Late onset and postadolescent acne in women

Assessment of patients with late onset or postadolescent acne should include identifying the presence of hyperandrogenism and possible underlying causes. Management options include topical keratolytics and antibiotics, systemic antibiotics, isotretinoin and hormonal agents.

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What are late onset acne and postadolescent acne?

Acne vulgaris is a common, self-limiting disorder affecting adolescents and teenagers. Acne may, however, continue or develop after the age of 20 years and even persist until menopause.

Patients may have postadolescent acne (acne continuing past the teenage years) or late onset acne (that which develops at or after age 20). It is important to recognise these patients as a distinct group because:

- increasing numbers of women are presenting with this problem[1]
- the psychosocial effects of acne in this age group may be profound and disproportionate to the severity of acne – many women find that their acne affects their working life or professional careers (such as when having to give office presentations or deal with clients)
- some women with late onset acne have abnormal serum androgen levels that require further investigation
- late onset acne typically responds very well to hormonal therapy alone or as an adjunct to other acne therapy.

Acne, hormones and the sebaceous gland

Acne is a complex multifactorial disorder that involves:

- abnormal keratinisation of the pilosebaceous opening
- increased sebum production by the sebaceous gland
- colonisation by *Propionibacterium acnes*
- inflammation.

Blockage of the sebaceous duct by abnormal keratinisation produces a sebaceous plug, called a microcomedo. Colonisation of the pilosebaceous opening by bacteria such as *P. acnes* may produce an inflammatory response that manifests as papules, pustules and inflammatory cysts. Effective acne management involves targeting several of these steps concurrently.

IN SUMMARY

- **Late onset acne is acne that develops at or after the age of 20 years, whereas postadolescent acne is acne continuing past the teenage years.**
- **Females may have normal or raised serum androgen levels.**
- **Polycystic ovary syndrome is often an underlying cause in women with late onset or persistent acne.**
- **Assessment should include a menstrual history and examination for clinical signs of hyperandrogenism, such as hirsutism.**
- **Hormonal therapy is a very effective adjunct in the management of these patients, including those with normal serum androgen profiles.**

Table 1. History checklist

- Pattern of onset of the acne
- Duration of acne lesions – weeks rather than days
- Characteristics of acne lesions – recur in same area, tender
- Menstrual history – irregular periods, premenstrual exacerbation of acne
- Symptoms of hyperandrogenism – deepening voice, increased libido, hirsutism, male-pattern baldness
- Family history
- Lifestyle factors – make-up, sport headgear
- General medical history, including medications – e.g. phenytoin, lithium

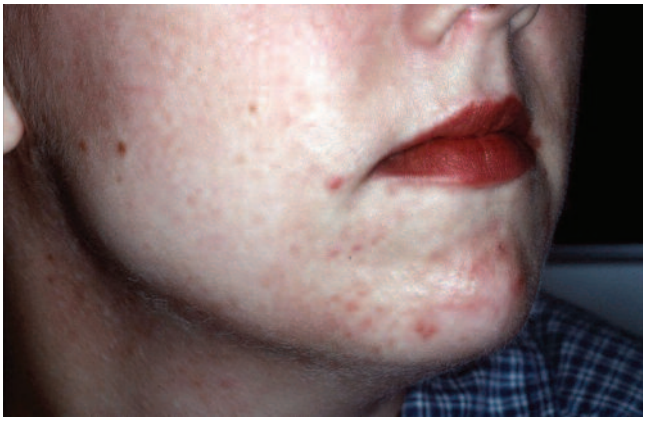

Figure 1. Typical distribution of late onset or postadolescent acne.

Sebaceous glands are found throughout the body and are present in greatest quantity and density on the face. They secrete sebum in response to androgenic stimulation. In general, patients with acne produce more sebum than do those without acne, and sebum production is greater in those with more severe acne.

Under normal conditions, the ovary contributes 50% of circulating androgens in the female. Overproduction of androgens by the ovary can occur in conditions such as polycystic ovary syndrome (PCOS) or ovarian tumours. The adrenal gland contributes the remaining 50% of circulating androgens in females.

How to recognise late onset and postadolescent acne

History

The clinical history should include enquiry about the following factors, which are summarised in Table 1.

Pattern of onset

At what age did pimples start in the patient? Although most patients claim their pimples started after the age of 20, some have acne in puberty that never improves and continues into their 20s and 30s.

Where did the pimples start or spread to? It is more typical for the lower third of the face to be affected (Figure 1), but the back and chest may also show signs of activity.

Duration of acne lesions

How long do the individual lesions last? Patients may complain that the acne lesions tend to last longer than adolescent lesions – for weeks rather than days.

Characteristics of the pimples

Do the pimples recur in the same area? Are there any symptoms? Patients often report that their pimples are tender or feel 'blind'.

Menstrual history

Is there any correlation with the menstrual cycle? It is common for the pimples to start a week prior to menses and continue for one to two weeks.

A careful menstrual history is important in the assessment of a woman who has late onset acne. About 60 to 70% of women may complain of worsening of their acne on a cyclical basis, usually premenstrually. An irregular menstrual cycle may suggest underlying hyperandrogenism and the presence of PCOS. It may be worthwhile for the patient to chart her menstrual cycle because patients often assume their cycle is regular. Menstrual irregularity is defined as amenorrhoea for more than three months or irregularity of the menstrual cycle of greater than seven days from a standard 28-day cycle over three consecutive cycles.[1]

Hyperandrogenism

Features of hyperandrogenism (Table 2) other than menstrual irregularity may need specific enquiry. Hirsutism may not be readily evident because patients may have waxed or had electrolysis. Mild hirsutism and irregular menstrual cycles have been reported in up to 29% and 14%, respectively, of women with late onset acne.[1]

Obesity, hirsutism and irregular menstrual cycles are features of PCOS but are not always present in the syndrome. Up to 50% of women with late onset or persistent acne have underlying PCOS.[2] It is beyond the scope of this article to discuss the diagnosis and management of PCOS. However, it should be noted that the diagnosis can be difficult in some cases because there are no universally accepted diagnostic criteria for PCOS.[3]

Family history

Ask about acne in the patient's mother or sisters. In one study, 50% of patients had a first-degree relative who also had postadolescent acne.[1]

Lifestyle factors

Lifestyle factors may promote or exacerbate acne. Many patients report flares of

acne when they are feeling increased stress. Creamy or 'greasy' cosmetics may promote plugging of the pilosebaceous follicle opening and are comedogenic. Some patients may be in occupations, such as working in kitchens, where heat may play a role.

Friction or trauma due to occlusive headgear (for example, worn in cycling, rollerblading or softball) may rupture existing comedones and bring about inflammatory lesions.

General medical history

Certain drugs taken for coexisting medical problems (such as phenytoin and lithium) may exacerbate acne.

Examination

Late onset acne may be clinically indistinguishable from adolescent acne. The examination should focus on:

- the distribution of acne – chin, jawline, neck, trunk
- the severity – nodules, cysts, scarring
- features of hyperandrogenism – especially hirsutism or androgenic alopecia.

Late onset acne typically localises to the lower third of the face, especially the chin, jawline and neck (Figures 2 and 3). This is in contrast to adolescent acne, which is often midfacial in distribution – in the 'T-zone' (i.e. forehead, nose and cheeks). Features of hyperandrogenism should be looked for (Table 2).

Investigations

While laboratory investigations are not indicated for most patients who have adolescent acne, hormonal abnormalities may be present in women with late onset acne.

A basic screening test for androgenic abnormalities (Table 3) should include serum free testosterone, dehydroepiandrosterone sulfate (DHEA-S), sex-hormone binding globulin, and the ratio of luteinising hormone (LH) to follicle stimulating hormone (FSH).

Elevated levels of free testosterone suggest hyperandrogenism but do not identify the source. Increased levels of DHEA-S suggest an adrenal cause and may be due to congenital adrenal hyperplasia or, rarely, an adrenal tumour. Elevated levels of testosterone with an increased LH:FSH ratio are consistent with PCOS.

Frequently, both the ovaries and the adrenals are implicated in androgen overproduction in women with late onset acne. Blood samples should be obtained in the early follicular phase (days 1 to 7) of the menstrual cycle where possible, and patients on oral contraceptives should discontinue their medication for one month before testing.

Depending on clinical circumstances, other investigations may be indicated. These include serum fasting sugars and lipids, prolactin, androstenedione, 17α-hydroxyprogesterone, and pelvic ultrasound to detect polycystic ovaries.

Compared with women of the same age without acne, women with late onset acne tend to have higher levels of free androgens in the plasma. It is important to appreciate, however, that in many patients the serum androgen measurements may be normal and this may reflect errors in sampling, contraceptive therapy or the end-organ response to androgens.

Sebaceous glands have a range of enzymes capable of metabolising androgens to more potent forms. The local concentration of androgen levels due to metabolism and/or end-organ hyperresponsiveness may be more significant in regulating sebum production than the

Table 2. Features of hyperandrogenism

- Male-pattern baldness
- Hirsutism
- Increased libido
- Acanthosis nigricans
- Deepening of the voice
- Menstrual irregularities
- Insulin resistance

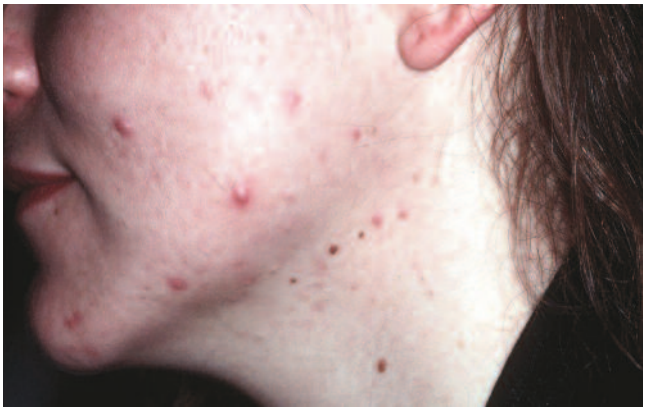

Figure 2. Acne involving the jawline and neck.

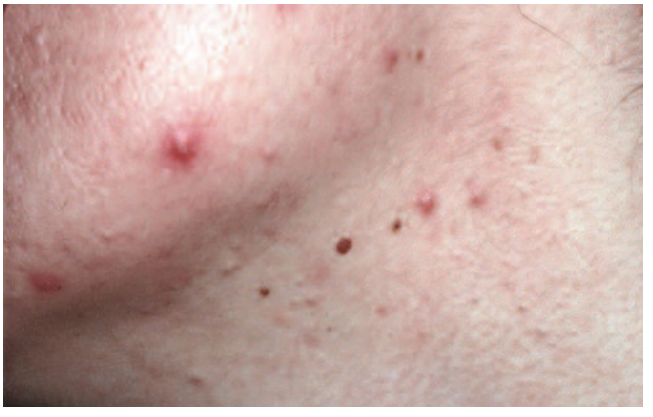

Figure 3. Close-up of Figure 2, showing comedones, papules and pustules.

Table 3. Guidelines for interpreting serum androgen profiles

Test result	Possible diagnosis
DHEA-S	
>20 µmol/L	Adrenal tumour
10 to 20 µmol/L	Congenital adrenal hyperplasia
Total testosterone	
5 to 7 nmol/L	Ovarian tumour
Mild elevations	Polycystic ovary syndrome
LH:FSH ratio >3	Polycystic ovary syndrome

Table 4. Therapeutic options in acne

Topical agents
Benzoyl peroxide
Glycolic acid
Salicylic acid
Azelaic acid (Skinoren)
Clindamycin (ClindaTech, Dalacin T)
Erythromycin (Eryacne 2%)
Tretinoin (Retin-A, ReTrieve, Stieva-A)
Isotretinoin (Isotrex Gel)
Adapalene (Differin)

Oral antibiotics
Tetracycline (Achromycin, Tetrex)
Minocycline (Akamin, Minomycin)
Doxycycline

Oral vitamin A derivatives
Isotretinoin (Accure, Isohexal, Oratane, Roaccutane)

Hormonal agents
Oral contraceptive combinations
Cyproterone acetate (Androcur, Cyprone, Cyprostat)
Spironolactone (Aldactone, Spiractin)
Prednisolone (Panafcortelone, Solone) or dexamethasone (Dexmethsone)

levels of circulating androgens. This is important to explain to patients because they often cannot understand why hormonal treatments are prescribed in the presence of a 'normal' hormonal assay.

Management

General advice and counselling

Excessive washing, antibacterial soaps and scrubs are not necessary and may irritate the skin. Gentle cleansing using an oil-free soapless cleanser is suitable, particularly for those with sensitive skin, while a foaming cleanser may be more appealing to those women who have a very oily skin. General measures include using oil-free sunscreens, make-up and moisturisers.

Giving the patients education and counselling regarding their acne is vital. Myths regarding their acne (dietary factors, 'poor hygiene') should be dispelled. The patients' expectations about the treatment should be clarified because it may take up to three months before significant improvement is observed. Encouragement during this period is helpful to promote compliance. Patients often require combination topical and oral therapy.

Women with PCOS may have abnormal lipid profiles and are at increased risk of type 2 diabetes. Lifestyle modifications, including weight reduction measures and exercise, are recommended for these patients.[4]

Topical agents

The therapeutic options for acne are summarised in Table 4.

Topical salicylic acid, glycolic acid, azelaic acid (20% cream; Skinoren) and benzoyl peroxide (2.5, 5 and 10% gel and cream) preparations are keratolytic and reduce comedone formation.

The topical antibiotic preparations include clindamycin solutions (ClindaTech, Dalacin T Topical Lotion) and 2% erythromycin gel (Eryacne 2%). Both these agents may be used in pregnant women, but they may be present in breastmilk and should be avoided during lactation. They are particularly helpful in inflammatory acne.

Topical tretinoin (Retin-A, ReTrieve Cream, Stieva-A), isotretinoin (Isotrex Gel) and adapalene (Differin) are vitamin A analogues that act mainly as keratolytic agents. They should be applied at night. Patients should be advised about their side effects of irritation and photosensitivity. These agents should be avoided in pregnancy.

Systemic antibiotics

Systemic antibiotic therapy is effective for moderate acne and suppresses acne until spontaneous clearing occurs. Tetracycline (Achromycin, Tetrex), minocycline (Akamin, Minomycin) and doxycycline are usually used as first line antibiotics. Erythromycin and trimethoprim–sulfamethoxazole are alternative options if tetracyclines are contraindicated.

A satisfactory response with antibiotics may not be obtained until after three to six months of therapy, and many practitioners feel that courses of antibiotics should not be continued for more than six months. Systemic antibiotics are therefore not an ideal option for long term therapy, which is often needed for hormonal acne. Patients should be warned of a potential interaction between oral antibiotics and oral contraceptives, which results in decreased effectiveness of the oral contraceptive.

Oral isotretinoin

Women who have severe, scarring acne should be referred to a dermatologist for treatment with oral isotretinoin (Accure, Isohexal, Oratane, Roaccutane). Oral isotretinoin reduces comedogenesis, reduces sebum secretion and is anti-inflammatory.

Counselling is essential with respect to contraception and the risk of birth defects while on medication. Pretreatment investigations include serum lipid levels, a serum pregnancy test and liver function tests, which are monitored during therapy.

Although patients with hormonal acne respond well to isotretinoin, they may relapse when their treatment course is over because of the underlying hormonal stimulation of the oil glands. If acne tends to recur quickly after a course of isotretinoin, antiandrogen hormonal therapy should be considered as maintenance treatment.

Hormonal therapy

Hormonal therapy is very effective in women with late onset acne with or without elevated serum androgens.[5] It reduces sebum production and therefore is most effective when used in combination with other antiacne therapies, such as topical keratolytic agents.

Hormonal therapy for women with acne is indicated:

- in women with ovarian, adrenal or peripheral hyperandrogenism
- in polycystic ovary syndrome
- for moderate to severe acne unresponsive to other therapy
- when there is relapse after multiple courses of antibiotics
- when there is quick relapse after a course of isotretinoin
- as an alternative to repeated courses of isotretinoin.

The therapeutic effect of hormonal therapy is slow, and patients should be warned not to expect noticeable improvement for three months. Therapy should be continued for at least 12 months. Relapses are not uncommon when hormonal therapy is ceased.

Combined oral contraceptives

The oestrogenic component of the oral contraceptive pill suppresses ovarian production of androgens and stimulates the production of sex-hormone binding globulin, thus reducing free testosterone levels. This therefore has a benefit in acne because the oil gland is exposed to less androgenic stimulus.

While all combined oral contraceptives are effective in acne because of the oestrogenic component, certain combination

pills contain androgenic progestins such as norgestrel and levonorgestrel, which are theoretically less effective.

Preparations containing more recently developed, low-androgenic progestins, such as desogestrel (Marvelon 28), gestodene (Femoden ED, Minulet 28, Tri-Minulet 28, Trioden ED) and norgestimate, are available as antiacne therapies.

Side effects of hormonal therapy include nausea, mastodynia, weight gain and headache. A small increase in the risk of breast cancer has been suggested by epidemiological studies, but this must be balanced against the significant psychological impact of acne and long term benefits of oral contraceptive therapy, including a reduced risk of ovarian and uterine cancer.[6] Appropriate patient selection and counselling are required with the use of these agents.

Oral contraceptive therapy should be avoided before puberty because of the risk of accelerated epiphyseal closure.

The efficacy of oral contraceptives in acne is due largely to the oestrogenic component. Progestin-only pills and implants are therefore unsuitable as antiacne therapies. Patients should be warned that acne improvement may be slow (at least three months), treatment is long term (at least one year), and combination treatment may give improved efficacy.

Cyproterone acetate

Cyproterone acetate is an antiandrogenic progestin that acts by both inhibiting ovulation and blocking the androgen receptor. The combination of 2 mg cyproterone acetate and 35 µg ethinyl oestradiol (Diane-35 ED, Brenda-35 ED, Juliet-35 ED) is very effective for the treatment of acne in women with mild to moderate hyperandrogenism.

Cyproterone acetate is also available as a single agent in tablets of 10 or 50 mg (Androcur, Cyprone, Cyprostat), which can be prescribed in addition to a combined oral contraceptive preparation.

The dose of cyproterone acetate can be increased if the acne is unresponsive to the low-dose combination. For example, 50 mg of cyproterone acetate may be added to the first 10 days of a cycle of Diane (or other combined oral contraceptive), starting with the first active pill. Alternatively, 10 mg of cyproterone acetate can be added to the first 15 days of the pill cycle. In postmenopausal women or those who have undergone hysterectomy, 50 mg of cyproterone acetate may be added to the entire cycle of Diane therapy (21 days).

Improvement can be seen in 75 to 90% of women with acne treated with doses of 50 to 100 mg cyproterone acetate per day. Oestrogen is necessary in these regimens because cyproterone acetate has strong antioestrogenic effects.

Side effects of cyproterone acetate include menstrual abnormalities, breast tenderness and enlargement, mood changes, headache, nausea, melasma and fluid retention.

Glucocorticoids

If the hyperandrogenism is due to an adrenal disorder, low dose prednisolone (2.5 mg; Panafcortelone, Solone) or dexamethasone (0.25 mg; Dexmethsone) daily can be used to suppress adrenal production of androgens. Long term use of these agents poses a risk of adrenal cortisol suppression, and patients should be monitored for this with periodic ACTH stimulation tests.

Spironolactone

Spironolactone (Aldactone, Spiractin) is useful for women who are intolerant to oestrogens, who have a contraindication to oestrogen therapy, or who do not wish to use oral contraceptives. Spironolactone acts as a competitive androgen receptor antagonist and is effective in doses of 50 to 200 mg daily. Treatment may be prolonged (six months or more), but dosages may be reduced once an adequate clinical response is achieved.

Dose-dependent side effects to spironolactone include menstrual irregularities, breast tenderness, hyperkalaemia, headache, dizziness, drowsiness and hypotension. Side effects may be minimised if therapy is started with a low dose of 25 to 50 mg daily. As an antiandrogen, spironolactone may cause feminisation of a male fetus, and therefore contraception is required. Blood pressure and serum electrolytes may require monitoring, although most young, healthy patients show no abnormalities.

Conclusion

Women with late onset acne are a relatively common presentation in general practice. Assessment of such patients should include identifying the presence of hyperandrogenism and possible underlying causes. Hormonal agents, such as combination oral contraceptive preparations, are very effective in the management of late onset acne and should be combined with conventional therapies such as topical agents and/or oral antibiotics. MT

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