of acne.

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Acne vulgaris predominantly occurs during puberty and can persist beyond 25 years of age, most commonly in women.[1,2] Although acne does not cause physical impairment, it can be associated with a considerable psychosocial burden including increased levels of anxiety, anger, depression, and frustration, which in turn can affect vocational and academic performance, quality of life (QOL), and self-esteem.[3]

Quality of life measures provide valuable insight into the debilitating effects of acne.[1] It has been suggested that acne patients may experience poor body image and low self-esteem as well as social isolation and constriction of activities.[4] Self-esteem is a favorable and unfavorable attitude toward oneself.[5] A marked emphasis has been placed on body image in society, fueled by external cues such as the media.[3,6] This study was carried out to assess QOL and self-esteem in acne patients.

Methods

This prospective, hospital-based, cross-sectional, case-control study was conducted at The Oxford Medical College, Hospital & Research Center (Bangalore, India), over a period of 3 months. One hundred consecutive acne cases (age range, 12–45 years) and 100 age- and gender-matched controls who did not have any skin disease provided consent and were included in the analysis. Guardians gave consent for individuals who were younger than 18 years. Exclusion criteria for cases included a medical disorder (eg, epilepsy, diabetes mellitus, hypertension) or medications that would likely interfere with acne assessment.

The cases and controls were administered a semistructured questionnaire to collect

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sociodemographic details. Acne was graded for the predominant lesions, QOL was assessed using the Cardiff Acne Disability Index (CADI) and World Health Organization Quality of Life–BREF (WHOQOL-BREF) scale, and self-esteem was measured using the Rosenberg self-esteem scale (RSES). The study was approved by the institutional review board.

Acne Grading—Acne was graded according to the predominant lesions using the following criteria: grade 1=comedones and occasional papules; grade 2=papules, comedones, and few pustules; grade 3=predominant pustules, nodules, and abscesses; and grade 4=mainly cysts, abscesses, and widespread scarring.[1]

Quality of Life Assessment—The CADI questionnaire was used to assess the level of disability caused by acne.[6] It is a 5-item questionnaire with scores ranging from 0 to 3 for a total maximum score of 15 and minimum score of 0. Total scores were classified as low (0–4), medium (5–9), and high (10–15).[7]

The WHOQOL-BREF is a self-reported questionnaire containing 26 items that make up the 4 domains of physical health (7 items), psychological health (6 items), social relationships (3 items), and environment (8 items); there also are 2 single questions regarding the overall perception of QOL and health. Questions were scored on a series of 5-point scales with higher scores denoting better QOL.[8]

Self-esteem Assessment—The RSES uses a 5-point Likert scale from strongly agree to strongly disagree to rate a series of 10 statements. The total score ranges from 0 to 30. Scores less than 15 suggest low self-esteem, while scores of 15 and greater indicate high self-esteem.[5]

Statistical Analysis—Results were analyzed using descriptive and inferential statistical methods. A χ^2 test was used for categorical data, and a Student *t* test and an analysis of variance were used for continuous data.

Results

The study consisted of 100 cases and 100 controls. The mean age was 21 years. The majority of cases reported an age of onset of acne of 11 to 20 years (66%), were predominantly female (58%) from rural backgrounds, and had a family history of acne (68%). The majority of lesions ceased within 24 months (60%). The face was the most commonly involved area (80%) and papules were the most prevalent lesion type (62%).

Cases predominantly had grade 2 acne (46%), and there was medium to high impairment in QOL according to CADI scores.

The scores for all the domains of the WHOQOL-BREF as well as the total score were lower in cases compared to controls (Table). There was a statistically significant difference between the 2 groups in the psychological (*P*=.0402) and environment (*P*=.006) domains.

WHOQOL-BREF Scores in Cases and Controls

	Scores, mean (SD)		
Questionnaire Item	Cases (n=100)	Controls (n=100)	Statistical Analysis[a]
Question 1	3.76 (0.3)	3.8 (0.6)	*t*=1.49; *P*=.13
Question 2	3.9 (0.4)	3.9 (0.6)	*t*=0.0; *P*=1
Physical health domain	46.16 (9.77)	47.90 (8.37)	*t*=1.35; *P*=.17
Psychological health domain	53.44 (11.56)	56.60 (10.02)	*t*= 2.0656; *P*=.0402
Social relationships domain	60.96 (16.75)	61.60 (12.95)	*t*=0.299; *P*=.76
Environment domain	53.90 (11.13)	57.84 (8.95)	*t*=2.75; *P*=.006
Total	53.6 (12.31)	55.98 (10.07)	*t*=1.49; *P*=.131

Abbreviation: WHOQOL-BREF, World Health Organization Qualify of Life–BREF.
[a]*P*<.05 indicates statistical significance.

The RSES mean (SD) score was higher in controls (19.74 [4.23]) than in cases (15.72 [5.06]) and was statistically significant ($P<.0001$). Low self-esteem was noted in 38% of cases and 16% of controls, and high self-esteem was noted in 62% and 84%, respectively.

In reviewing the correlation between acne severity, CADI, WHOQOL-BREF, and RSES scores, we found a positive correlation between acne severity and CADI scores ($R=0.51$), which implies that as the severity of acne worsens, the QOL impairment increases. There was a negative correlation between acne severity, WHOQOL-BREF score ($R=-0.13$), and RSES score ($R=-0.18$), which showed that as the severity of acne increases, QOL and self-esteem decrease. We observed that as the grade of acne increases, there is a statistically significant impairment in the QOL according to CADI ($P<.001$), while there is a reduction in QOL and self-esteem according to WHOQOL-BREF and RSES, respectively ($P>.05$).

Comment

Patients are more likely to develop acne than any other skin disease in their lifetime. Only in recent years has the psychodermatologic literature begun to address the possibility of acne having a psychological and emotional impact.[4] Although the cause-and-effect relationship between acne and psychological trauma has been debated for decades, only recently has the measurement focus shifted from psychological correlates (eg, personality) and emotional triggers (eg, stress) to the effect of acne on patients' QOL and self-esteem. This shift occurred as validated instruments for measuring disability, QOL, and self-esteem, specifically in patients with skin diseases, became available.[9]

In our study, the age of onset of acne was 11 to 20 years and it affected predominantly females (58%), which is in concordance with other studies, as acne develops in adolescence and subsides in adulthood.[1,10] Acne is more common in females due to hormonal factors and use of cosmetics. We observed that the face (80%) was most frequently affected, followed by the back (14%) and chest (6%), which is similar to prior studies.[1,10] Because the face plays an important role in body image, the presence of facial lesions may be unacceptable for patients and therefore they may present more frequently to dermatologists.

In our study, 68% of cases and 22% of controls had a family history of acne. A similar correlation also was noted in other studies, which suggests acne has an inherited predisposition due to involvement of the cytochrome P450-1A1 gene, *CYP1A1*, and steroid 21-hydroxylase, P-450-c21.[1,11] We found 46% of cases had grade 2 acne and 36% had grade 1 acne, which was congruent with prior studies.[12,13] Patients with severe acne are more likely to seek medical intervention in hospitals.

In our study, 58% of the cases had medium to high impairment in QOL according to CADI scores. We noticed as the severity of acne increased there was severe impairment in QOL. Similar findings have been found in studies that used other scales to assess QOL.[1,6,9]

In our study, 38% of cases and 16% of controls had low self-esteem, which was statistically significant ($P<.0001$). There was a negative correlation between the severity of acne and self-esteem. In a prior study of 240 professional college students, 53% had feelings of low self-esteem and 40% revealed they avoided social gatherings and interactions with the opposite sex because of their acne.[14] In a questionnaire-based survey of 3775 students, it was observed that the presence of acne correlated with poor self-attitude in boys and poor self-worth in girls.[3] We found patients with grade 1 acne had higher self-esteem as compared to other grades of acne. Similarly, a cross-sectional study by Uslu et al[15] found a direct correlation between acne severity and lower self-esteem using the RSES questionnaire. Although acne may be viewed as a minor cosmetic issue, it can have a negative impact on self-esteem and interpersonal relationships. Many of the studies had not used a validated structured questionnaire to assess self-esteem and there is a paucity of literature in relation to acne and self-esteem.[3,16,17]

According to the WHOQOL-BREF, the psychological domain was affected more in cases than in controls, which was a statistically significant difference. One study observed that patients experience immediate psychological consequences of acne such as reduced self-esteem, poor self-image, self-consciousness, and embarrassment.[3] These effects are exacerbated by taunting, stigmatization, and perceptions of scrutiny and being judged, causing patients to avoid interaction and social situations. Similarly, Pruthi and Babu[18] observed that acne had an impact on the psychosocial aspects of adult females using the Dermatology Life Quality Index and CADI.

Financial resources, health and social care accessibility, and opportunities for acquiring new information and skills were the factors that were considered in the environment domain of the WHOQOL-BREF.[8] We noted that the environment domain scores were significantly lower in cases than in controls. The cases could have had a detrimental effect on the latest opportunities in occupational

functioning due to acne, and as most of the population was from a rural area, they were having less favorable circumstances in acquiring new information about the management of acne.

There was no statistically significant difference between cases and controls in the social and physical domains of the WHOQOL-BREF, which suggests that these fields do not influence QOL. Similarly, patients in Sarawak, Malaysia, were least affected in the domain of social functioning, which was likely attributed to the upbringing of this population encouraging stoicism.[19]

In the current study, QOL impairment showed a positive correlation with acne severity according to CADI scores; however, there was no significant difference between WHOQOL-BREF score and acne grading, which suggests that QOL impairment does not depend on severity of acne alone. Physical, psychological, social, and environment domains play an important role in impaired QOL. Hence, by using the WHOQOL-BREF we can evaluate the actual domain that is adversely affected by acne and can be treated with a holistic approach. This point must be stressed in the training of medical faculty, as the treatment of acne should not be based on acne severity alone but also on the degree of QOL impairment.[19]

These results indicate that more data are required and there is a need to consider other variables that could play a role. This study was a hospital-based, cross-sectional study with a small sample group that cannot be generalized, which are limitations. Longitudinal follow-up of the cases before and after treatment was not done. The questionnaires helped us to detect psychosocial aspects but were insufficient to diagnose psychiatric comorbidity.

The strengths of this study include the use of a specific scale for the assessment of self-esteem. The usage of comprehensive (WHOQOL-BREF) and specific (CADI) scales to evaluate QOL has mutual advantage.

Conclusion

Acne vulgaris is a disease that can adversely affect an individual's QOL and self-esteem. This study suggested the importance of screening for psychosocial problems in those who present for management of acne. It is important for dermatologists to be cautious about psychological problems in acne patients and be aware of the importance of basic psychosomatic treatment in conjunction with medical treatment in the management of acne.

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Debunking Acne Myths: Should Patients With Oily Skin Use a Moisturizer?

Myth: Moisturizers Make Acne Worse in Patients With Oily Skin

Excessive sebum production can lead to oily skin that appears greasy and shiny, which contributes to the development of acne on the face. Acne patients with oily skin may be deterred from using moisturizers out of fear that their condition will worsen, yet therapeutic moisturizers have been shown to maintain hydration and overall integrity of the stratum corneum.

In a study of patient experiences with oily skin, 68% (n=37) of participants said their skin felt unclean, dirty, or grimy. Some participants noted a feeling of having clogged pores or an additional layer of skin, and others reported that their skin felt oily or greasy to the touch. The study also reported that participants with oily skin felt self-conscious, which impacted their daily life. These domains also are affected by having acne.

In the same study, 18% (n=10) of participants reported washing their face 6 to 15 times per day, 50% (n=27) washed their face 3 to 5 times per day, and 42% (n=23) washed their face 1 to 2 times per day. Instead of applying heavy moisturizers, acne patients with oily skin may feel the need to constantly wash their face. Gentle face washing is recommended to help improve and prevent acne, but patients who wash their face excessively are at risk for skin barrier impairment and development of dry skin.

Acne patients can use noncomedogenic moisturizers to prevent and alleviate skin irritation and soothe the skin by slowing the evaporation of water. Many moisturizers on the market claim to be suitable for acne treatment and may independently contribute to improving the signs and symptoms of acne. It is important for dermatologists to direct patients with oily skin to oil-free moisturizers containing ingredients such as dimethicone, which is known to reduce transepidermal water loss without a greasy feel and contains both occlusive and emollient properties. Dimethicone is suitable for use in patients with acne and sensitive skin and is noncomedogenic and hypoallergenic. Many oil-free moisturizers also contain certain metals and botanical extracts, such as aloe vera and witch hazel, that are known to have anti-inflammatory and skin-soothing properties. Some liquid face cleansers also moisturize, which may be all that is needed in patients with oily skin.

It also is important to inform patients with oily skin that common acne treatments such as benzoyl peroxide, retinoids, salicylic acid, and oral isotretinoin commonly cause dry skin or irritation, leading to barrier disruption in the stratum corneum and subsequently causing increased transepidermal water loss and inflammation. Concomitant use of noncomedogenic moisturizers can enhance treatment efficacy, alleviate dryness, and improve skin comfort in acne patients who are taking these medications.

Expert Commentary

An often forgotten element of acne vulgaris is that it is in fact a disease of barrier dysfunction and disruption. As mentioned above, many of the medications used to treat this chronic inflammatory disease are either directly cytotoxic to keratinocytes (benzoyl peroxide) or alter the thickness and composition of the stratum corneum (retinoids), impairing its protective functions. The inflammatory cascade associated with acne itself can impair the barrier, synergizing with the array of aforementioned medications. Both etiological factors disrupt an often overlooked yet crucial component of the skin barrier, the cutaneous microbiota. The altered landscape, or petri dish if you will, unhinges the balance between the >500 species of organisms living in harmony on the skin, decreasing bacterial diversity and facilitating the overgrowth of specific organisms, here specifically certain types of *Propionibacterium acnes*, which contribute to the ongoing inflammatory cascade. If that's not enough, sebum, which is certainly in excess in acne, contributes very little to barrier function and skin hydration but can be used to cause a different form of disruption by *P acnes*, which when converted into short-chain fatty acids can impair cutaneous immune tolerance ultimately creating, you guessed it, more inflammation (thank Dr. Rich Gallo for tying this all together). All in

all, the barrier is a mess, highlighting the need for barrier repair with a moisturizer to restore the "balance" on every level: Repair and replace the stratum corneum, restore the tools for the right bacteria to grow (water, carbs, lipids, etc). Moisturizers are a must in acne!

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Neonatal and Infantile Acne Vulgaris: An Update

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Practice Points

- Infantile acne needs to be recognized and treated.
- Acne in early childhood may represent virilization.

Acne may present in neonates, infants, and small children. Neonatal and infantile acne vulgaris are not considered to be rare. The presentation of acne in this patient population sometimes represents virilization and may portend later development of severe adolescent acne. Neonatal and infantile acne vulgaris must be distinguished from other cutaneous disorders seen in newborns and infants. Infantile acne tends to be more pleomorphic and inflammatory, thus requiring more vigorous therapy than neonatal acne.

Cutis. 2014;94:13-16.

Acne vulgaris typically is associated with adolescence and young adulthood; however, it also can affect neonates, infants, and small children.[1] Acne neonatorum occurs in up to 20% of newborns. The clinical importance of neonatal acne lies in its differentiation from infectious diseases, the exclusion of virilization as its underlying cause, and the possible implication of severe acne in adolescence.[2] Neonatal acne also must be distinguished from acne that is induced by application of topical oils and ointments (acne venenata) and from acneform eruptions induced by acnegenic maternal medications such as hydantoin (fetal hydantoin syndrome) and lithium.[3]

Neonatal Acne (Acne Neonatorum)

Clinical Presentation—Neonatal acne (acne neonatorum) typically presents as small closed comedones on the forehead, nose, and cheeks (Figure 1).[4] Accompanying sebaceous hyperplasia often is noted.[5] Less frequently, open comedones, inflammatory papules, and pustules may develop.[6] Neonatal acne may be evident at birth or appear during the first 4 weeks of life[7] and is more commonly seen in boys.[8]

Etiology—Several factors may be pivotal in the etiology of neonatal acne, including increased sebum excretion, stimulation of the sebaceous glands by maternal or neonatal androgens,[4] and colonization of sebaceous glands by *Malassezia* species.[2] Increased sebum excretion occurs during the neonatal period due to enlarged sebaceous glands,[2] which may result from the substantial production of β-hydroxysteroids from the relatively large adrenal glands.[9,10] After 6 months of age, the size of the sebaceous glands and the sebum excretion rate decrease.[9,10]

Both maternal and neonatal androgens have been implicated in the stimulation of sebaceous glands in neonatal acne.[2] The neonatal adrenal gland produces high levels of dehydroepiandrosterone,[2] which stimulate sebaceous glands until around 1 year of age when dehydroepiandrosterone levels drop off as a consequence of involution of the neonatal adrenal gland.[11] Testicular androgens provide additional stimulation to the sebaceous glands, which may explain why neonatal acne is

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more common in boys.[1] Neonatal acne may be an inflammatory response to *Malassezia* species; however, *Malassezia* was not isolated in a series of patients,[12] suggesting that neonatal acne is an early presentation of comedonal acne and not a response to *Malassezia*.[2,12]

Differential Diagnosis—There are a number of acneform eruptions that should be considered in the differential diagnosis,[3] including bacterial folliculitis, secondary syphilis,[13] herpes simplex virus and varicella zoster virus,[14] and skin colonization by fungi of *Malassezia* species.[15] Other neonatal eruptions such as erythema toxicum neonatorum,[16] transient neonatal pustular melanosis, and milia and pustular miliaria, as well as a drug eruption associated with hydantoin, lithium, or halogens should be considered.[17] The relationship between neonatal acne and neonatal cephalic pustulosis, which is characterized by papules and pustules without comedones, is controversial; some consider them to be 2 different entities,[14] while others do not.[18]

Treatment—Guardians should be reassured that neonatal acne is mild, self-limited, and generally resolves spontaneously without scarring in approximately 1 to 3 months.[1,2] In most cases, no treatment is needed.[19] If necessary, comedones may be treated with azelaic acid cream 20% or tretinoin cream 0.025% to 0.05%.[1,2] For inflammatory lesions, erythromycin solution 2% and benzoyl peroxide gel 2.5% may be used.[1,20] Severe or recalcitrant disease warrants a workup for congenital adrenal hyperplasia, a virilizing tumor, or underlying endocrinopathy.[19]

Infantile Acne Vulgaris

Clinical Presentation—Infantile acne vulgaris shares similarities with neonatal acne[21,22] in that they both affect the face, predominantly the cheeks, and have a male predominance (Figure 2).[1,10] However, by definition, onset of infantile acne typically occurs later than acne neonatorum, usually at 3 to 6 months of age.[1,4] Lesions are more pleomorphic and inflammatory than in neonatal acne. In addition to closed and open comedones, infantile acne may be first evident with papules, pustules, severe nodules, and cysts with scarring potential (Figure 3).[1,2,5] Accordingly, treatment may be required. Most cases of infantile acne resolve by 4 or 5 years of age, but some remain active into puberty.[1] Patients with a history of infantile acne have an increased incidence of acne vulgaris during adolescence compared to their peers, with greater severity and enhanced risk for scarring.[4,23]

Etiology—The etiology of infantile acne remains unclear.[2] Similar to neonatal acne, infantile acne may be a result of elevated androgens produced by the fetal adrenal glands as well as by the testes in males.[11] For example, a child with infantile acne had elevated luteinizing hormone, follicle-stimulating hormone, and testosterone levels.[24] Therefore, hyperandrogenism should be considered as an etiology. Other causes also have been suggested. Rarely, an adrenocortical tumor may be associated with persistent infantile acne with signs of virilization and rapid development.[25] *Malassezia* was implicated in infantile acne in a 6-month-old infant who was successfully treated with ketoconazole cream 2%.[26]

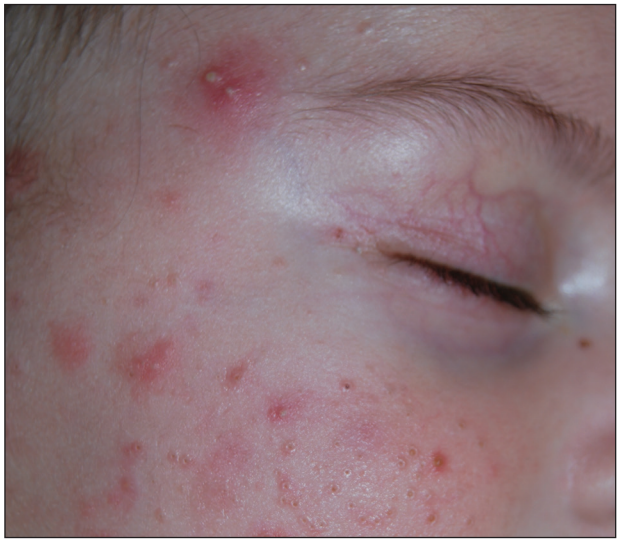

Figure 1. Neonatal acne on the cheeks with pustules.

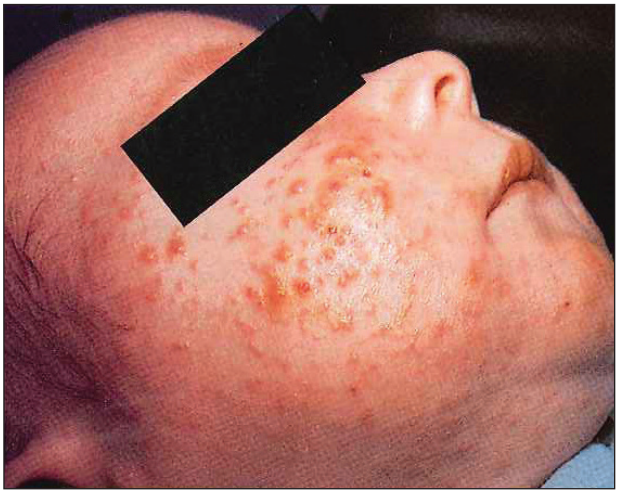

Figure 2. Infant with facial acne. Reprinted with permission from *Cutis.* 1993;52:16. ©1993, Frontline Medical Communications Inc.[22]

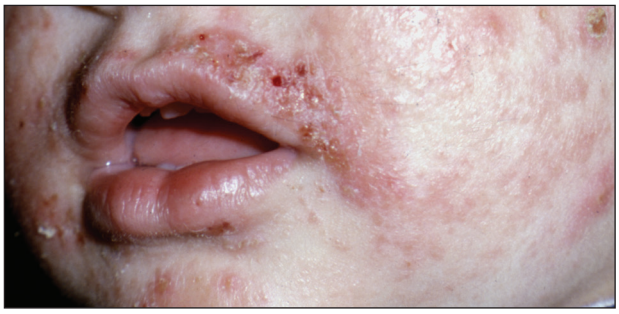

Figure 3. Infantile acne is more pleomorphic and inflamed than neonatal acne.

Differential Diagnosis—Infantile acne often is misdiagnosed because it is rarely considered in the differential diagnosis. When closed comedones predominate, acne venenata induced by topical creams, lotions, or oils may be etiologic. Chloracne also should be considered.[14]

Treatment—Guardians should be educated about the likely chronicity of infantile acne, which may require long-term treatment, as well as the possibility that acne may recur in severe form during puberty.[1] The treatment strategy for infantile acne is similar to treatment of acne at any age, with topical agents including retinoids (eg, tretinoin, benzoyl peroxide) and topical antibacterials (eg, erythromycin). Twice-daily erythromycin 125 to 250 mg is the treatment of choice when oral antibiotics are indicated. Tetracyclines are contraindicated in treatment of neonatal and infantile acne. Intralesional injections with low-concentration triamcinolone acetonide, cryotherapy, or topical corticosteroids for a short period of time can be used to treat deep nodules and cysts.[2] Acne that is refractory to treatment with oral antibiotics alone or combined with topical treatments poses a dilemma, given the potential cosmetic sequelae of scarring and quality-of-life concerns. Because reducing or eliminating dairy intake appears beneficial for adolescents with moderate to severe acne,[27] this approach may represent a good option for infantile acne.

Conclusion

Neonatal and infantile acne vulgaris may be overlooked or misdiagnosed. It is important to consider and treat. Early childhood acne may represent a virilization syndrome.

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