What is “women’s dermatology?” I questioned this myself after agreeing to guest edit this issue of the Dermatologic Clinics. Although vulvar diseases and dermatoses of pregnancy first came to mind, I realized that there are many other important issues affecting the dermatologic care of women. Women have several unique times in their lives that affect either the skin conditions they develop or the treatment that these require. In this issue, the authors address dermatologic issues of teenage years, pregnancy, and later life. Dr. Ardis Olson and her associate, Pamela Starr, delve into behaviors that contribute to teenage tanning and offer insights into what might be done to help curb this potentially harmful habit. Dr. Julie Harper provides us with an articulate discussion of the role of androgens in skin and hair disease as she reviews the available antiandrogen therapies and their uses. Drs. Lucinda and Keith Buescher combine their expertise to introduce us to body dysmorphic syndrome, which, although primarily affecting women in their 30s, may begin in their teens.

Pregnancy complicates the management of dermatologic patients. Drs. Sancy Leachman and Barbara Reed provide us with a wonderful discussion of the use of medical therapies during pregnancy. Drs. Susan Sweeney and Mary Maloney offer a very thorough and practical approach to performing surgical procedures during pregnancy, which should be particularly appreciated because Drs. Marcia Driscoll and Jane Grant-Kels emphasize the importance of removing suspicious pigmented lesions during pregnancy.

No discussion of women’s dermatology is complete without addressing vulvar diseases. In “Vulvar Disease Pearls,” Dr. Lynette Margesson shares her secrets for the successful management of these often difficult to treat diseases. No dermatologist with a conscience should ever again be able to omit the vulvar examination after reading her lively article! Ammar Ahmed and Drs. Vandana Madkan and Stephen K. Tyring focus on human papillomavirus and genital diseases in their very informative article, which includes a discussion of the newest vaccine therapies that may help prevent the spread of HPV and its complications for women in the near future.

Although the use of cosmetics by men is increasing, women remain the primary consumers of cosmetics in the United States. Dr. Erin Warshaw and Katherine Biebl have provided us with an incredibly thorough discussion of the allergenic potential of cosmetics. If you have ever used or contemplated the use of nail cosmetics, I urge you to read the enlightening article by Drs. Dahdah and Scher, which discusses the many complications that can arise from their use. Dermatologic disease in the broader context of women’s occupational health issues is highlighted by Drs. Antoine Amado and James Taylor. Although not limited to women, osteoporosis is a potentially preventable side effect of corticosteroid...
use. Dr. Vicky Werth and Angela Lamb address strategies and offer a simple algorithm for managing patients on systemic corticosteroids.

We conclude this issue, not unfittingly, with Dr. Wendy Roberts’ discussion of dermatologic problems faced by older women. I offer my sincere thanks to each author for his or her contribution to this exciting issue. It is my hope that readers will appreciate the unique aspects of the dermatologic care of women and that they will be better able to render safe and appropriate care to women at all stages of their lives. I know that I will.

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The Challenge of Intentional Tanning in Teens and Young Adults

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Skin cancer is the most common form of cancer in the United States, with rates increasing 3% to 5% per year [1,2]. Rates of malignant melanoma, the most lethal skin cancer, are increasing more rapidly than any other type of cancer [3]. Although etiologies are multifactorial and involve personal susceptibility, increased outdoor ultraviolet (UV) light exposure early in life has been linked to the development of skin cancers as an adult [4]. UV exposure is a significant risk factor for the later development of basal and squamous cell carcinoma and malignant melanoma [5]. Recently epidemiologic studies have shown that chronic UV exposure from tanning lights also increases the risk for melanoma [6,7] and other skin cancers [8,9]. A European study showed that 40 hours of sunbed use resulted in a 55% increased risk for melanoma [10]. While excess UV exposure from indoor and outdoor sources is a problem for all ages, it is particularly important to address these issues in youth and young adults. Inadequate use of sun protection is common in this age group. Routine use of sun protection begins to decline in the pre-adolescent period (age 11–12) and reaches the lowest rate by high school for boys and girls in the United States and Australia [11,12]. Less than one third of adolescents currently practice effective sun protection [13].

The growth of the indoor tanning industry has increased adolescent UV exposure further. Over 2 million teens use tanning salons yearly and the prevalence of tanning light use in girls increases fivefold from 9th to 12th grade [14]. In a cross-sectional national survey, 36% of white teen girls [15] and 11% of white boys between the ages of 13 and 19 had used a tanning booth at least once and 28% of adolescent girls and 9.5% of boys had used a tanning booth three times or more. Use was much higher in older girls (11% of 13–14-year-olds versus 36.5% of 17-year-old girls [16]). Similar results were found in another national survey in which tanning light use by girls in the past year varied from 5% of 13- to 14-year-olds to 39.6% of 17- to 18-year-olds [14]. In these studies tanning light use is 50% to 80% more likely in rural communities than suburban or urban settings. Teens using tanning lights also actively sought tans outdoors and were less likely to use sun protection.

What do we know about these tan-seekers? Common to many studies of adolescent tanning behaviors in indoor and outdoor settings is the appeal of the tan look [17–19]. Whether feeling better, more attractive, or healthier, pro-tan attitudes are endorsed by the vast majority of adolescents who sunbathe outdoors and use tanning booths [13]. These attitudes are reinforced by the tanned image of youth-oriented musicians, movie stars, and models, and messages from the tanning light industry.

The influence of parents and peers in reinforcing the tan image has been shown for outdoor and indoor tanning behaviors [17,20–22]. Peer attitudes about a
tan and the number of friends who seek tans are predictors of sun protection [13] and tanning light use [19]. In addition, teen-perceived social norms about use of sun protection and tanning lights predicted their tanning behaviors [23,24].

Understanding more about what motivates tanners

To counsel intentional tanners effectively it is important to understand more fully what motivates them. Girls are much more likely to intentionally tan outdoors and indoors. The most common reasons given by tanners are that they feel more attractive and paradoxically healthier with a tan. Teen tanners are more likely to perceive indoor tanning to be the norm among friends and adults [24]. Knowledge about the risks of skin cancer, acquiring a burn from indoor tanning, or other negative aspects of indoor tanning (eg, sweating, claustrophobia, cost of tanning) did not alter teens’ intention to indoor tan in the future. Tanning to obtain a base tan to prevent burning before winter vacations or pre-summer is another commonly cited reason. It is common for young women to seek an indoor tan before a special dance or event. Although these reasons are cited often in adolescents who are average tanners (≤25 times per year) we have less information to understand what leads to girls becoming more addicted to tanning.

Frequent indoor tanners cite that it makes them feel better and marketing for “winter blahs” or seasonal affective disorder is common. While studies of tanning do not show increased endorphins produced from the experience there is some evidence for a physiologic effect reinforcing tanning behaviors. In a recent blinded study with UV and non-UV producing lights there was a clear preference among tanners for lights producing UV and reported changes in mood after UV light use [25]. These mood and physiologic reinforcers may play a role for outdoor tanning also. In one study 53% of beach-goers showed an addictive behavior pattern of tanning that was linked to tann-seeking at least two times per week [26]. Hillhouse also describes a subset of hard-core intentional tanners who tan more 100 times per year who have seasonal affective disorder and addictive tendencies in their tanning behaviors [27].

It is important in individual counseling to understand the tanning patterns, the level of obsessive tanning, and the reasons young women tan. Tanning for mood change requires assistance with alternative ways to help the mood disorder. When attractiveness is the predominant reason for tanning the remoteness of skin cancer is not an effective motivator. As we discuss later, focusing on more immediate outcomes of how tanning lights are damaging the skin has been shown to be an effective motivator in adolescents. For obsessive tanners a harm-reduction approach rather than total discontinuation may need to be used. Hillhouse [28] demonstrated better success in tanning college students with a general harm-reduction philosophy [29], in which giving up intentional tanning is the goal, but failing that, reducing the behavior is desired. Working with young women to decrease the frequency of tanning light use [25], use artificial tanners, use sunscreen to avoid burns when tanning outdoors, and consider alternative enjoyable activities to beach-going for tanning have all been advocated. Moving beyond informing to exploring the pros and cons of tanning compared with alternative ways to have an attractive appearance has been effective in reducing tanning [28].

The tanning industry

Despite evidence that UV radiation causes skin cancer, the use of indoor tanning devices that emit UV light in beauty parlors, fitness centers, tanning salons, and homes has never been more popular. Indoor tanning is big business, with tanning trade publications reporting this as a $2 billion a year industry in the United States. According to industry estimates, 28 million Americans are tanning indoors annually at about 25,000 tanning salons around the country.

In the last couple years, the indoor tanning industry has taken an aggressive marketing stand, claiming that not only is indoor tanning harmless, but it is actually healthy. For example TanningTruth.com, a web site of the tanning booth industry, claims to be “The only source for scientifically supported material on the balance between the benefits and risks associated with ultraviolet light exposure and sun tanning” [30]. Along with articles, such as Indoor Tanning is Smart, Truth about Skin Cancer, and Help Promote Tanning Truth, the option to join the organization and receive promotional materials is offered. There is support to help tanning booth operators with various issues. One statement proclaims, “solve your toughest problems regarding medical issues, respond to tanning critics and the media, staff training issues and product resources.” These products include Project Smart Teen, a package to promote teen tanning and give salons the tools to address legislative issues. A poster, “We Care About Teenage Skin,” is provided and marketed as a product to “Let
everyone entering your salon know of your stand on youth sunburn prevention and smart teen tanning education." Tanning Trends magazine, a trade publication, writes: "Moderate tanning has never been linked scientifically to skin cancer. In fact, by helping people tan with a reduced incidence of sunburn, indoor tanning may reduce your risk of ever contracting skin cancer."

In 1994 the American Medical Association adopted a resolution calling for a ban on the sale and use of tanning equipment for nonmedical (ie, cosmetic) purposes. The US Federal Trade Commission (FTC), which regulates the sale and marketing (but not the use) of indoor tanning equipment, declined to institute such a ban, however. The FTC did prohibit the industry marketing indoor tanning from making health claims and provides the public with a brochure warning about false health claims [31]. The Skin Cancer Foundation reports that the tanning industry has requested a change in this regulation and is seeking actively the ability to market the health benefits of indoor tanning [32]. The case for such benefits is weak, whereas the case for the risks of indoor tanning is strong.

Physicians and medical groups around the world have undertaken extensive campaigns to decrease excessive exposure to UV light to reduce the current epidemic of skin cancer. These efforts have been successful at educating the public and there is increasing awareness that UV light causes skin cancer. Despite this knowledge, tanning indoors and outdoors is more popular than ever. Most studies suggest young women are the most frequent patrons of tanning salons. The development of photoaging and skin cancer will take years to become apparent in these young tanners, whereas the perceived social value of a tan is apparent immediately.

The indoor tanning industry is expected to actively continue to market its services, including the claim that indoor tanning is not only harmless but is healthy. Regulation of the tanning industry at the state and national level is important, especially to prevent false health claims from being made.

Approaches used to changing intentional tanning

Legislation and regulations

Legislation defining the age at which adolescents can use tanning facilities and requiring parental permission is being enacted in many states. This is an increase since 2003 when only three states were reported to have such laws. Studies show that compliance with these laws is variable by state and depends on state enforcement [33]. Unfortunately, it is common for parents to see tanning as benign and to give permission. In addition, mothers who tan indoors themselves are likely to give their teens permission. Our data show that one third of teens who tan indoors have a mother who uses tanning lights. Although legislation is an important step, it may not be sufficient to deter teen tanning.

The FDA has established regulations about maximal initial and later UV exposure schedules for specific tanning units and the use of eye protection. A study of tanning facilities in one state showed that 95% of patrons exceeded the recommended exposure and 33% initially began tanning at times intended only for maintenance [34]. Professionals at the state level need to advocate for enforcement of these regulations to reduce burns and excess exposure times.

Public education campaigns

Most United States public health efforts have targeted younger children, and there have been fewer programs involving adolescents [35]. Middle school and high school sun protection educational programs have focused on health (future cancer risk) and have changed knowledge and attitudes but not actual behaviors [36,37]. Despite the marked increase in tanning light use during high school years, effective interventions to prevent or change these behaviors have not been developed for this age group. The effectiveness of media campaigns or school programs alone is questionable. The Australian experience has shown decreasing sun protection in high school students during a period of extensive public media campaigns [38]. Australian researchers have concluded that classroom health education alone without attention to the school and community environment as important social influences has not changed reported sun protection [39].

Community-wide programs

More comprehensive programs beyond public media are needed to change community norms and adolescent behaviors about sun protection. The Centers for Disease Control (CDC) Task Force on Community Preventive Services on Reducing Exposure to Ultraviolet Light [40] reviewed four areas of educational and policy intervention: health care settings and providers, recreational settings, schools, and parents. They found an insufficient number of effective studies and urged more research that assessed key behavioral outcomes, not just knowledge.
and attitudes. In particular, they noted a lack of effective interventions at the secondary school level.

Using this socio-ecologic approach, our researchers at Dartmouth developed the SunSafe program that intervened at the four levels advocated by the CDC for middle school students (sixth to eighth grades). Students and their parents received consistent messages from role models in health, school, athletic, and other recreational settings. The message was reinforced by a common program logo and materials used by all community participants. In the schools, a peer influence component was included. Teen sun teams developed their own messages for their peers. This community approach of changing social influences and school and community norms has resulted in improved early adolescent sun protection [41] and could be applied to secondary school students also.

Role of parents

While parental influence is recognized as important with younger children [42], parents still can have an important role in limiting UV exposure in adolescence [19]. Parents’ self-protection behaviors and parents taking an active role in promoting sun protection with their adolescents have been shown to predict adolescent sun protection behaviors in our work in rural communities and in national surveys [21]. Similarly, for white adolescent girls maternal indoor tanning behavior and active role in the teen’s tanning (concern over the teen’s indoor tanning and monitoring or gate-keeping) were important predictors of which teens were indoor tanners [43]. It is important, therefore, to direct efforts at both the teens and their parents. Adults seeking their own skin care are often parents also. In addition to discussing their UV exposure it is important to educate them as role models and monitors of their adolescents’ UV-related behavior.

New approaches based on risk to appearance from tanning

Appearance-related factors are the most common predictors of sunbathing and tanning light use [14,16,44]. Because adolescents have an optimistic assessment of health risks, later adult health problems do not motivate them to change risk behaviors that are currently pleasurable [45]. Recently college students have been shown to be more likely to change their behaviors when the immediate risks to appearance were emphasized rather than cancer risks [28,46]. This research has led to a new approach to skin cancer education that demonstrates personal vulnerability. The individual views early skin changes from sun exposure [47] visible under UV light (Dermascan) or from a picture taken with a camera with a UV flash. These methods have been used with college students and adults at school and beach settings where more than 90% show skin changes [48]. In several studies, the viewing of UV-filtered photographs along with written or video educational information about aging from the sun have resulted consistently in changes in planned and reported sun protection motivation and behaviors [49,50]. These changes in intention to use sunscreen also led to a subsequent decline in reported sunbathing in college students and young adults. In one study it resulted in self-reported increased rates of sun protection up to 2 years later [51,52]. This type of intervention recently was also shown to increase the use of sunscreen during nonintentional sun exposure. Providing sunless lotions resulted in their use in 37% of the subjects [53]. Risk-to-appearance interventions have been shown to be effective with both males and females. The authors have also found that the Dermascan had a powerful impact in younger ages where early skin damage existed in two thirds of seventh and eighth graders. Applying this work to the clinical setting would involve using UV-filtered photography for immediate feedback combined with a focus on the adverse impact of UV on appearance in addition to long-term cancer risks.

Summary

Changing UV exposure in adolescents and young adults has the potential to prevent years of excess exposure and subsequent skin cancer. Initial expectations were that an individual or media campaign informational approach would change this behavior. It is being recognized that current efforts have failed. Changing UV behaviors is challenging and has much in common with changing other health risk behaviors [54]. There are immediate rewards that at present exceed the perceived benefits from changing UV-exposure behaviors. Similar to tobacco and alcohol, there is also an industry that benefits from recruiting new participants in this risky behavior. Research is just beginning to show some promising approaches, and will benefit from our experience attempting to change other risky behaviors. It is likely to take unified multiple approaches, from more sophisticated individual counseling, to new community and educational approaches, to national efforts by public health and medical professionals to begin to change the increasing appeal of intentional tanning.
References


Androgen hormones play a critical role in common skin disorders including acne vulgaris, androgenetic alopecia, and hirsutism. There is both direct and indirect evidence to support this claim. For example, acne vulgaris begins to develop around the time of adrenarche, when the adrenal gland begins to produce androgen hormones. More specifically, the degree of comedonal acne present in prepubertal girls has been shown to correlate with serum levels of the adrenal-derived androgen dehydroepiandrosterone sulfate (DHEA-S) [1]. Additionally, individuals who are androgen insensitive and have nonfunctioning androgen receptors do not develop acne [2]. Lastly, antiandrogen therapies improve acne, which offers further indirect evidence of the importance of these hormones in the development of acne vulgaris [3,4].

The exact mechanism by which androgen hormones contribute to the development of acne is not certain. Based on current understanding, there are four key pathogenetic factors that contribute to acne: (1) follicular epidermal hyperproliferation and follicle plugging, (2) excess sebum, (3) the presence and activity of Propionibacterium acnes, and (4) inflammation. Androgen hormones are known to stimulate sebum production and secretion and likely contribute to the development of acne by this pathway. Additionally, androgen hormone receptors and enzymes involved in androgen biosynthesis are also present in the portion of the follicle where plugging first begins and androgen hormones may be involved in initiating the development of the earliest lesion of acne, the microcomedone [5,6].
and androstenedione may be converted to testosterone and dihydrotestosterone (DHT) in the skin. 3β-Hydroxysteroid dehydrogenase acts on DHEA converting it to androstenedione. 17β-Hydroxysteroid dehydrogenase then converts androstenedione to testosterone in a reversible reaction. Under the control of 5α-reductase, testosterone is converted to the much more potent androgen, DHT. Enzymes also exist that convert potent androgens into weaker androgens or estrogens. These include aromatase and 3α-hydroxy-steroid dehydrogenase. Both testosterone and DHT can bind and activate the androgen receptor, which in turn alters gene transcription and protein synthesis. The concentration of enzymes and different rates of activity from location to location may explain why certain areas of the body are susceptible to androgen-mediated conditions and others are spared [12].

DHT seems to be the effector androgen in the development of androgenetic alopecia, hirsutism, and perhaps acne. Some of the most convincing evidence to support the central role of DHT in androgenetic alopecia stems from observations that individuals who lack the enzyme 5α-reductase type 2 do not develop male pattern hair loss [13]. Recall that 5α-reductase converts testosterone to the more potent androgen DHT. 5α-Reductase type 2 is present in the hair follicle and the prostate gland, whereas the type 1 enzyme is present in the sebaceous gland [14]. A genetic defect in the type 2 enzyme does not diminish sebum production [2]. Recent studies have been performed evaluating the role of a 5α-reductase type 1 inhibitor in the treatment of acne vulgaris. Surprisingly, there was no significant improvement in acne [15]. DHT does not seem to play as central a role in acne as it does in alopecia. Still, treatments that block the androgen receptor or lessen circulating free testosterone improve acne. Testosterone is also capable of binding and activating the androgen receptor and may theoretically worsen acne even in the absence of DHT.

### Antiandrogen therapies

The role of androgen hormones in acne, alopecia, and hirsutism can be blocked by several mechanisms. First, androgen hormone production can be inhibited. Second, the androgen receptor can be blocked, inhibiting androgen hormone from binding and stimulating androgen-mediated changes in gene transcription. Third, the degree of unbound circulating androgen, the component available to activate the androgen receptor, can be lessened by increasing sex hormone-binding globulin. Last, enzymes that convert weaker to more potent androgens, like 5α-reductase, can be inhibited.

#### Antiandrogen therapies in the treatment of acne vulgaris

**Combination oral contraceptives**

Combination oral contraceptive pills (OCPs) combine an estrogen with a progestational agent. The estrogen component is ethinyl estradiol in various dosages, whereas the progestin varies widely from pill to pill. The progestins incorporated into the various OCPs also vary widely in their androgenic capabilities and there has been some concern that these agents may worsen acne. When combined with ethinyl estradiol, however, the net effect of a combination pill is antiandrogenic [16]. These combination oral contraceptives exert this net antiandrogen effect by increasing sex hormone-binding globulin and decreasing free, unbound testosterone and by decreasing ovarian production of androgen hormone.

Numerous combination oral contraceptives have been evaluated to determine efficacy in the treatment of acne vulgaris. A recent meta-analysis pooled and compared acne studies that were specifically evaluating the efficacy of OCPs in the treatment of acne [17]. Out of 77 trials originally identified, 24 studies met the inclusion criteria for evaluation. These studies evaluated a variety of OCPs with a total of eight different progestins. All of the included studies documented improvement in acne. The OCPs compared with placebo performed better than the placebo and when two OCPs were compared, all but two studies showed no significant difference between the groups. The two studies that did show a difference in efficacy both compared ethinyl estradiol, 30 μg, and levonorgestrel, 150 μg, with pills containing either ethinyl estradiol, 30 μg, and chlormadinone acetate, 2 mg, or ethinyl estradiol, 35 μg, and cyproterone acetate, 2 mg. The progestins chlormadinone acetate and cyproterone acetate are not available in the United States. Cyproterone acetate is a novel progestin that is also an androgen receptor blocker.

Drospirenone is another progestin with both antimineralocorticoid and antiandrogen properties. Drospirenone also effectively blocks the androgen receptor. Ethinyl estradiol, 30 μg, and drospirenone, 3 mg, has been compared with ethinyl estradiol, 35 μg, and cyproterone acetate, 2 mg, in the treatment of acne vulgaris. Both combination oral contraceptives improved total acne lesion by about 60%
after 9 months of treatment with no significant difference between the two OCPs under evaluation [18]. Ethinyl estradiol and drospirenone is available in the United States but is not approved by the Food and Drug Administration (FDA) for the treatment of acne. To date, two combination oral contraceptives have FDA approval for acne treatment. These include ethinyl estradiol, 20, 30, or 35 μg, and norethindrone acetate, 1 mg, and ethinyl estradiol, 35 μg, and norgestimate, 0.180, 0.215, or 0.250 mg.

Combination OCPs do have potential serious adverse effects. These include an increased risk of venous thromboembolism, stroke, and myocardial infarction [19]. The risks of venous thromboembolism, ischemic stroke, and myocardial infarction are heightened with higher doses of ethinyl estradiol. The risks of stroke and myocardial infarction are also more likely in individuals with hypertension, diabetes, and migraine headaches and in individuals who smoke cigarettes. There is some controversy as to whether or not OCPs increase the risk for the development of breast cancer. A large meta-analysis examined a total of 54 studies enrolling 53,297 women with breast cancer and 100,239 control patients. Current users of OCPs had a relative risk of developing breast cancer of 1.24 versus nonusers and this small increased risk persisted for approximately 10 years [20]. More common side effects of OCPs include mood changes, breast tenderness, nausea, and breakthrough bleeding. Combination OCPs do have protective effects against ovarian and endometrial cancer and help to regulate the menstrual cycle [19].

**Spironolactone**

Spironolactone may be used effectively to treat acne vulgaris in some women. Spironolactone blocks the androgen receptor, inhibits androgen production, and inhibits the 5α-reductase enzyme. Spironolactone is also an aldosterone antagonist and diuretic and side effects may include polyuria, nocturia, dizziness, and hyperkalemia. Irregular menstrual periods may be experienced in some women taking spironolactone. Doses prescribed for the treatment of acne range from between 50 and 200 mg each day. Lower doses are associated with fewer side effects [3]. Women of childbearing potential must use a reliable form of birth control. Exposure of a male fetus to spironolactone may cause feminization of the male genitalia. Co-administering spironolactone with an oral contraceptive helps protect against this risk, helps to avoid spironolactone-induced dysmenorrhea, and may further improve acne.

Lower dosages of spironolactone are associated with fewer side effects and are still effective in the treatment of acne vulgaris. In one study, 85 women were treated with spironolactone, 50 to 100 mg each day, either alone or in combination with a systemic antibiotic or an oral contraceptive [3]. Those studied received treatment from between 2 months to 2 years. Thirty-three percent of patients cleared with low doses of spironolactone and 33% had marked improvement. Twenty-seven percent showed a partial improvement and 7% showed no improvement. Fifty-seven percent of patients reported no adverse effects. Seventy-three of the 85 women evaluated had serum potassium measurements and only 13% of these patients exhibited mild hyperkalemia, which was reported to be clinically insignificant.

In another study, 38 women with acne were treated with spironolactone, 50 mg twice each day, on days 5 through 21 of the menstrual cycle. Thirty-two patients completed the study and all but one of them experienced improvement in acne. No electrolyte abnormalities were reported [21]. This small study lends support to the observation that low doses of spironolactone are well-tolerated and still effective in the treatment of acne vulgaris.

**Flutamide**

Flutamide has also been used in the treatment of acne vulgaris. Flutamide is a nonsteroidal androgen receptor blocker FDA approved for the treatment of prostate cancer. Its efficacy has been measured in both the treatment of acne vulgaris and hirsutism. Improvement in acne was reported in 11 of 15 patients receiving 250 mg twice a day of flutamide [22]. Potential adverse effects include fatal hepatitis [23]. There is also a risk of feminization of the male fetus and women of childbearing potential must use an effective form of birth control while taking flutamide. Although flutamide has proved efficacy in the treatment of acne vulgaris, potential adverse effects and cost may limit its usefulness.

**Antiandrogen therapies in the treatment of androgenetic alopecia**

Androgen-mediated hair loss is characterized by thinning of the hair in a bitemporal pattern and on the vertex of the scalp. This pattern is referred to as “male pattern hair loss.” It may, however, be seen in men and women and seems to have a strong underlying androgen influence. Women with male pattern hair loss may or may not exhibit other signs of
hyperandrogenism including hirsutism, acne, and abnormal menstrual periods. Male pattern hair loss is often responsive to antiandrogen therapies. Female pattern hair loss presents differently. It is characterized by thinning of the scalp hair on the midfrontal scalp with sparing of the frontal hair line. This type of hair loss does not seem to be under the influence of androgens and does not respond well to antiandrogen therapy [7,8].

Finasteride

Finasteride inhibits 5α-reductase type 2, inhibiting the conversion of testosterone to the more potent DHT. Men with 5α-reductase type 2 deficiency do not develop male pattern hair loss, suggesting a key role for this enzyme and DHT in some types of alopecia [13]. Finasteride has been evaluated in men with both vertex balding and frontal balding [24,25]. Studies evaluating vertex balding enrolled 1553 men who were randomized to receive either finasteride, 1 mg each day, or placebo. Forty-eight percent of the men treated with finasteride exhibited improvement in hair growth at 1 year compared with those men receiving placebo and the results were sustained throughout the 5-year study. Only 10% of men receiving finasteride demonstrated worsening of alopecia compared with 75% of those receiving placebo [24]. Finasteride has also proved effective for some men with frontal hair loss [25]. Finasteride has been evaluated in women with female pattern hair loss. No clinical improvement was measured in postmenopausal women receiving finasteride versus placebo [8]. Oral finasteride, 1.25 mg each day, may offer improvement in women with hyperandrogenism [26]. Additionally, a small case series did show improvement in alopecia in five women without hyperandrogenism treated with 2.5 to 5 mg each day of finasteride [27].

Finasteride is FDA approved for androgenetic alopecia in women at doses of 1 mg each day. Side effects are not common. In particular, there is no affect of spermatogenesis and the amount of finasteride secreted in the semen does not pose a threat to a pregnant woman or the developing fetus [28]. Potential sexual side effects have been evaluated. Decreased libido, erectile dysfunction, and decreased ejaculate volume were experienced by 1.8% of men aged 18 to 41 receiving finasteride versus 1.1% of men receiving placebo [24]. In the 41 to 60 age group, 8.7% of men receiving finasteride experienced sexually related side effects versus 5.1% of those receiving placebo [29].

Other antiandrogens may be useful in alopecia in women but generalized antiandrogen effects make these medications unsuitable for androgenetic alopecia in men.

Flutamide

Flutamide is a nonsteroidal antiandrogen that has shown some success in women with alopecia and hyperandrogenism. Twelve women with hyperandrogenism and alopecia were treated with flutamide, 250 mg each day, for 1 year. At the end of the treatment period, women treated with flutamide did exhibit a modest improvement, which was statistically significant compared with the other treatment groups evaluating finasteride, cyproterone acetate, and no treatment. These other treatment groups did not show significant improvement in alopecia [30].

Flutamide is FDA approved for the treatment of prostate cancer. Fatal hepatotoxicity has been reported with the use of flutamide [23]. Additionally, female patients must not become pregnant while taking flutamide because of the potential risk of feminization of the male fetus.

Spironolactone

Spironolactone blocks the androgen receptor, inhibits 5α-reductase activity, and inhibits biosynthesis of androgen hormone. It has been used to treat acne, hirsutism, and alopecia in female patients but evidence to support its efficacy in female pattern hair loss is difficult to find. A recent report assessed spironolactone versus cyproterone acetate in the treatment of female pattern hair loss. Eighty women between the ages of 12 and 79 years were included in the study; 40 of these women received spironolactone, 200 mg each day, and the remaining 40 subjects received cyproterone acetate, 50 mg each day, in postmenopausal women and 100 mg for 10 days during the menstrual cycle in premenopausal subjects. There was no significant difference in improvement between the two groups but overall 44% of women experienced hair regrowth and 44% experienced no improvement or no worsening during the treatment period [31]. Other small studies have also documented improvement in alopecia in women with known hyperandrogenism [32].

Cyproterone acetate

Cyproterone acetate blocks the androgen receptor and exhibits overall antiandrogen effects. It is used widely for the treatment of androgen-mediated
conditions in women including acne and hirsutism. It is not available in the United States.

Cyproterone acetate was recently evaluated in the treatment of female pattern hair loss. Eighty women age 12 to 79 were included in the study. Forty women were treated with cyproterone acetate and 40 were treated with spironolactone. Women treated with cyproterone acetate were given different doses depending on whether or not they were premenopausal or postmenopausal. Premenopausal women received cyproterone acetate, 100 mg each day, on days 5 through 15 of the menstrual cycle in combination with an oral contraceptive. Postmenopausal women received cyproterone acetate, 50 mg each day. No significant differences in hair regrowth were seen between the two groups. Overall, 44% of women had hair regrowth. Only 12% experienced further hair loss during the study [31].

Antiandrogen therapies in the treatment of hirsutism

Hirsutism is defined as male patterned terminal hair growth in a female. It may be a sign of androgen excess but may also be seen in women with normal circulating androgen levels. Hirsutism in the presence of normal ovulatory function and normal circulating androgen levels is referred to as “idiopathic hirsutism.”

Combination oral contraceptive pills

OCPs decrease free circulating testosterone by increasing sex hormone–binding globulin and the bound fraction of testosterone. Additionally, they decrease ovarian androgen production. OCPs have shown efficacy in the treatment of hirsutism associated with hyperandrogenism [33]. A more recent study evaluated a small group of women with hirsutism with or without serum androgen elevations. Ten subjects were treated with the combination OCP containing ethinyl estradiol and levonorgestrel for 9 months. An additional 11 subjects were treated with ethinyl estradiol and desogestrel. Third-generation OCPs contain progestins like desogestrel that have less androgenic capability than do first- and second-generation progestins. In this small study, both OCPs significantly decreased hirsutism [34].

Cyproterone acetate

Cyproterone acetate is an androgen receptor blocker with progestational activity. It is not available in the United States but is used widely in other countries both alone and as a component of a combination OCP. Cyproterone acetate, 12.5 mg each day, for the first days of each month in combination with ethinyl estradiol was compared with low-dose flutamide, finasteride, and ketoconazole in the treatment of hirsutism. The cyproterone acetate–treated group showed significant improvement in hirsutism as did the flutamide-treated group. Both of these medications out performed finasteride in hair reduction [35]. Cyproterone acetate and ethinyl estradiol has the added benefit of contraceptive benefits. Flutamide and finasteride may cause feminization of the male fetus and women of childbearing potential must use effective contraception while undergoing treatment.

Spironolactone

Spironolactone may also be used in the management of hirsutism. It has been compared with flutamide and finasteride in several studies [36,37]. Erenus and coworkers [37] evaluated 40 premenopausal women with idiopathic hirsutism. Patients were randomly assigned to receive either finasteride, 5 mg each day, or spironolactone, 100 mg each day, for 9 months. Both treatment groups improved but those treated with spironolactone had significantly greater improvement than those treated with finasteride at both 6 and 9 months. Interestingly, five women in the spironolactone-treated arm of the study took oral contraceptives after 6 months because of irregular menstrual bleeding. These results were not included in the final statistical analysis but they did show an overall decrease in hirsutism score of 48.25% at 9 months. This is compared with 42.36% overall decrease in hirsutism in women treated with spironolactone alone and 15.15% in those treated with finasteride. Spironolactone may cause feminization of an exposed male fetus and irregular menstrual bleeding. Both of these potential side effects can be managed by the addition of an OCP. The addition of an OCP may also offer added benefit in the treatment of hirsutism.

Flutamide

Flutamide also has proved efficacy in the management of hirsutism. In particular, one study treated subjects with idiopathic hirsutism with flutamide, 500 mg each day, for 12 months. Significant reductions in hirsutism were noted in treated subjects [38]. Flutamide, 250 mg each day, may also improve hirsutism [39]. Flutamide, 250 mg each day, has been compared with finasteride in hirsute women and
showed greater reduction in hair growth than the 5α-reductase inhibitor [39]. Although effective in the treatment of hirsutism and other androgen-mediated conditions of the skin and hair, potential hepatotoxicity, including fatal hepatotoxicity, limits the usefulness of flutamide in these conditions.

Finasteride

Finasteride has been evaluated for efficacy in the management of hirsutism and has been compared with other antiandrogen therapies including spironolactone and flutamide [36,37,39]. In one comparative study, 20 women with idiopathic hirsutism were treated with spironolactone, 100 mg each day, whereas another 20 subjects received finasteride, 5 mg each day. Spironolactone resulted in a greater reduction in hirsutism than did finasteride [37]. Finasteride has also been compared with flutamide and cyproterone acetate. Both flutamide and cyproterone acetate led to greater reductions in hirsutism than did finasteride [35].

Laboratory evaluation for hyperandrogenemia

Females with hirsutism or male pattern hair loss certainly warrant an evaluation for excess circulating androgens. Additionally, females with acne that does not respond to traditional treatments or that is associated with other signs of hyperandrogenism should be evaluated. Screening laboratory evaluation should include total and free testosterone, DHEAS, 17-hydroxyprogesterone, and luteinizing hormone/follicle-stimulating hormone ratio. Elevations in testosterone may signify polycystic ovary syndrome or an androgen-secreting ovarian tumor. Elevations in DHEAS signal adrenal hyperplasia or an adrenal tumor. An elevated 17-hydroxyprogesterone also signals adrenal hyperplasia. A luteinizing hormone/follicle-stimulating hormone ratio greater than 2 indicates polycystic ovary syndrome. Male patients may also be diagnosed with congenital adrenal hyperplasia or androgen-secreting neoplasms. Clinical signs of androgen excess are less apparent in males than in females but severe or difficult-to-treat acne should prompt an evaluation for underlying hormonal abnormalities.

Summary

Antiandrogen therapies may be beneficial in the management of androgenetic alopecia, hirsutism, and acne vulgaris. Improvement may be observed in both individuals with hyperandrogenemia and in those with normal circulating levels of androgen hormones.

References


Vulvar Disease Pearls

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Vulvar disease is an orphan disease. Diseases of the vulva are not a priority in any of the women’s health initiatives. These diseases fall through the cracks of medical education at all levels and in all specialties. Although the area involves significant and problematic skin surfaces it is rarely taught to dermatologists. Many caregivers looking after women’s genital diseases are busy passing through the vulva and seldom stop to look. Even if they see changes, these may not be recognized.

Women themselves have little to no genital education. Many were brought up with the prevailing cultural taboos about the female genitalia and are members of the “down there” generation [1] where almost no words are spoken to refer to the female genitalia, internal or external. Unfortunately, these taboos and embarrassment are shared by their medical caregivers and inaccuracies are perpetuated even in the public experience, where “The Vagina Monologues” [2] are mostly about the vulva, not the vagina.

Because of these factors women suffer with undiagnosed symptoms. They waste millions of dollars on antifungals because they think everything is a “yeast” infection. They hide and scratch in their embarrassment. They endure chronic vulvar pain and dyspareunia. Many are desperate for help. Dermatologists, as the experts in skin care, are vital for vulvar care. The following pearls make vulvar care and management better.

Normal vulvar anatomy

The first pearl for managing vulvar disease is recognizing normal vulvar anatomy. The vulva is defined as the structures between the thighs bounded laterally by the genitocrural fold, anteriorly by the mons pubis, and posteriorly by the posterior commissure. The main anatomic structures include the mons pubis, labia majora, labia minora, clitoris, vestibule, urethral meatus, and the hymen with its surrounding vestibular glands including Bartholin’s glands. The innermost aspect of the vulva is the vestibule. It encompasses the opening of the urinary tract with the urethral meatus, and the opening to the vagina with its hymenal ring. The vestibule extends posteriorly from the clitoral frenula to the posterior commissure and laterally to Hart’s line, where the nonkeratinized transitional epithelium of the vestibule joins the keratinized squamous epithelium at the base of the medial aspects of the labia minora. This nonkeratinized squamous epithelium of the vestibule contrasts with the keratinized surface of the labia majora and of the skin elsewhere. The surface is like that of the mucous membranes of the oropharynx. It lacks a protective keratinized surface, resulting in diminished barrier function, explaining why this tissue is easily irritated and infected under certain circumstances, such as incontinence.

The normal appearance of the vulva varies considerably depending on age and ethnic background. Hormone factors modify the size and shape of the labia, hymenal ring, the degree of pigmentation, and the hair growth. Labia minora vary widely in size, shape, and texture. They can be small and smooth or very asymmetric, long or stubby, with or without...
notched edges. At birth the hymen, vestibule, and the clitoris are plump from maternal hormones. In infancy the labia minora are very small and the mons and labia majora are hairless with an intact hymen. These change significantly at puberty and again after menopause.

It is very important that the normal anatomy of the vulva is recognized [3–5]. The whole vulvar architecture becomes flattened with scarred areas in chronic vulvar dermatoses, such as lichen sclerosus. Often the clitoris and labia minora are scarred and lost. Make sure there are no “missing bits.” Make sure the clitoris with its prepuce is intact and one can retract the prepuce exposing the clitoris. Make sure the small frenula that attach the labia minora to the base of the clitoris are present. The folds of the labia minora and labia majora with the clitoris give the vulva a typical three-dimensional appearance (Figs. 1 and 2).

A good general vulvar diagram (Fig. 3) is important for not only the caregiver but also the patient. When examining vulvar patients it is always important to do an educational vulvar examination so that not only is the patient examined well but is also taught to examine herself, empowering her to look at herself in this area, so often neglected, and participate more fully in her own care. Fig. 3 is available on the website for the International Society for the Study of Vulvovaginal Disease at www.issvd.org.

Normal vulvar anatomic variations

The second pearl is recognizing vulvar anatomic variations. These normal variations can be misinterpreted as abnormality.

The most frequent is sebaceous hyperplasia, which is found in 75% to 95% of women in the reproductive age group. These are small, yellow sebaceous glands found along the inner aspects of the labia minora and up around the edges of the clitoris. They can be prominent and can coalesce into cobbled, yellow plaques. They are completely harmless.

Vulvar papillomatosis, another normal variation, is found in 8% to 48% of normal women in the reproductive age group. These are symmetric, frond-like, or filiform soft projections in the central margin of the vulvar vestibule. Unlike condyloma acumina-
tum, these are soft (Figs. 4 and 5) [3,6]. Hypertrophy of the labia minora is not uncommon. It is noted at puberty. It is defined as a labial length from the base to the edge of over 4 cm. Usually asymptomatic, it can cause problems for hygiene, physical activity, or sexual intercourse.

Atrophic vulvovaginitis develops when there is inadequate estrogen. It affects the tissues of the vagina and vulva so that they become thin and atrophic. This estrogen loss with epithelial thinning causes alteration of the barrier function resulting in susceptibility to irritation and infection. The mucosa pales, the pubic hair thins, and pigmentation fades. The labia majora atrophy and the labia minora shrink. There can be introital stenosis, fissuring, and even a malodorous discharge. Patients complain of vulvar burning, dysuria, pruritus, tenderness, and dyspareunia. Lack of estrogen is most commonly caused by natural or surgical menopause but it also can occur, to a partial degree, postpartum, with birth control pills, with breast-feeding, and with the use of estrogen blockers like tamoxifen. This condition is important because it can easily be overlooked. It is a complicating factor in the management of all vulvar diseases, such as lichen sclerosus, lichen planus, contact dermatitis, and so forth (Fig. 6) [3,7].

Recognizing candidiasis

Common conditions affecting the vulva are missed because of atypical presentations and misinformation. The most common misdiagnosis is candidiasis, so the next pearl is to recognize candidiasis.

Vaginitis is one of the most common complaints in clinical medicine and vulvovaginal candidiasis is one of the most common causes. The result is that most women and their caregivers mistakenly assume that any itchy, burning, vulvar irritation whether it is caused by a dermatosis, bacterial vaginosis, or urinary tract infection is caused by “yeast.” Women quickly reach for an over-the-counter tube or tablet to treat themselves [8,9]. Too often a telephone diagnosis of yeast is made by their caregivers. Even if the patients are seen and examined, there is a 50% chance the infection is missed. Candidiasis is frequently not easy to diagnosis and can be difficult to treat [10].

Vulvovaginal candidiasis is classically recognized to be associated with diabetes and the use of
antibiotics but is often missed in patients who are locally immunocompromised by topical steroids used for vulvar dermatoses, such as lichen sclerosus or lichen planus. It not only can complicate these chronic vulvar dermatoses, but it can also be a major promoting factor. Look for candidiasis in every chronic, itchy, or burning vulvar eruption.

Eczematous vulvar candidiasis produces a pattern that is often unfamiliar, with itching, irritation, and redness but little to no vaginal discharge. The clues include marked redness and fissuring. Chronic pruritus and resultant scratching produces a picture of lichen simplex chronicus but this chronic dermatosis is actually caused by yeast. KOH and culture confirm the diagnosis.

Painful fissuring is an often overlooked hallmark of candidiasis. It is found classically periclitorally, in the interlabial sulcus and in the small folds around the introitus.

For diagnosis, a KOH may be positive in only 40% of cases. A culture using Sabouraud’s medium is best. Seventy-five percent of cases are caused by the common Candida albicans, 25% are caused by the imidazole-resistant Candida glabrata or Candida tropicalis. C albicans responds well to treatment with any of the intravaginal imidazoles for 1 to 7 days or an oral dose of fluconazole, 150 mg or a single dose [11]. The imidazole-resistant candidal infections require treatment with boric acid and rarely topical flucytosine [12]. Recurrent yeast infections [13] affect about 5% of women and they may need long-term suppression using 150 mg of fluconazole weekly for up to 6 months [14,15].

**Herpes simplex virus**

Herpes simplex virus (HSV) is the most common sexually transmitted disease in the world and the most common cause of vulvar ulcers. This genital infection is familiar to all caregivers but is far too often overlooked because of atypical presentations. Genital herpes is caused by HSV-2 in 80% of cases but the frequency of genital HSV-1 is now rising [16]. HSV infections affect 20% of the sexually active population in the United States with an estimate of 500,000 new cases of genital HSV annually. In Africa, the HSV-2 prevalence rate is 40%. This is a worldwide epidemic.

Transmission occurs through contact, mostly from partners unaware of their own oral or genital herpes infections and who are free of lesions at the time of contact. About 70% of all genital HSV-2 infections are transmitted during asymptomatic shedding. Primary genital HSV is uncommon. Almost all cases seen are recurrent because acquisition of the infection is not recognized by the patient or by their caregivers. Ninety-one percent of HSV-2 carriers are unaware of their infection but 80% do have symptoms. Patients self-misdiagnose their symptoms of recurrent HSV as vaginitis, soap allergy, lack of lubrication, irritation from tight jeans or G-strings, recurrent urinary tract infections, or even hemorrhoids. Because of this most women present with nonprimary, recurrent disease and are shocked to learn that HSV is the cause.

In patients presenting with acute, painful, vulvar ulcers at any age, look carefully for the typical herpetiform pustules that are classically seen with this infection. Laboratory tests are necessary to confirm the clinical impression. The diagnosis of herpes simplex usually requires the gold standard test, HSV culture. This needs to be done in the first 48 hours of an outbreak for any undiagnosed patient presenting with acute or recurrent vesicles, pustules, or ulcers. For any atypical lesions, symptoms, or presentations, type-specific serology for HSV-1 and HSV-2 can be helpful to identify patients who have been infected [16,17]. Consider HSV as a cause for painful, necrotic vulvar ulcers in an immunosuppressed patient. It can sometimes be a problem in patients using long-term superpotent topical corticosteroids. Very rarely herpes simplex can present with recurrent pain and burning in the vulvar area on an episodic basis without any cutaneous changes. This is called herpes simplex sine eruptione. Antiviral treatment can be effective for suppression of infection and to control transmission.

Fig. 7. Severe primary HSV with necrotic vulvar ulcers in a young girl. Note the typical groups of herpetiform pustules in the left periurethral area in the upper vulvar trigone.
Continuous once daily valacyclovir, 500 mg per day, can reduce genital transmission (Figs. 7 and 8) [18–20].

**Vulvar contact dermatitis**

The next pearl is to recognize contact dermatitis on the vulva. Vulvar contact dermatitis is frequent and complicates all vulvar conditions. It can be difficult to diagnosis because the clinical presentation may vary from minor to extreme and often may be superimposed on pre-existing conditions, such as lichen simplex chronicus; lichen sclerosus; herpes simplex; or even a tumor, like squamous cell carcinoma.

Vulvar contact dermatitis can be irritant, allergic, acute, subacute, or chronic. The commonest type in the vulva is irritant contact dermatitis, a common cause of pruritus vulvae. This is not surprising because the barrier function of vulvar skin is substantially weaker than other skin surfaces. Complicating this is a combination of vulvar taboos and ill-informed hygiene practices. It is not uncommon for women, fearing any detectable odor or infection, to develop overzealous hygiene habits with the use of harsh soaps, detergents, face cloths, and so forth. In the presence of estrogen deficiency, the barrier function of the vulva is further lowered and the results can be disastrous. Adding insult to injury is a weak pelvic floor resulting in urinary or fecal incontinence. Urinary incontinence is an underrecognized, hidden problem in women. This is particularly difficult as patients age. Up to 20% of women 80 years old and older have quite severe urinary incontinence [21]. This can be a difficult problem, especially in uncooperative, elderly, or handicapped patients. Keeping the area clean and dry may be difficult especially if there is associated arthritis or obesity. The use of appropriate pads to control this incontinence is vital but the cost may be prohibitive.

Allergic contact dermatitis of the vulva is less common than irritant dermatitis. It should be ruled out in all chronic vulvar dermatoses, especially if unresponsive [22]. It is caused by a long list of potential allergens particularly fragrances, topical antibiotics, preservatives, and topical anesthetics. Even sanitary napkins have been reported to cause allergic reactions.

**Box 1. Common vulvar contactants**

**Allergens**
- Benzocaine
- Preservatives
- Neomycin
- Latex condoms
- Chlorhexadine
- Lanolin
- Perfume
- Nail polish

**Irritants**
- Soaps and cleansers
- Sweat, urine, feces
- Creams (alcohol)
- Douches
  - Medications: TCA, 5FU
- Spermicides
- Panty liners
Contact dermatitis [23]. Patients with itchy vulvar dermatoses are at higher risk for problems. Benzocaine can cause a particularly devastating contact dermatitis. It is often used by patients to control their vulvar discomfort and they may end up using it many times a day with a severe, catastrophic allergic dermatitis (Fig. 9) [24].

Vulvar contact dermatitis is a common problem. Both irritants and allergens can play a role or even overlap in the same patient. Be sure to stop all vulvar irritants and consider patch testing in poorly responding cases (Boxes 1 and 2) [25].

White vulvar conditions

All white vulvar conditions in the vulvar are not lichen sclerosus. Lichen sclerosus is the commonest chronic vulvar condition and the most familiar. White vulvar areas can be seen with lichen planus, less likely lichen simplex chronicus, rarely mucous membrane pemphigoid, and even in vulvar intraepithelial neoplasia.

Lichen sclerosus has a prevalence of between 1 in 300 and 1 in 1000. It most commonly affects women 30 to 40 years of age and presents as an itchy, white, scarred vulvar condition. Typically located around the clitoris and posterior aspect of the vulva and down the interlabial sulcus, there is a cellophane-like sheen on the white surface with varying degree of scarring. Classically, there may be a figure-eight pattern around the vulva and anus. Symptoms are variable and can range from asymptomatic vulvar scarring to mostly itching and, less commonly, pain. Scarred patients presenting to their caregivers for regular Pap smears can be missed because they are presumed to have early menopause to account for the loss of their normal architecture. Infrequently there may be ulcers and erosions, especially if there is an associated contact dermatitis or an infection from bacteria or yeast, or trauma, or tumor. Four percent of patients develop squamous cell carcinoma of the vulva. When seeing a patient who presents with scarring (loss of labia minora, loss of the clitoris) and whiteness of the vulva, confirm the diagnosis with the appropriate biopsy [26,27]. Note that lichen sclerosus does not involve the vagina. Lichen sclerosus responds well to superpotent steroids, such as clobetasol or halobetasol 0.05% ointment used regularly for 12 weeks [28]. Without long-term treatment these patients relapse in 85% of cases. Although controversial, it is recommended that maintenance treatment once or twice a week be ongoing [29] and long-term regular follow-up is indicated (Figs. 10 and 11) [26].

Lichen planus is the other classic white vulvar condition. It is often missed or is confused with vulvar lichen sclerosus because they both present white areas, loss of architecture, and scarring. The onset of lichen planus is between ages 50 and 60. This condition may be widespread involving skin, oral, anal, vaginal, and esophageal mucosa and less commonly even the bladder, nose, and larynx. The pattern on the skin, nails, scalp, and oral mucosa is well known to dermatologists and should trigger an inspection of the vulva [30]. Although there can be symptoms of itching, most usually there is burning pain with a history of dysuria plus dyspareunia if there is vaginal involvement. Vulvar erosions are seen in 95% of

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**Box 2. Tips on vulvar contact dermatitis**

- Commonest: Irritant contact dermatitis
- Skin protective barrier compromised by
  - Urine and feces (burn enzymatically or chemically)
  - Inadequate estrogen
  - Existing dermatosis
- Stop all vulvar irritants
- Consider patch testing to define the role of allergens
- Continue to reassess vulvar patients for contact dermatitis
cases of vulvar lichen planus and of these 50% to 60% have vaginal and 60% oral involvement. About 20% of oral lichen planus patients have vulvovaginal involvement.

Classically, there are white, lacy, or fern-like areas, or flat-topped papules forming plaques, most commonly on the perictitoral area and vulvar trigone. Consider the diagnosis of lichen planus when a patient presents with painful, glossy red, vulvar erosions. This is the typical glazed erythema associated with scarring around the labia minora and vestibule. The borders of these lesions may be white or smudgy to smoke gray. The vaginitis of lichen planus is referred to as “desquamative vaginitis” and can present as vaginal erosions, atrophy with a purulent malodorous discharge, and varying degrees of synechiae and scarring. The vagina may be completely obliterated (Figs. 12 and 13).

The whiteness of this condition is not usually as white, shiny, and well demarcated as in lichen sclerosus. Erosions are much more common. In lichen planus, the perianal area and especially the vagina must be examined. Biopsies are important but unfortunately the pathology is often nonspecific. Direct immunofluorescence may be helpful. Diagnosis is usually made using a combination of clinical findings and histology, although histologic diagnosis is frequently difficult [31,32].

Most cases respond well to superpotent steroid ointments but not as easily as lichen sclerosus. In more severe cases systemic or intravaginal steroids are needed. Topical tacrolimus ointment may help as a steroid sparer. For very severe involvement cyclosporine, retinoids, and even methotrexate have been used [30,33]. As in lichen sclerosus there is a 2% to 3% risk of squamous cell carcinoma [34,35].

Lichen simplex chronicus of the vulva presents with somewhat whitish gray discoloration caused by lichenification and maceration. It can usually be differentiated from lichen planus and lichen sclerosus by the severe, intolerable itch; the absence of scarring; and the epidermal thickening and dyspigmentation of the vulva [36]. This is the classical itch-scratch-itch condition seen in the vulvar area in vulvar disease pearls 151.

Fig. 11. Traumatic vulvar lichen sclerosus with very shiny white color and purpura from scratching.

Fig. 12. Erosive vulvar lichen planus showing scarring with loss of the clitoris and labia minora with the glazed erythema and lacy white to smudgy gray edges.

Fig. 13. Erosive vulvovaginal lichen planus with extensive scarring, loss of clitoris and labia minora, and generalized glazed erythema.
patients with a background of atopy or, less commonly, a tendency toward psoriasis. Contact dermatitis plays an important role here because these patients often scrub the area with irritating washcloths or sponges, and use caustic soaps and numerous irritating and sensitizing topical preparations that worsen the problem. With the skin surface open they are more susceptible to secondary infection and allergic contact dermatitis. When seeing patients with vulvar lichen simplex chronicus one has to think of more than one problem. Usually there are several factors, such as contactants (irritant and allergic); infection; and underlying dermatoses. The diagnosis is usually clinical but biopsies may be necessary. To treat these patients, infection and contact dermatitis must be properly addressed and sometimes sedation is necessary to stop the scratching. The treatment algorithm for lichen simplex chronicus is a good template for treating any itchy vulvar conditions (Box 3) [37,38].

Concomitant vulvar conditions

Dermatologists are the experts in skin diseases and excel in recognizing the concomitant cutaneous problems often present in the vulvar area. It is not unusual to see any of these conditions with secondary candidiasis, contact dermatitis, HSV, atrophy, and even cancer. Any of these conditions can be found separately or together to complicate other problems. Always look for more than one problem (Fig. 14).

Pearls for vulvar therapy

Vulvar patients take time. It is important to explore their expectations and be supportive. Sometimes the chief complaint is not the chief worry. They may be complaining of itching or burning and be very

![Fig. 14. Concomitant vulvar conditions. Atrophic white vulva with scarring from lichen sclerosus; multiple ulcers and erosions from HSV on the right upper vulva; and ulcerating squamous cell carcinoma on the left side of the vulva. HSV, herpes simplex virus; LS, lichen sclerosus; SCC, squamous cell carcinoma.](image)
worried about sexually transmitted disease, infidelity, or cancer. Be sure that the clinical picture fits their chief complaint. Avoid telephone diagnoses. Because the area is unfamiliar and is fraught with embarrassment and taboo it is important that patients understand their condition, the entire treatment regimen, and limitations of treatment. Some of these conditions are chronic and recurrent but controllable. Being realistically optimistic is important. An educational vulvar examination helps patients become familiar with themselves and their condition, and the addition of solid factual information improves their acceptance of their problem and enables them to participate more effectively in their own care. Patient education is particularly important in this area where there is so little information and so much misinformation. The resources of the International Society for the Study of Vulvovaginal Disease can be very helpful providing educational handouts. At www.ISSVD.org, click on Patient Education. Patients with vulvar conditions often have loss of intimacy with secondary anger and hostility that makes their care challenging, but with time and a patient attitude they do very well. Counseling may be important for the patient and her partner. Always include her partner in the care plan if possible.

For all vulvar conditions avoid irritants whether they are soaps, sanitary napkins, wipes, vulvar cleansing routines, and so forth. Cleanse with bare hands only. For itching conditions, correct the barrier function by stopping irritants. To restore the physiologic barrier function, soaks can be done in the Sitz bath or with a gentle hand-held shower for 3 to 5 minutes, one to two times a day. Use a thin film of petrolatum or vegetable oil after the soak to retard the water loss from the epithelial cells so the surface retains moisture. Estrogen replacement, either topical or systemic, can be beneficial if indicated. Incontinence needs appropriate management. Incontinence is an embarrassing problem that most women neglect to discuss; it should be asked about.

To break the itch-scratch-itch cycle, sedation is often necessary with up to 75 mg hydroxyzine or doxepin at night. For morning sedation, consider citalopram or fluoxetine, 20 mg. Nonspecific techniques for stopping itching include the use of soft cool gel packs. These can be kept in a plastic bag in the refrigerator and used as needed. Do not freeze them because contact causes frostbite. Plain cold yogurt on a sanitary napkin may be helpful.

To reduce inflammation, corticosteroids are usually the mainstay of topical treatment for itchy, inflamed dermatoses. These may not be the cure but they reverse inflammation and start the healing process. Limit the amount prescribed to 15 g. Instruct the patient in its use. A tiny dab spread in a very thin film to the involved areas is all that is necessary. Vulvar mucous membranes (vulvar trigone and inner labia minora) are relatively steroid resistant, whereas the outside of the labia minora, labial crural fold, labia majora, and thighs and the perianal skin thin more easily so overflow must be avoided. As the patient improves, decrease the frequency of topical steroid application or switch to a lower potency product. Make sure secondary yeast infection is controlled. The superpotent steroids, clobetasol and halobetasol, are excellent products for the chronic vulvar dermatoses, lichen sclerosus, lichen planus, and lichen simplex chronicus. To be used effectively, a long enough course is essential. Unfortunately, topical steroids are often given for too short a time or too mild a product is chosen. Overuse of these products can cause classic complications that are familiar to all dermatologists. Patients with very severe weeping irritated vulvar eruptions require oral administration of antibiotics, antifungals, and corticosteroids because topicals are not tolerated; they can irritate and burn eroded areas [37,39–41].

**Long-term supervision**

Effective vulvar care requires long-term supervision. Supervision not only ensures improvement and monitors for complications but also improves compliance. Many of these conditions are chronic with no cure. In the case of treated lichen sclerosus, up to 96% are symptom improved and about 70% symptom free, but without treatment 85% of them relapse in 4 years. The cancer risk is about 4%. The difficulty with lichen sclerosus and even lichen planus is that these conditions can so often be asymptomatic despite progressive scarring and loss of architecture with resulting dysfunction including sexual dysfunction. With good treatment these patients do well and can stay functioning but they must be seen one to two times a year. Although lichen sclerosus and lichen planus may generate no symptoms, the most important asymptomatic vulvar condition is malignancy.

Compliance issues in vulvar care can be complex. Ignorance can be overcome with good education and communication. Secondary gain may be a problem because some patients may wish to avoid sexual contact and it is in their interest not to treat their problem. Good communication aimed at recognizing expectations is very important. There are rare patients who are phobic about touching “down there.” These
individuals need counseling. Most vulvar patients have some degree of sexual dysfunction and having access to a good sexual counselor is important to help sort out the patient with hypoactive sexual desire, sexual aversion, arousal disorder, or orgasmic disorder. These counselors are especially important in managing the vulvar pain disorders that are not discussed in this article. With a good doctor-patient relationship and good education most patients do very well.

Summary

Dermatologists are vital for vulvar care. They are the best trained in pattern recognition of disorders of the skin and so are the most effective physicians for recognizing vulvar conditions. With an understanding of the normal vulvar anatomy and normal anatomic variations, and capable of recognizing and diagnosing contact dermatitis of the vulva and the chronic white conditions (lichen sclerosus, lichen planus, and lichen simplex chronicus), dermatologists are uniquely positioned to diagnose vulvar conditions accurately. They are the best at juggling the gentle general care, avoidance of irritants, and use of the topical applications and systemic medications required in managing vulvar cutaneous problems. Dermatologically trained physicians deliver the best vulvar care.

References


The extraordinarily high prevalence of human papillomavirus (HPV) infection of the genital tract and the major morbidity and mortality associated with it mandate that all dermatologists and primary care providers be closely familiar with this entity. Data from DNA detection and serologic studies have shown that more than 50% of sexually active women have been infected at some point with one or more of the more than 40 HPV types that infect the anogenital tract [1,2]. Although the bulk of the attention has been given to HPV infection in women, it appears that age-matched men have similar or only slightly decreased infection rates [3], and it is clear that the benign and malignant clinical sequelae of HPV genital infection are a significant problem for both genders. The problem is increasing steadily in frequency; data on first-time treatment-seekers for genital warts, for example, show an increase in presentation of around 500% over the past 3 decades [4,5].

The papillomaviruses are a family of double-stranded DNA, nonenveloped viruses that preferentially infect several different hosts, from humans to cottontail rabbits. Among the HPVs, genomic sequencing has led to the identification of about 100 types, with partial-genome polymerase chain reaction (PCR) amplicons suggesting the presence of an additional 100 [6]. HPV types can be divided roughly into those that cause genital and mucosal lesions (eg, types 6, 11, 16, and 18) and those that cause nongenital cutaneous lesions (eg, types 1, 2, and 3, the causes of palmoplantar, common, and flat warts, respectively). This discussion is limited to the HPV types that cause genital lesions, and the manifestations and treatment of those lesions.

The single most clearly established risk factor for genital HPV infection is an increased number of lifetime sexual partners [7–13]. Burk and colleagues also showed that the number of partners that a woman reports her partner having had sex with is associated with her risk for HPV infection [8]. It has been proposed that smoking and oral contraceptive use are risk factors for HPV infection. Although some studies have shown a connection between smoking and HPV infection [14], the literature does not support a consistent association between HPV acquisition and either smoking or oral contraceptive use [1]. Age is an important determinant in HPV infection. For women, the peak point prevalence of genital HPV infection is in the 15- to 25-year-old age group [15,16]. Exact prevalence numbers are difficult to assess because most studies have sampled only one genital area (eg, cervix), many studies only focus on the high-oncogenic risk HPV types, and results have varied considerably based on the location of the study. But a recent large study in the United Kingdom of women presenting for routine cervical screening showed a 42% detection rate of HPV DNA (either high- or low-risk types) in women aged 16 to 25 compared with 23% in women...
Pathogenesis and host response

Infection with HPV occurs by direct inoculation of the virus into the epidermal layers through epithelial defects. Because a history of local cutaneous trauma is rarely present, it is likely that the virus enters through microdefects, with skin maceration being an important factor [18]. Genital infections are acquired predominantly through sexual contact and can be vertically transmitted to newborns by passage through an infected birth canal [19–22]. The rate of infectivity of HPV between sexual partners is estimated to be 60% [23]. The epithelial tropism of HPV is striking and has important implications for therapeutics and vaccine development; only surface epithelial cells are infected, and viremia is nonexistent [24]. The virus sets up infection in the basal layers, where it undergoes a variable period of latency or pseudo-latency (with only low-level viral DNA replication) [18]. Eventually, the virus stimulates proliferation of the basal layers, possibly through the expression of viral early proteins [25], producing a clinically apparent lesion. As the virus migrates up the epidermal strata inside the differentiating keratinocytes, viral DNA replication and mature virion assembly amplify.

Although there is much to be elucidated about the host’s immune response to HPV infection, several important concepts have been worked out. First, it is now generally accepted that in immunocompetent patients, most genital HPV infections are cleared spontaneously by the body’s defenses. The data cited previously in this article regarding the decreasing frequency of HPV DNA isolation from women of increasing age corroborate the fact that many infections are cleared spontaneously. More direct evidence comes from longitudinal studies showing a loss in the ability to detect cervicovaginal HPV DNA in most women 1 year after initial DNA detection [26]. Even in instances in which overt manifestations of HPV infection are present, such as cervical dysplasia or condylomata acuminata, infections often can be cleared. The 1-year regression rate of cervical low-grade squamous intraepithelial lesions (LSILs) has been found to be more than 60% [27], and it is estimated that 10% to 30% of genital warts resolve in 3 months from onset without treatment [23]. Second, it is apparent that cell-mediated immunity, as opposed to humoral defense, is the key component in clearing HPV infections. Pathologic and reverse transcriptase PCR studies on regressing papillomas in humans and canines have showed a local abundance of CD4+ and CD8+ T cells and associated mRNA transcripts [28,29]. Furthermore, patients with deficiencies in cell-mediated immunity, such as HIV-positive patients or post-transplant patients, have more frequent and severe HPV-induced diseases, from extensive, refractory warts to anogenital cancers [30–33]. The third important finding is that HPV has developed numerous methods of evading immune detection and attack, and indeed viral escape is a key factor in leading towards malignancy. The virus’s methods of decreasing immune attack include inducing a low level of local inflammation, downregulating key cytokines through viral gene expression, and pushing the immune response toward a Th2 rather than Th1 character, an advantageous situation for the virus [34]. It is the HPV E6 and E7 proteins, the proteins that are highly expressed in high-oncogenic risk HPV types, that are the main culprits in avoiding innate and adaptive immunity, thus promoting viral persistence and an increased risk for neoplasia [34].

Although more than 20 anogenital HPV types have been associated with malignancy [18], more than 70% of all HPV-related anogenital cancers contain DNA from either HPV-16 or HPV-18 [35–37]. These types are high risk for malignancy because of the unique properties of their E6 and E7 viral proteins. In the minority of individuals who cannot clear their high-risk HPV infections spontaneously (which may be related to a person’s human leukocyte antigen (HLA) haplotype [38]), altered transcriptional regulation of the E6 and E7 genes can cause these genes to be overexpressed in the proliferating basal layers of the epidermis. This process has been hypothesized to be related to integration of the viral DNA into the host genome, a phenomenon that has been observed in most cervical carcinoma cells and a subset of highly dysplastic lesions [39]. By interfering with the cell cycle control activities of tumor suppressor genes p53 and Rb, respectively, E6 and E7 overexpression induces genetic instability. The resultant accumulation of mutations leads to cellular immortalization, and in time the collection of other unspecified genetic or epigenetic alterations leads to full malignant transformation [40]. Although HPV infection is a core component, even a necessary component, in the oncogenic process, it is clear that HPV infection alone does not cause cancer; other cellular events must occur to provide the immortalized, genetically unstable cells with a truly invasive phenotype. Whether these other events are related to...
cigarette smoking, other transactivating viruses, diet, or other preventable cofactors is yet to be determined [41].

Clinical manifestations

The various clinical manifestations of genital HPV infection can be broken down into benign and malignant diseases. In addition to its therapeutic utility, this distinction is particularly logical because, in general, different HPV types cause malignant disease (the high-risk HPV-16, -18, -31, -33, -45, and so forth) and benign disease (HPV-6, -11, and so forth).

Benign diseases

Condyloma acuminatum

Condyloma acuminatum (anogenital warts) is one of the most prevalent sexually transmitted diseases worldwide, with an incidence in the developed world of 2.4 cases per 1000 per year and an estimated annual incidence of 1.2% in individuals aged 20 to 24 years [42]. Apart from subclinical or latent infection, condyloma acuminatum is the most common presentation of genital HPV infection. The vast majority of condylomata acuminata are clinically benign and attributable to infection with HPV-6 or -11. These warts can present as small, verrucous papules; discrete, sessile, smooth-topped papules or nodules; or even as large exophytic, cauliflower-like masses (Fig. 1). Color ranges from flesh-colored to pink to reddish-brown. The lesions have a moist, fleshy feel. The warts are generally no more than a few centimeters in diameter, but may be larger if individual warts coalesce. Lesions are often multifocal. The distribution of these lesions matches with the areas of highest friction during sexual activity; in uncircumcised men, the subpreputial region is particularly affected [43]. In both men and women, the lesions can involve the perineum, external genitalia, crural folds, anus, rectum, and urethra, and in women they may extend to the vagina and cervix. Cervical condylomata are notoriously difficult to detect and diagnose. Condylomata acuminata most often are asymptomatic, but can cause pruritus or mild burning. The primary differential diagnosis is syphilitic condyloma lata (which often can be distinguished only by darkfield microscopy or serology), molluscum contagiosum (which often have central umbilication), verrucous carcinoma, and benign penile pearly papules. Diagnosis is primarily clinical. For hard-to-detect lesions, such as those on the cervix, diagnosis can be aided by the application of 5% acetic acid solution to the suspect region; within minutes condylomata should appear as whitish patches on the mucosa. This acetowhitrning technique, however, is associated with a high number of false negative and false positive results [18]. If biopsy is required for diagnosis, the lesions of condyloma acuminatum show papillomatosis, hyperkeratosis, and marked acanthosis, with extensive elongation and branching of the rete ridges. Spread diffusely throughout the wart are large, vacuolated keratinocytes with clumped keratohyalin granules. HPV DNA detection can be used for diagnosis, but this method is generally limited to research facilities. Because of inconsistency of detectable antibody response to viral capsid proteins, serology has no role in routine diagnosis of condyloma acuminatum. The inability of HPV to grow in most culture systems also precludes viral culture as a method of diagnosis.

Bowenoid papulosis

A rarer genital manifestation of HPV infection is Bowenoid papulosis. The classic lesions of Bowenoid papulosis are multiple groups of well-demarcated, 2 to 3 mm papules on the external genitalia that may be somewhat red in color or hyperpigmented (Fig. 2). Differential diagnosis includes psoriasis, lichen planus, genital warts, and Bowen disease. Bowenoid papulosis is unique in that it is caused most often by the high-risk HPV-16, and yet it generally behaves in a benign manner. Biopsy samples do, however, show cellular dysplasia resembling squamous cell carcinoma in situ. Although development of invasiveness is rare, it has been reported [44,45], and thus effective treatment and close lifelong follow-up is necessary. Partners of patients with Bowenoid papulosis should be closely screened for
HPV-16–associated anogenital neoplasia, most importantly cervical and anal intraepithelial neoplasia.

Premalignant and malignant diseases

Penile, anal, vulval, and vaginal neoplasia

Although the association of high-risk HPV infection with cervical intraepithelial neoplasia and carcinoma is well known, it has become apparent in recent years that several other anogenital squamous cell carcinomas and their precursor lesions are also attributable to HPV. Anal cancers have shown rates of HPV detection ranging from 70% to 100% [46–48]. For vaginal and penile carcinomas the detected HPV prevalence rates have been 60% [49,50] and 30% to 42% [51,52], respectively. Although the HPV prevalence rate in vulvar carcinomas is significantly lower, certain subtypes do show an HPV prevalence rate approaching 100% [53]. The key to effective management of these cancers is diagnosis and treatment in the preinvasive stages. For all of these noncervical anogenital lesions, pruritus often is a sign of an intraepithelial neoplastic process. Vaginal lesions generally appear white with sharp borders and are often multifocal. Vulvar, anal, and penile lesions can present as irregular, sharply demarcated, slightly raised lesions, with pigmentation ranging from white to red to brown. The higher-risk Bowen disease and erythroplasia of Queyrat lesions cannot be differentiated histologically from Bowenoid papulosis, but certain clinical characteristics can help to differentiate these entities. Bowenoid papulosis is common in younger patients, whereas Bowen disease and erythroplasia of Queyrat rarely are seen before the age of 50 [54]. Also, a reddish hue and the presence of multiple lesions point toward Bowenoid papulosis (compare Fig. 3, Bowen disease, with Fig. 2 of Bowenoid papulosis). For penile, anal, vulvar, and vaginal intraepithelial lesions, acetic acid solution can help to visualize the dysplastic lesion. Biopsy is imperative to assess for invasiveness.

A unique malignancy caused by HPV is verrucous carcinoma (termed giant condyloma acuminata of Buschke and Lowenstein when it occurs on the genitals). This low-grade squamous cell carcinoma is most often attributable to infection with HPV-6 and -11, types generally not associated with malignancy. These lesions present as large, exophytic tumors up to several centimeters in diameter. Although locally invasive and destructive, these tumors rarely metastasize and can be managed with local excision.

Cervical neoplasia

Cervical cancer is the second most common cancer among women worldwide and the third most deadly cancer, with the vast majority of cases and deaths in the developing world [55]. Even in the United States, however, there are approximately 12,000 cases of invasive cervical cancer per year, with about 4000 deaths [56]. The current opinion is that high-risk HPV infection is necessary for cervical cancer development, with HPV DNA being found in up to 99.7% of cervical squamous cell carcinomas [57,58] and 94% to 100% of cervical adenocarcinomas or adenosquamous carcinomas [59,60]. Premalignant intraepithelial dysplasia is generally asymptomatic and is picked up on routine Pap smear. HPV DNA testing has a role, albeit somewhat undefined, in the management of cases of atypical cytology of undetermined significance. When frank dysplasia is found on cytology, colposcopy with aceto-whitening and biopsies is used to assess histology.
**Oral lesions**

A thorough discussion of HPV-induced lesions of the upper aerodigestive tract is beyond the scope of this article, but these lesions merit a brief mention here because genital–oral spread of HPV through sexual contact or childbirth is a major mechanism of transmission. Oral papillomas and the verrucae seen in respiratory papillomatosis, a disease of infancy, contain primarily the HPV-types seen in condyloma acuminata (HPV-6 and -11) [61]. In the case of respiratory papillomatosis, epidemiologic studies have shown an increased frequency of the condition in infants of mothers who have condylomata acuminata [18], supporting a theory of infection through direct oral contact with infected genitalia. More recently it has been shown that a substantial minority of head and neck cancers contain high-risk HPV DNA, primarily HPV-16 [62]. This finding is important because it opens the possibility of future antiviral methods for preventing and treating head and neck cancers.

**Treatment and prevention**

**Treatment of condyloma acuminatum**

Anogenital warts can be treated by one or more of an extensive array of pharmacologic and nonpharmacologic methods, with no definitive first line therapy at this point. Although benign, these warts are often embarrassing and cosmetically unacceptable to the patient, and if left untreated they commonly enlarge and multiply. The vast majority of patients with conspicuous condylomata therefore choose to get them treated. Treatment options can be broken down into four broad categories: antiproliferative agents, destruction or excision therapies, antiviral agents, and immunomodulatory therapy.

The antiproliferative class of agents includes podophyllin/podophyllotoxin and 5-fluorouracil. Of these, only podophyllotoxin is used routinely as a first line drug. Podophyllin/podophyllotoxin act primarily by binding to microtubule subunits and arresting cell division in mitosis [63]. The physician-applied podophyllin has fallen out of favor because of studies finding that it contains significant quantities of two known mutagens [64]. Not only are the podophyllotoxin preparations free of these mutagenic substances, but podophyllotoxin solution and cream are applied to the lesions by the patient, an arrangement often preferable to patient and physician.

The destructive methods of condyloma management include local cryotherapy, application of topical trichloroacetic acid, electrocautery, CO2 laser treatment, or excision by scissor, curette, or scalpel. Manual excision can be performed in the office for small lesions, but larger lesions often need to be managed in the operating room by an anogenital surgeon or gynecologist.

Cidofovir and interferons are drugs with direct antiviral activity that have been used in the treatment of condyloma acuminatum. Cidofovir, a nucleotide analog with broad antiviral activity, is licensed only as an intravenous agent for the treatment of cytomegalovirus retinitis, but has been used experimentally as a topical gel with fair success [65]. Its further use has been limited by cost and by the need for specialized pharmaceutical input and facilities to make topical preparations of this toxic drug. Interferons (specifically recombinant interferon-alpha) have received significant attention, but have been disappointing in primary and adjuvant treatment of condylomata, and thus are not recommended for routine clinical practice.

In the immunomodulatory realm, one drug has made a major impact on the primary treatment of condyloma acuminatum: imiquimod. A new addition to the pharmacologic arsenal, this topically-applied imidazquinoline works by stimulating toll-like receptors (ie, TLR 7) on antigen-presenting cells, and thus enhancing the local production of Th1 cytokines and a T cell-mediated, cytotoxic immune response. Imiquimod has come to prominence from studies showing that it produces a significantly lower wart recurrence rate than many of the other commonly used therapies, with a recurrence rate of 9% at 3 months [66] and 15% in a study with an average follow-up of 5.7 years [67]. In addition to condyloma acuminatum, imiquimod has been used off-label with success for bowenoid papulosis and Bowen disease, and vulvar, penile, and even high-grade cervical intraepithelial neoplasia [68–70].

Most of the aforementioned treatments for condyloma acuminatum have been associated with clearance or significant decrease in lesions in most patients and, with the exception of imiquimod, roughly equivalent recurrence rates. For pregnant patients, cryotherapy, trichloroacetic acid, or surgery are preferred because of poor safety records or lack of safety information in pregnancy for the other agents. For most other patients, choice of primary therapy is dependent on location and size of lesions, patient preferences, physician skill and experience, and cost. Because of the high risk for concomitant infection with high-oncogenic risk HPV types [71], it is im-
portant that patients with condylomata acuminata and their partners receive thorough genital and anal examinations (including anoscopy), with Pap smear for all women. Colposcopy is also recommended for women who have cervical condylomata.

**Treatment of Bowenoid papulosis**

Like treatment of condylomata, treatment of Bowenoid papulosis can take many forms, the most common being topical 5-fluorouracil, imiquimod, cryotherapy, laser treatment, and surgery. Primary treatment is decided on a case-to-case basis. For penile Bowenoid papulosis, circumcision is also recommended to remove a potential reservoir of HPV infection [54].

**Treatment of anogenital neoplasia**

Early detection and treatment of intraepithelial neoplasia is essential to prevent invasive carcinoma. For cervical specimens, low-grade intraepithelial lesions are generally treated conservatively, whereas high-grade intraepithelial lesions are treated by excision of the transformation zone, most commonly through the LLETZ procedure (large loop excision of transformation zone). Noncervical high-grade squamous intraepithelial lesions are treated differently based on the site. For vulvar lesions, excision surgery is the gold standard, but imiquimod is being used more frequently. Vaginal high-grade intraepithelial neoplasia is managed with excision, either by knife, loop, or laser; topical treatments are avoided because of fear of chronic ulceration or acquired adenosis [72]. For anal intraepithelial neoplasia, surgery and ablative treatments generally are avoided because of the incidence of anal stenosis postexcision, so close follow-up with frequent biopsies is the most commonly used strategy [72]. Imiquimod again has been shown to be effective in selected cases [73], and may have more of a role in the future. Premalignant penile lesions (Bowen disease and erythroplasia of Queyrat) are treated similarly to Bowenoid papulosis, with any number of different agents used on a case-by-case basis. The treatment of invasive anogenital malignancies (usually squamous cell carcinoma) is beyond the scope of this discussion but can involve surgery, chemotherapy, and radiation, alone or in combination.

**Vaccines and prospects for the future**

Currently the most exciting aspect of HPV therapy is the development of vaccines that within the next several years could reduce dramatically the mortality and morbidity from cervical carcinoma and other HPV-associated diseases. There have been two lines of research in recent years, one line developing therapeutic vaccines that rely on the induction of cell-mediated immunity to eradicate established infections and associated neoplasia, and the other line developing prophylactic vaccines wherein neutralizing antibodies to viral particles would block viral cellular infection. The results to date of therapeutic vaccine trials have been largely inconclusive. Although there is a fair amount of evidence from animal models supporting this approach, vaccine studies in humans using viral peptides, recombinant proteins, plasmid DNA, and live recombinant vaccinia virus have not yet proved clear therapeutic benefit [34,74].

Prophylactic vaccines, on the other hand, have shown a great deal of promise in much publicized studies [75,76]. These vaccines make use of DNA-free virus-like particles, highly immunogenic structures that self-assemble from viral capsid proteins and are virtually indistinguishable from mature virions. Currently, large, multi-center, phase III trials are ongoing for two candidate vaccines: Cervarix, which covers HPV types 16 and 18, and Gardasil, which covers types 16 and 18, plus the condylomata-causing HPV-6 and -11. Villa and colleagues published the results of Gardasil’s phase II trials in May of 2005, in which they showed a 90% drop in incidence of persistent infection or disease from HPV types 6, 11, 16, and 18 [77]. Interim analysis on Gardasil’s phase III trials have shown it to be 100% effective in preventing moderate- to high-grade cervical intraepithelial neoplasia caused by HPV types 16 and 18 [78]. Cervarix has demonstrated comparable efficacy, with phase II trials showing 91.6%, 100%, and 93.5% efficacy in preventing incident infection, persistent infection, and cytologic abnormalities, respectively, caused by HPV-16 and -18 [76]. If these vaccines continue to show this level of efficacy they could be on the market in less than five years. It is estimated that these candidate vaccines potentially could prevent 70% of cervical cancer cases among women not already infected with high-risk HPV [79]. In developing countries where Pap smear programs are cost-prohibitive, the institutionalization of an HPV-vaccination program could be monumental in decreasing mortality from cervical and other anogenital cancers. The potential prevention of genital warts could affect millions in both developed and developing countries. The year 2006 should bring with it exciting data regarding the uses of these vaccines in young women. In the meantime, a fierce debate rages on the numerous public
health issues surrounding an immunization program: At what age should immunizations begin? What should the immunization schedule be? Should men be immunized? As prospects appear for the potential eradication of HPV-related disease, individual countries and international public health organizations will struggle to produce feasible and cost-effective answers to these questions.

Summary

Human papillomavirus infection is an extraordinarily common sexually transmitted disease which is associated with several benign, premalignant, and frankly malignant lesions of the anogenital tract. Most HPV infections are asymptomatic and spontaneously cleared by a predominantly cell-mediated immune response. Condyloma acuminatum, generally caused by HPV types 6 and 11, is the most common benign clinical manifestation of HPV infection, and several antiproliferative, destructive, antiviral, and immunomodulatory treatments are available for this condition. Although HPV infection by high-risk types is a necessary prerequisite for cervical cancer development and is causally related to other squamous cell carcinomas of the anogenital tract, HPV infection alone does not cause full malignant transformation, and other genetic or epigenetic events must occur for cancer to develop. Treatment of noncervical anogenital intraepithelial neoplasia depends on the site of the lesion and can involve excision, topical chemotherapy, or observation with frequent biopsies. In the near future, the release of one or more prophylactic vaccines against the most common HPV types may revolutionize the approach to HPV-related disease.

References


The Use of Dermatologic Drugs in Pregnancy and Lactation

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Physicians of pregnant and nursing women are wary of prescribing drugs given the often inadequate data pertaining to indirect effects of drugs on fetuses and nursing infants. Not all such effects are known or even studied. When studies are available, their results are often conflicting. Given the limits of pharmaceutical knowledge, doctors must “know what they do not know” and proceed with due caution, making judgment calls in the absence of secure data.

Although physicians of pregnant and nursing patients are reluctant to provide dermatologic medications, many drugs display few or no apparent contraindications during pregnancy and lactation. Just as awareness of the dangers of certain drugs or of the limits of the data is important, so is awareness of the documented safety of other drugs.

Reasons for avoiding the use of dermatologic drugs during pregnancy and nursing are many. First, because treatment of many dermatologic conditions is elective, physicians and their patients prefer to wait until after nursing ceases before treating certain conditions. Second, because some drugs used by the dermatologist have potentially harmful effects on the mother, fetus, or nursing infant, physicians are anxious to avoid harm. Third, because not every pregnancy results in the delivery of a perfectly healthy baby, physicians are concerned to avoid litigation for having prescribed a medication that may be deemed to have contributed to the problem. Clinicians treating dermatologic conditions often delay pharmaceutical therapy until their patients have ceased to nurse or have opted against nursing.

Reasons for choosing to use drug treatment during pregnancy and nursing are as many as the needs of patients suffering from skin conditions. Knowing that a given drug has been well studied and can be used without fear of harming mother, fetus, or nursing infant aids the practice of dermatology.

This article compiles drug information allowing the physician to make informed decisions regarding dermatologic treatment. It identifies and discusses indications and contraindications to various drugs to the extent possible given available information. When treatment with drugs presenting contraindications is essential, data must be carefully examined and evaluated so that a risk-benefit ratio may be determined in consultation with the patient. In cases of significant risk, truly informed consent should be obtained and documented.

To maximize ease of comparison of drug safety during all of the phases of childbearing, information is presented in this article by use of tables and boxes (Tables 1–15 and Boxes 1–3). Table 1 provides a list of dermatologic agents that may interact with contraceptives. Additional tables are categorized by class of drug: analgesics, local anesthetics, antibacterial agents, antifungals, antihistamines, antiscabetic agents, antivirals, biologic agents, cortico-steroids, topical immunomodulators, and miscellaneous (Tables 2,4,6–15). Each of the tables also lists the U.S. Food and Drug Administration’s (FDA) pregnancy rating and the Teratogen Information System risk and data assessments (TERIS) along with
warnings and comments. Other ratings and their sources are included when available (see later for background on the ratings). A discussion of the importance of choosing or avoiding drug therapy in relation to the phases of childbirth and a summary of cautions aligned to those phases introduce the tables. A set of four readily accessed lists of drugs of high risk and of minimal risk is included.

Risk as related to the phases of childbearing

The phases of childbearing determine in large part the choice or avoidance of given drug therapies in treating all women patients of childbearing age and a significant portion of a dermatologist’s practice. Awareness of a patient’s individual periodicity, whose phases include contraception, preconception, the three trimesters of pregnancy, preterm, and lactation, is essential. Cautions and contraindications change according to temporal phase, requiring the dermatologist to stay apprised of the movement of a patient from one phase to another.

The time before conception comprises the greatest portion of the life of a woman of childbearing age and yet is often overlooked. This phase itself is divided into contraception and preconception. Some dermatologic drugs may interact with contraceptives (Table 1) and may be contraindicated for use in patients who are seeking to avoid pregnancy. Other drugs are contraindicated in those women seeking to become pregnant or not avoiding pregnancy. Aspirin and the nonsteroidal anti-inflammatory agents (NSAIDs) ibuprofen and naproxen [1–4] offer prime examples, increasing risk of miscarriage when taken around the time of conception.

Pregnancy is distinguished by its three trimesters, the last of which includes preterm. Some drugs that are to be avoided during the first trimester are safe to use during the latter two, such as certain antibiotics of the cephalosporin family. Others may be deemed safe throughout pregnancy, except in the last 2 weeks when membrane rupture may put the fetus at risk. Certain antihistamines may fall into this category [5]. Table 2 and later in the text, the third trimester or preterm section, provide more details [5–25]. Drugs labeled as teratogenic may put a fetus at risk for only a few weeks of pregnancy. Nevertheless, avoiding these drugs during the entire pregnancy is generally recommended.

The postnatal phase of nursing also affects treatment choices. Drugs that place a nursing infant at risk may be different from those that affect a fetus during pregnancy. Ivermectin, which is teratogenic in animals at high doses and is excreted in breast milk, is to be avoided throughout pregnancy pending further human studies, yet use during lactation in third-world nations has presented no identifiable problems for infants [26,27]. NSAIDs are to be avoided during the final trimester for reasons given later, but the American Academy of Pediatrics (AAP) lists them as “usually compatible” with lactation [6].

Differences in the type of preparation of a pharmaceutical agent also may make for differences in treatment options within a given phase of childbearing. The antifungal miconazole, for example, is rated according to its topical and oral forms by TERIS. In its topical form, miconazole is unlikely to result in risk, whereas its risk in oral form is underdetermined [28]. The antibiotic clindamycin also receives different ratings according to type of pharmaceutical preparation and source. The AAP rates the oral form as compatible with lactation [6] and a manufacturer does not stipulate caution in oral use [29]; the manufacturers of topical clindamycin, however, advise discontinuation until nursing has ceased [30,31].

Before conception

Physicians prescribing a drug for women of childbearing age who are not pregnant or nursing should

### Table 1

<table>
<thead>
<tr>
<th>Agent</th>
<th>Contraceptive agent Proposed mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>Intrauterine devices Unknown</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>Intrauterine devices Unknown</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>Oral contraceptives Increased estrogen metabolism by hepatic microsomal enzyme induction</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Oral contraceptives Increased estrogen metabolism by hepatic microsomal enzyme induction or Reduced enterohepatic circulation of estrogens</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Oral contraceptives Reduced enterohepatic circulation of estrogens</td>
</tr>
<tr>
<td>Sulphonamides</td>
<td>Oral contraceptives Reduced enterohepatic circulation of estrogens</td>
</tr>
</tbody>
</table>

* Aside from CYP enzyme inducers (griseofulvin and rifampin), significant controversy plagues other antibacterial agents regarding a causal role in contraceptive failure.
Table 2
Antihistamines in pregnancy and lactation

<table>
<thead>
<tr>
<th>Class</th>
<th>Data [Ref.]</th>
<th>FDA pregnancy category</th>
<th>TERIS Risk</th>
<th>Data rating</th>
<th>Notes when applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamines, sedating</td>
<td>During lactation, use is contraindicated [8–10]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Controversy reigns over use of sedating antihistamines during lactation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Briggs: probably compatible with lactation, except doxepin, which has potential toxicity [11]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AAP: no listing, except doxepin, whose effect during lactation is unknown but may be of concern [6]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>USP DI: first-generation antihistamines have anticholinergic effects and may inhibit lactation; use of antihistamines is not recommended because of risk of irritability or unusual excitement in infants. If a sedating antihistamine is chosen, mother should be advised to stop if infant becomes jittery or stops feeding well [12]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetirizine*</td>
<td>By prescription in US; over-the-counter in Canada</td>
<td>B</td>
<td>Unlikely</td>
<td>Limited</td>
<td>Insufficient data to claim no risk</td>
</tr>
<tr>
<td></td>
<td>Metabolite of hydroxyzine</td>
<td></td>
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<tr>
<td></td>
<td>A small prospective study failed to determine any increased fetal risk when used during pregnancy [13]</td>
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</tr>
<tr>
<td>Cyproheptadine*</td>
<td>Not strictly an antihistamine, but used to control itch</td>
<td>B</td>
<td>Undetermined</td>
<td>Limited</td>
<td>High risk is unlikely</td>
</tr>
<tr>
<td></td>
<td>Not been associated with problems during pregnancy [14–16]</td>
<td></td>
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<tr>
<td></td>
<td>Manufacturer: no increased risk of abnormalities throughout pregnancy, but should be used “only when clearly needed” [17]</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>No large studies demonstrate safety</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Diphenhydramine*</td>
<td>Long history of relatively uneventful use during pregnancy [18]</td>
<td>B</td>
<td>Undetermined</td>
<td>Fair to good</td>
<td>Insufficient data to claim no risk</td>
</tr>
<tr>
<td></td>
<td>Briggs: avoid during last 2 weeks in case of prematurity [8]</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Antihistamine of choice for treatment of pruritus during pregnancy among many physicians</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Use during pregnancy has been called “safe” [8]</td>
<td></td>
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</tr>
<tr>
<td>Doxepin*</td>
<td>Systemic form has been associated with fetal ileus close to term (mother had used a phenothiazine compound also) [19]</td>
<td>Systemic = unrated; topical = B</td>
<td>Undetermined</td>
<td>Limited</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>In early pregnancy, no congenital human malformations have been reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Topical form is associated with less risk than oral form</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AAP: effect during lactation is unknown but may be of concern [6]</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

(continued on next page)
have several concerns: (1) contraceptive failure caused by medication interactions, (2) potential risk to mother and fetus caused by the drug should pregnancy occur, (3) possible interference with conception, (4) potential risk of spontaneous abortion. Moreover, in a few cases, treatment of men anticipating pregnancy must be approached cautiously. Some medications have been associated with a possible risk of contraceptive failure (see Table 1). Azathioprine [32] and NSAIDs [33], for example, have been associated with increased risk of contraceptive failure of the intrauterine device. Oral contraceptive failure may occur when the oral contraceptive is taken along with hepatic enzyme inducers, such as griseofulvin [34], which may increase metabolism of estrogen (including oral contraceptives) because of induction of hepatic microsomal enzymes. Other oral

Table 2 (continued)

<table>
<thead>
<tr>
<th>Class</th>
<th>Data [Ref.]</th>
<th>FDA pregnancy category</th>
<th>TERIS</th>
<th>Data rating</th>
<th>Notes when applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fexofenadinea</td>
<td>No human studies during pregnancy yet conducted [20]</td>
<td>C</td>
<td>Undetermined</td>
<td>Very limited</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Manufacturer: benefits should outweigh risks [20]</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Briggs: no human data; animal data have shown toxicity to embryo and fetus;</td>
<td></td>
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<tr>
<td></td>
<td>suggests that if oral antihistamine is needed, chlorpheniramine or triphenanamine should be considered; if these fail, cetirizine and loratadine are considered acceptable [21]</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>AAP, Briggs: during lactation, thought to be usually compatible [6,21]</td>
<td></td>
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</tr>
<tr>
<td>Hydroxyzinea</td>
<td>Briggs: a teratogen in animals given multiples of human doses [22]</td>
<td>Unrated</td>
<td>Unlikely</td>
<td>Fair</td>
<td>High risk is unlikely</td>
</tr>
<tr>
<td></td>
<td>During early pregnancy, manufacturer: use is contraindicated [23]</td>
<td></td>
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<tr>
<td></td>
<td>Some studies list as safe during pregnancy [7,24]</td>
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<tr>
<td>Loratadine</td>
<td>Briggs: during pregnancy, has been associated with adverse outcomes (cleft palate, microtia, microphthalmia, deafness, dysmorphism, diaphragmatic hernia). No clear relationship to use is established [25]</td>
<td>B</td>
<td>Unlikely</td>
<td>Fair</td>
<td>High risk is unlikely</td>
</tr>
<tr>
<td></td>
<td>Not thought to be teratogenic but, if an oral antihistamine is required during pregnancy, Briggs recommends chlorpheniramine or triphenanamine as first-line [25]</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>AAP, Briggs: during lactation, thought to be usually compatible [6,25]</td>
<td></td>
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</tbody>
</table>

General warning: in a retrospective cohort study of 3025 infants of birth weight <1750 g, use of antihistamines during the last 2 weeks of pregnancy was associated with increased incidence of retrolental fibroplasia [5].

a See also Antihistamines, sedating above.

Table 3
Pregnancy category D or unrated: drugs to avoid in pregnancy and lactation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category D</th>
<th>Unrated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirina</td>
<td></td>
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<tr>
<td>Azathioprine</td>
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<tr>
<td>Bleomycin</td>
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<td>Colchicine</td>
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<tr>
<td>Cyclophosphamide</td>
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<tr>
<td>Griseofulvin</td>
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<tr>
<td>Hydroxyurea</td>
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<tr>
<td>Mechlorethamine</td>
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<tr>
<td>Penicillamine</td>
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<tr>
<td>Potassium iodide</td>
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<tr>
<td>Spironolactone</td>
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<tr>
<td>Tetracycline</td>
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</tr>
</tbody>
</table>

a High-dose, extended-release form should be avoided.
<table>
<thead>
<tr>
<th>Class</th>
<th>Data [Ref.]</th>
<th>FDA pregnancy category</th>
<th>TERIS Risk</th>
<th>Data rating</th>
<th>Notes when applicable</th>
<th>Class Data [Ref.]</th>
<th>Notes when applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azelaic acid</td>
<td>Has not shown mutagenicity, teratogenicity, or embryotoxocity in animals [62]</td>
<td>B</td>
<td>Unrated</td>
<td>—</td>
<td>—</td>
<td>—</td>
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</tr>
<tr>
<td></td>
<td>Minimal absorption occurs</td>
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<td></td>
<td>Therefore small doses unlikely to pose risk during pregnancy</td>
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<tr>
<td></td>
<td>A manufacturer: data is too limited to assess safety [63]</td>
<td></td>
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<tr>
<td></td>
<td>USP DI, a manufacturer: no problems reported during lactation [63,64], though</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>may be absorbed in small amounts</td>
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</tr>
<tr>
<td>Benzoyl peroxide</td>
<td>USP DI: may be systematically absorbed</td>
<td>C</td>
<td>Undetermined</td>
<td>None</td>
<td>High risk of congenital anomalies is unlikely; small risk cannot be excluded</td>
<td></td>
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<tr>
<td></td>
<td>Human studies have not been conducted [65]</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>During pregnancy, not contraindicated [66]</td>
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<tr>
<td></td>
<td>USP DI, manufacturer: no problems reported during lactation [67,68], though</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>may be absorbed in small amounts</td>
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<tr>
<td>Clindamycin</td>
<td>See Antibacterial agents (Table 8)</td>
<td>—</td>
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<tr>
<td>Erythromycin</td>
<td>See Antibacterial agents (Table 8)</td>
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<tr>
<td>Metronidazole</td>
<td>Oral form has not been associated with congenital anomalies in animals [69], or in humans when used in the first [56–58] or last [59,60] trimesters</td>
<td>—</td>
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<tr>
<td></td>
<td>Throughout pregnancy, no contraindication of topical use</td>
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<tr>
<td></td>
<td>Manufacturers: “only if clearly needed” for topical and vaginal forms [70,71]</td>
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<tr>
<td></td>
<td>During lactation, topical form is unlikely to be absorbed in significant amounts.</td>
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<tr>
<td></td>
<td>USP DI does not contraindicate use during lactation [69], although some manufacturers do [70,71]</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Retinoids, adapalene</td>
<td>Very low systematic absorption.</td>
<td>C</td>
<td>Unrated</td>
<td>—</td>
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<tr>
<td></td>
<td>A congenital anomaly of the eye was reported in association with use [72]</td>
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<tr>
<td></td>
<td>Manufacturer advises potential maternal benefit should be weighed against potential infant risk during pregnancy [73]</td>
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<td></td>
<td>Briggs: doubtful that absorption might represent any risk to the infant during lactation [74]</td>
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</tr>
<tr>
<td>Retinoids, isotretinoin</td>
<td>FDA: can cause birth defects in human beings [61]</td>
<td>X</td>
<td>Undetermined</td>
<td>Very limited</td>
<td>High risk is unlikely</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>In 2006, special registration is required to dispense or use [61]</td>
<td></td>
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</tr>
<tr>
<td>Retinoids, tazarotene</td>
<td>Absorbed minimally [39,40]</td>
<td>X</td>
<td>Undetermined</td>
<td>—</td>
<td>—</td>
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<td>—</td>
</tr>
<tr>
<td></td>
<td>Caused retinoid-like anomalies in animals [41]</td>
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<tr>
<td></td>
<td>Thus manufacturer recommends negative pregnancy test within 2 wk before treatment [41]</td>
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</tr>
<tr>
<td></td>
<td>During lactation, risk not known, but has been contraindicated [41]</td>
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</tr>
</tbody>
</table>

(continued on next page)
medications that may reduce oral contraceptive effectiveness include rifampin [35], which may stimulate estrogen metabolism or reduce enterohepatic circulation of estrogens, and penicillins [36], which also reduce enterohepatic circulation of estrogens. Tetracyclines [37] and sulfonamides [38] may increase breakthrough bleeding and reduce contraceptive effectiveness, although this is quite controversial. Although the retinoid tazarotene is absorbed minimally [39,40], its manufacturer recommends a negative pregnancy test within 2 weeks before treatment, because it has caused retinoid-like anomalies in animals [41].

Both men and women should avoid methotrexate [42] if pregnancy is anticipated. Although there are no published studies implicating thalidomide in the production of congenital anomalies when men use it around the time of conception, the manufacturer [43] and U.S. Pharmacopeia Drug Information (USP DI) [44] recommend that men taking thalidomide use a latex condom during intercourse.

**First trimester**

During very early pregnancy, encompassing the first 2 to 2.5 weeks of gestation (4–4.5 weeks after the first day of the last normal menstrual cycle), cells are undifferentiated. Drugs administered during this period tend to affect all cells equally, resulting in most cases in either a terminally toxic event or an uneventful continuation of life. That is, the net

<table>
<thead>
<tr>
<th>Class</th>
<th>Data [Ref.]</th>
<th>FDA pregnancy category</th>
<th>TERIS Risk</th>
<th>Data rating</th>
<th>Notes when applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinoids, tretinoin</td>
<td>During <strong>first trimester</strong>, associated with teratogenicity [75–77], but a controlled study failed to confirm [78] One study, assuming maximal absorption, estimated the 1 g/d of 0.1% preparation would result in serum levels of &lt;15% of the vitamin A from a standard prenatal vitamin A preparation [79] Given availability of alternatives, avoid during <strong>first trimester</strong> No problems reported in infants of mothers treated <strong>after first trimester</strong> During <strong>second and third trimesters</strong>, use may be considered in consultation with patient and her obstetrician to avoid misunderstanding One article argues for safety of use during <strong>pregnancy</strong> [7] Minimal amounts found in breast milk are not thought to be harmful to <strong>lactating</strong> infants [80] During <strong>lactation</strong>, animal studies show no adverse effects [79,81]</td>
<td>C</td>
<td>Unlikely</td>
<td>Fair</td>
<td>—</td>
</tr>
</tbody>
</table>
### Table 6
Analgesics in pregnancy and lactation

<table>
<thead>
<tr>
<th>Class</th>
<th>Data [Ref.]</th>
<th>FDA pregnancy category</th>
<th>TERIS Risk</th>
<th>Data rating</th>
<th>Notes when applicable</th>
</tr>
</thead>
</table>
| Acetaminophen  | Analgesic of choice in pregnancy  
Briggs: during pregnancy, high dose caused severe anemia in one mother; infant died of renal problems. Overdose may result in hepato- or nephrotoxicity in infant or mother. Low dose not linked with identifiable risk throughout pregnancy [99]  
Briggs: May be used during lactation [99] | B                       | None to minimal except at toxic dose | Good       | —                      |
|                 | Aspirin                       | C                       | None to minimal for occasional low dose | Fair to good | —                      |
|                 | Known animal teratogen        |                         |            |             |                        |
|                 | Extended-dose, Briggs: D rating [45]  
Low-dose: No appearance of teratogenicity. High-dose, Briggs: Anomaly increase in animals; no consistency in anomalies in humans. Avoidance recommended [45]  
Many studies show prevention of fetal growth retardation, pregnancy-induced hypertension, stillbirth [100]  
Time of conception: increased risk of miscarriage [1,2]  
Final trimester: fetal or neonatal hemorrhage [101,102] and premature closure of ductus arteriosus [103] are greatest concerns. Also postmaturity syndrome [104], gastroschisis [105]  
Briggs: human data are limited; potential toxicity during lactation [45]  
AAP: recommends avoidance during lactation, given possible association with Reye’s syndrome [6]  
Low dose: Infant of lactating mother using aspirin presented dose-related metabolic acidosis; serum salicylate level was 24 mg/dL. No maternal milk or serum salicylate levels were obtained [106]  
|                 | NSAIDs, ibuprofen             | B                       | Minimal    | Fair        | Final trimester: neonatal renal failure; premature closure of ductus arteriosus; consequent risk to perinatal adaptation; oligohydramnios (continued on next page) |
|                 | NSAIDs, naproxen               | B                       | Undetermined | Limited     | Just before delivery: may be associated with abnormalities of neonatal cardiovascular adaptation |

(continued on next page)
negative effect tends to be spontaneous abortion rather than the production of any congenital anomalies. Animal studies reflect this finding as toxicity, which is considered to be a potentially adverse outcome of pregnancy in the current FDA pregnancy categories. Human toxicity studies are not done, because of difficulties in performing ethical drug studies in this population.

Organogenesis lasts from 2 to 8 weeks of gestation of the pregnancy (weeks 4–10 after the first

<table>
<thead>
<tr>
<th>Class</th>
<th>Data [Ref.]</th>
<th>FDA pregnancy category</th>
<th>TERIS Risk</th>
<th>Data rating</th>
<th>Notes when applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid narcotics, general</td>
<td>May be used for very short periods in small amounts Low dose: except for morphine, not associated with teratogenicity in isolated use Greatest risks: respiratory depression from high dose near time of delivery withdrawal symptoms after chronic maternal use Excreted in low amounts through lactation</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Opioid narcotics, codeine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Briggs: high dose, during pregnancy, inconsistent congenital malformations have suggested association with fetal risk [109] High dose, late in pregnancy: as in use by addicts, has been associated with development of withdrawal symptoms in infants [110] AAP lists as compatible with lactation [6]</td>
<td>C</td>
<td>Unlikely</td>
<td>Fair to good</td>
<td>—</td>
</tr>
<tr>
<td>Opioid narcotics, meperidine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>AAP lists as compatible with lactation [6]</td>
<td>C</td>
<td>Unlikely</td>
<td>Fair</td>
<td>—</td>
</tr>
<tr>
<td>Opioid narcotics, morphine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>USP DI: not reported to be a teratogen, except at high dose in animals [111] Low dose: in occasional doses, not thought to cause problems in children. However, animal studies show persistent problems in offspring exposed in utero [112,113] Significant withdrawal syndrome in infants of addicted mothers [114] AAP lists as compatible with lactation [6]</td>
<td>C</td>
<td>Congenital abnormalities: unlikely; Neonatal neurobehavioral defects: moderate</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Opioid narcotics, oxycodone&lt;sup&gt;b&lt;/sup&gt;</td>
<td>AAP: compatibility with lactation has not been rated</td>
<td>C</td>
<td>Undetermined</td>
<td>Limited</td>
<td>—</td>
</tr>
<tr>
<td>Opioid narcotics, propoxyphene&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Briggs: associated with occasional congenital abnormalities, though relation to the anomaly is thought to be spurious [115] Chronic maternal use has produced long-lasting behavioral abnormalities in infants [116] High Dose: Chronic maternal use has produced withdrawal symptoms in infants. Risk of overdose to infant is unknown [117,118] AAP lists as compatible with lactation [6]</td>
<td>C</td>
<td>None</td>
<td>Good</td>
<td>—</td>
</tr>
</tbody>
</table>

<sup>a</sup> See NSAIDs, ibuprofen above.

<sup>b</sup> See also Opioid narcotics, general above.
day of the last menstrual cycle). At this stage, cells begin to specialize and may be differentially affected by particular drugs, resulting in congenital anomalies. Avoiding all medications known to have possible teratogenic effects in these weeks is especially important. Under this category are included all medications listed as FDA pregnancy category X or D, and some drugs with higher ratings or drugs that are unrated. In animal models, aspirin (with a B rating) has been found to block implantation in the blastocyst phase, and NSAIDs (with C ratings) have been associated with spontaneous abortions and possibly with congenital malformations (Table 5) [45]. Exceptions on an individual basis may be considered when use is essential. For example, the standard of care for pregnant women suffering from antiphospholipid syndrome, who are at higher risk of pregnancy loss, fetal death, preeclampsia, and placental insufficiency, is low-molecular-weight heparin in combination with low-dose aspirin [46–48]. A list of medications that have been most clearly established as teratogenic is included in Table 3 and Box 1.

Second trimester

In midpregnancy, fetal development may be affected by maternal drug use as maturation of various organ systems occurs. For example, dentition is affected by tetracycline, which is well known to produce dental staining and enamel hypoplasia [49–51] because of its binding with calcium. Spironolactone, used for treatment of adult-onset acne in women, has been associated with feminization of male fetuses, in particular of their external genitalia, in an animal study [52]. Drug metabolism by the fetus may occur at a rate different from that of the mother. If fetal metabolism is lower than maternal metabolism, removal is slower and results in prolonged exposure while levels of the agent at any given time are higher, leading to potential harmful consequences. An example is maternal iodide use, which may result in fetal hypothyroidism [53,54].

Drug excretion by the fetus into amniotic fluid may theoretically promote prolonged exposure by virtue of skin contact with amniotic fluid or through amniotic fluid ingestion by the infant. No known examples are available.

In most cases, the second trimester is not singled out in the ratings used as peculiarly affected by the use of dermatologic drugs. Rather, it is usually coupled with the first trimester or the third trimester when any distinction of periodicity within the 9 months of pregnancy is indicated. Silver sulfadiazine, for example, is thought to pose potential risk during the third trimester but not the second. Here, the worry is that kernicterus or hemorrhage may occur in a premature or glucose-6-phosphate dehydrogenase-deficient infant [55]. The retinoid tretinoin, however, is cautioned against during the first trimester, because of its association with teratogenicity, but no problems have been reported in infants of mothers treated during second and third trimesters. Use of tretinoin, a C-category drug, may be considered during those trimesters, but consultation with the patient’s obstetrician is advised. Tretinoin’s rating should not be confused with the X-category isotretinoin, marketed under several trade names. See the section on ratings later for further discussion of isotretinoin.

<table>
<thead>
<tr>
<th>Class</th>
<th>Data [Ref.]</th>
<th>FDA pregnancy category</th>
<th>TERIS Risk</th>
<th>Data rating</th>
<th>Notes when applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>No contraindication to use during pregnancy</td>
<td>B</td>
<td>None for local administration</td>
<td>Fair</td>
<td>—</td>
</tr>
<tr>
<td>Lidocaine with epinephrine</td>
<td>No contraindication to use during pregnancy</td>
<td>B</td>
<td>Unlikely for use of therapeutic doses of epinephrine</td>
<td>Fair</td>
<td>—</td>
</tr>
<tr>
<td>Lidocaine-prilocaine</td>
<td>No contraindication to use during pregnancy</td>
<td>B</td>
<td>Undetermined for local administration of prilocaine</td>
<td>Very limited</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 7
Local anesthetics in pregnancy and lactation
Table 8
Antibacterial agents in pregnancy and lactation

<table>
<thead>
<tr>
<th>Class</th>
<th>Data [Ref.]</th>
<th>FDA pregnancy category</th>
<th>TERIS Risk Data rating</th>
<th>Notes when applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>Chemically related to erythromycin</td>
<td>B</td>
<td>Undetermined</td>
<td>Very limited</td>
</tr>
<tr>
<td></td>
<td>Briggs: during pregnancy, no association with a reported risk [120]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Briggs: during lactation, use with caution [120]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacitracin</td>
<td>Has not been associated with teratogenicity.</td>
<td>Unrated</td>
<td>Undetermined</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Small-dose use has not been associated with risk to the fetus, though</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>large studies have not been conducted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalosporins, general</td>
<td>In second and third trimesters, no problems in fetus identified.</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Briggs: during lactation, use with caution [121,122]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalosporins, cefaclor</td>
<td>Briggs: during first trimester, an association with congenital</td>
<td>B</td>
<td>Undetermined</td>
<td>Very limited</td>
</tr>
<tr>
<td></td>
<td>malformations was found in one large surveillance study [121]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalosporins, cefadroxil°</td>
<td>Briggs: in first trimester, no finding of association with congenital</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>malformations [122]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalosporins, cephalexin°</td>
<td>Briggs: during first trimester, an association with congenital</td>
<td>B</td>
<td>Undetermined</td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td>malformations was found in one large surveillance study [121]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalosporins, cephradinea°</td>
<td>Briggs: during first trimester, an association with congenital</td>
<td>B</td>
<td>Unlikely</td>
<td>Limited to fair</td>
</tr>
<tr>
<td></td>
<td>malformations was found in one large surveillance study [121]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Has not been associated with teratogenicity</td>
<td>B</td>
<td>Oral use: undetermined</td>
<td>Limited</td>
</tr>
<tr>
<td></td>
<td>Has been associated with pseudomembranous colitis, though risk is not</td>
<td></td>
<td></td>
<td>High risk is unlikely</td>
</tr>
<tr>
<td></td>
<td>increased during pregnancy [123]</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Small-dose use has not been associated with risk to the fetus, though</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>large studies have not been conducted</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>In lactating mother, bloody stools reported in an infant, but etiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>was not proven [124]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AAP rates oral form as compatible with lactation [6]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A manufacturer of the oral form does not caution against such use [29];</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>but manufacturers of the topical form advise discontinuation [30,31]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapsone</td>
<td>Has been used during pregnancy for treatment of leprosy [125]</td>
<td>C</td>
<td>Undetermined</td>
<td>Very limited</td>
</tr>
<tr>
<td></td>
<td>Literature supports safety during pregnancy for treatment of leprosy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>and dermatitis herpetiformis [84–86]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Briggs: during pregnancy, no major fetal risk [87]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Last month of pregnancy: stopping treatment may minimize a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>theoretic risk of neonatal kernicterus [88]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Briggs [87], USP DI [86], and the manufacturer [126] advise against</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>use during lactation, but AAP claims “usually compatible” [6]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Erythromycin and related macrolides

Throughout **pregnancy**, oral antibiotic of choice, along with penicillins. Except for erythromycin estolate, no reported risk of pyloric stenosis.

**Briggs:** during **lactation**, use oral form with caution [127]

During **first 2 weeks of life**, oral form associated with increased risk of pyloric stenosis [128]

Topical form has not been associated with teratogenicity

Topical form may be used during **pregnancy**.

**Briggs:** topical form is compatible with **lactation** [127]

**AAP** has no rating for topical form during **lactation**

#### Erythromycin estolate

Used longer than 3 weeks, has been associated with a subclinical maternal hepatotoxicity and should be avoided [129–131]

**Briggs:** during **lactation**, use oral form with caution [127]

### Fluoroquinolones:

- ciprofloxacin
- ofloxacin
- levofloxacin
- lomefloxacin
- norfloxacin
- enoxacin
- trovafloxacin
-sparfloxacin
- nalidixic acid

**During pregnancy**, congenital anomalies are inconsistent [132–134]; use as a first-line drug is not advised

**Briggs:** accidental administration should not be an indication for abortion [135]

Listed as probably compatible with **lactation**. However, manufacturer advises discontinuation of ciprofloxacin because of potential of serious adverse reactions in infant [91]

**During lactation**, USP DI recommends avoiding unless no alternate may be prescribed [92]

#### Mupirocin

Has not been associated with teratogenicity

Small-dose use has not been associated with risk to the fetus, though large studies have not been conducted

#### Neomycin

Has not been associated with teratogenicity

May be used during **pregnancy**

#### Penicillins

Throughout **pregnancy**, antibiotic of choice along with erythromycin

**Briggs:** during **pregnancy**, use not contraindicated

Beta-lactam antibacterial agents of the penicillin family have not been associated with an increased risk of congenital anomalies

**Briggs:** penicillin G, penicillin V, amoxicillin, ampicillin, dicloxacillin are unlikely to be teratogenic [136]

**PDR:** penicillin G benzathine and penicillin G procaine is excreted in breast milk. Use caution during **lactation** [127]

#### Polymyxin B

Has not been associated with teratogenicity

Small-dose use has not been associated with risk to the fetus, though large studies have not been conducted

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(continued on next page)
<table>
<thead>
<tr>
<th>Class</th>
<th>Data [Ref.]</th>
<th>FDA pregnancy category</th>
<th>TERIS Risk Data rating</th>
<th>Notes when applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonamides, oral sulfa methoxazole trimethoprim</td>
<td>Briggs: possible association with increased risk of congenital abnormalities is documented [82] During early pregnancy, use not contraindicated, yet alternatives have better data indicating no risk. During lactation, pose a potential risk of hemolysis in glucose-6-phosphate dehydrogenase (G6PD)-deficient newborns [138,139]</td>
<td>C</td>
<td>Sulfa methoxazole: unlikely</td>
<td>Sulfa methoxazole: limited to fair Trimethoprim: small Trimethoprim: good</td>
</tr>
<tr>
<td>Silver sulfadiazine, topical</td>
<td>USP DI: during late third trimester, use thought to pose potential risk for kernicterus and hemorrhage in premature infant or infant with G6PD deficiency [55]. Though risk may be theoretic, an alternate topical antibiotic is preferred AAP, USP DI: during lactation, use is discouraged if infant has jaundice or G6PD deficiency [6,55]</td>
<td>B</td>
<td>Unlikely</td>
<td>Poor to fair</td>
</tr>
<tr>
<td>Sulfur, topical, with or without sodium sulfacetamide or resorcinol</td>
<td>Has not been associated with kernicterus During pregnancy, not contraindicated Compatible with lactation [140,141] AAP has no rating for use during lactation</td>
<td>C</td>
<td>None</td>
<td>Poor to fair</td>
</tr>
<tr>
<td>Tetracyclines, general</td>
<td>During early pregnancy, use not associated with congenital anomalies [142,143] During second or third trimesters, risk of dental staining and enamel hypoplasia [49–51] During lactation, systematic use is controversial. AAP states that use is compatible with lactation because of negligible absorption [6]</td>
<td>D</td>
<td>Congenital abnormalities: none to minimal</td>
<td>Congenital abnormalities: fair Dental anomalies: high</td>
</tr>
<tr>
<td>Tetracyclines, minocycline&lt;sup&gt;b&lt;/sup&gt;</td>
<td>During second or third trimesters, not advised given structural similarity to tetracycline [49–51] During lactation, black milk has been reported [144]</td>
<td>D</td>
<td>Congenital abnormalities: undetermined</td>
<td>Congenital abnormalities: very limited</td>
</tr>
<tr>
<td>Tetracyclines, doxycycline&lt;sup&gt;b&lt;/sup&gt;</td>
<td>During second or third trimesters, not advised given structural similarity to tetracycline [49–51]</td>
<td>D</td>
<td>Congenital abnormalities: unlikely</td>
<td>Congenital abnormalities: limited to fair Dental anomalies: undetermined</td>
</tr>
</tbody>
</table>

<sup>a</sup> See also Cephalosporins, general above.  
<sup>b</sup> See also Tetracyclines, general above.
Because of absence of relevant data, one example against the rule of nonsingularity of the second trimester is the oral form of metronidazole. Another antiacne drug, oral metronidazole has not been associated with congenital anomalies in human beings when used in the first [56–58] and third [59,60] trimesters. This is not to say that congenital anomalies are associated with its use in the second trimester, but other choices may be preferred given the lack of data specific to the second trimester (Table 4) [39–41,56–81].

Third trimester and preterm

Late in pregnancy, especially near the time of delivery, nonteratogenic conditions may occur. Such drugs as sulfonamides, which may produce risk in infants who are premature [82], and NSAIDs, which may promote persistent fetal circulation or oligohydramnios [83], are to be avoided. As in other phases of pregnancy, studies can be conflicting. For example, dapsone is supported in the literature as safe during pregnancy for treatment of leprosy and dermatitis herpetiformis [84–86] and Briggs and coworkers [87] state that its use poses no major risk to the fetus during pregnancy, yet one article claims that, in the last month of pregnancy, stopping treatment with dapsone minimizes a theoretic risk of neonatal kernicterus [88].

Keeping in mind that a drug may be dangerous in one phase, while safe in another, is crucial to the treatment of women in their third trimester. From the second trimester to the rupture of the membrane, topical clotrimazole has not been associated with adverse effects, whereas during the first trimester, oral or topical use of clotrimazole for treatment of vaginitis has been associated with a slightly increased risk of human congenital defects [89] (although Briggs and coworkers [90] state that the association is not supported by the data).

Awareness of the due date of the maternal patient is especially important to treatment. Antihistamines provide a prime example. In a retrospective cohort study of 3025 infants with birth weight of less than 1750 g, use of antihistamines during the last 2 weeks of pregnancy was associated with an increased incidence of retrolental fibroplasias [5]. Findings regarding the antifungal clotrimazole exemplify the occasional need for subtle distinction-making in prescribing drugs during the final weeks of pregnancy. Although use of clotrimazole in the third trimester has not been associated with problems, studies neither indicate nor contraindicate its safety in use after the membrane breaks [90].

Lactation

Nearly all adverse effects in nursing infants have occurred during the first 6 months of life. Sedation and diarrhea are easy to detect. Less apparent are possible neurotoxic effects. In general, use of drugs known to be teratogenic is not advised during lactation (see Table 1 and Box 1). This includes all retinoids and antineoplastic agents.

As with pregnancy, findings regarding the use of dermatologic drugs during breast-feeding are sometimes controversial and require weighing the evidence carefully. Ratings of a single drug may differ. The antibiotic family of fluoroquinolones, for example, is listed as probably compatible with lactation, yet the manufacturer of ciprofloxacin advises discontinuation of breast-feeding while using fluoroquinolones given the potential of serious adverse reactions in the infant [91]. The USP DI recommends avoiding fluoroquinolones during lactation unless an alternative antibiotic cannot be prescribed [92].

Many women elect to avoid exposure to all drugs, fearing some as yet undiscovered problem. The physician should be aware and respectful of this wish while being able to advise patients of drugs that place them and their babies at minimal risk. Further, physicians should be mindful that treatment of some dermatologic conditions, such as onychomycosis, can be safely deferred until the completion of pregnancy and lactation.

Ratings used in drug tables and other sources

Several ratings are available to assist physicians in determining the relative safety of dermatologic drugs to the fetus or nursing infant and in recognizing the existence of conflicting opinion in the absence of solid data or the presence of probable bias. The tables in this article provide two catalogs of risk. The FDA pregnancy categories can be located in the Physicians’ Desk Reference under the product information list supplied by drug manufacturers [93]. The TERIS is available on-line by subscription [28]. In addition, several other rating sources are also used. Drugs in Pregnancy and Lactation is a regularly updated textbook reviewing the risks of using drugs during pregnancy and lactation [94]. The AAP [6] reviews information on effects of drugs on lactation, publishing an updated rating list every several years. The USP DI has compiled three volumes on the use of drugs and includes indications and contraindications during pregnancy and lactation [95].
<table>
<thead>
<tr>
<th>Class</th>
<th>Data [Ref.]</th>
<th>FDA pregnancy category</th>
<th>TERIS Risk</th>
<th>Data rating</th>
<th>Notes when applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butaconazole, topical</td>
<td>Has not been studied in humans</td>
<td>C</td>
<td>Unrated</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ciclopirox, topical</td>
<td>Has not been studied in humans. No association reported with problems during pregnancy</td>
<td>B</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Clotrimazole, topical</td>
<td>During <strong>first trimester</strong>, for oral or topical treatment of vaginitis, has been associated with a slightly increased risk of human congenital defects in <strong>one study</strong> [89] Briggs: association of vaginal treatment and congenital defects is not supported by data [90] From <strong>second trimester to membrane rupture</strong>, topical use has not been associated with adverse effects</td>
<td>B</td>
<td>Unlikely</td>
<td>Limited-to-fair</td>
<td>Data insufficient to claim no risk</td>
</tr>
<tr>
<td>Econazole, topical</td>
<td>During <strong>first trimester</strong>, manufacturer recommends use only when essential to welfare of the mother [145] <strong>Close to term</strong>, topical administration of intravaginal yeast medications is not advised, given risk of uterine contamination after membrane rupture [146]</td>
<td>C</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>In high doses, has been associated with human malformations [147–149] Briggs: during <strong>first two trimesters</strong>, pending further information, elective use of prolonged doses (&gt;400 mg/d) should be avoided [150] During pregnancy, single-dose use does not appear to be associated with increased risk to fetus [150] Manufacturer advises against use during lactation [151] Briggs, AAP: compatible with lactation [6,150]</td>
<td>C</td>
<td>Low, single, oral dose: unlikely High dose chronic use: undetermined</td>
<td>Low, single, oral dose: fair to good High dose chronic use: limited to fair</td>
<td>A low single oral dose is unlikely to pose a substantial risk</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>Several reports implicate use as a possible etiology for conjoined twins [152,153]. No other congenital anomaly is reported Briggs: animal studies show increased frequency of fetal death, growth retardation, and skeletal anomalies. Significance to human use unknown [154] <strong>Before</strong> and during <strong>early pregnancy</strong>, manufacturers thus recommend avoidance [155,156] Briggs: during lactation, compatible [154]</td>
<td>Unrated</td>
<td>Undetermined</td>
<td>Limited</td>
<td>High risk is unlikely; small risk cannot be excluded</td>
</tr>
<tr>
<td>Drug</td>
<td>Summary</td>
<td>Oral Risk</td>
<td>Topical Risk</td>
<td>Oral Use</td>
<td>Topical Use</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>-----------</td>
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<td>-------------</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Showed dose-related embryotoxicity and teratogenicity in rodents, thought to be because of adrenal effects [157] Used safely in a reported pregnancy [158] USP DI: risk of human teratogenicity is thought to the lowest of the systemic azole antifungal agents since, in contrast to fluconazole and ketoconazole, little effect on steroid hormones [159] During first trimester, Briggs: avoid, given that fluconazole has been responsible for malformations [160] During lactation, Briggs: has potential toxicity [160]</td>
<td>C Unlikely</td>
<td>Limited to fair</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Naftifine, topical</td>
<td>Has not been studied in humans No association reported with problems during pregnancy</td>
<td>B — — —</td>
<td>— — —</td>
<td>— — —</td>
<td></td>
</tr>
<tr>
<td>Nystatin</td>
<td>Associated with no known risk to fetus during pregnancy [168,169] Topical form has not been studied in humans Briggs: throughout pregnancy, no contraindication to use of oral form [170]</td>
<td>B Oral form: none</td>
<td>Fair to good</td>
<td>— —</td>
<td></td>
</tr>
<tr>
<td>Oxiconazole, topical</td>
<td>Has not been studied in humans No association reported with problems during pregnancy</td>
<td>B — — —</td>
<td>— — —</td>
<td>— — —</td>
<td></td>
</tr>
<tr>
<td>Selenium sulfide, topical</td>
<td>Manufacturer advises against use during pregnancy for treatment of tinea versicolor, because no animal or human studies have been conducted and thus risk to fetus is unknown [171] During lactation, one manufacturer recommends against use over large areas for treatment of tinea versicolor [171]</td>
<td>C* Undetemined</td>
<td>None</td>
<td>High risk is unlikely; small risk cannot be excluded</td>
<td></td>
</tr>
</tbody>
</table>

*(continued on next page)*
Table 9 (continued)

<table>
<thead>
<tr>
<th>Class</th>
<th>Data [Ref.]</th>
<th>FDA pregnancy category</th>
<th>TERIS Risk</th>
<th>Data rating</th>
<th>Notes when applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulconazole</td>
<td>Has not been studied in humans. No association reported with problems during pregnancy</td>
<td>C</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Terbinafine</td>
<td>USP DI: animal studies (oral form) in pregnancy show tumorogenicity (production of benign tumors) but not fetal loss (animal toxicity) [172]. No human studies have been done of oral or topical forms. No case reports of topical use associated with problems during pregnancy. Briggs, oral form: animal data suggest low risk; no human data are available [173]. Manufacturer advises against elective use of oral form during pregnancy for treatment of onychomycosis [174]. Briggs: systemic form has potential toxicity during lactation; topical form is probably compatible [173]. USP DI: should not be applied to breasts [172]. Manufacturer advises against use of systemic [174] and topical [175] forms during lactation though no data verify problems in use of topical form.</td>
<td>B</td>
<td>Unrated</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Tioconazole, topical</td>
<td>Has not been studied in humans. No association reported with problems during pregnancy</td>
<td>C</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>A known teratogen, avoid during pregnancy [176]. Manufacturer recommends against use during lactation [176]</td>
<td>D</td>
<td>Unrated</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* For tinea versicolor.
# Antiscabetics and antipediculocides in pregnancy and lactation

<table>
<thead>
<tr>
<th>Class</th>
<th>Data [Ref.]</th>
<th>FDA pregnancy category</th>
<th>TERIS</th>
<th>Risk</th>
<th>Data rating</th>
<th>Notes when applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crotamiton</td>
<td>No studies of human absorption During <strong>pregnancy</strong>, no adverse effects have been reported During <strong>lactation</strong>, no documentation of problems</td>
<td>C</td>
<td>Undetermined</td>
<td>None</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Ivermectin</td>
<td>Teratogenic in animals at high doses. Human teratogenicity, toxicity have not been observed [177] Use for scabies is not FDA-approved Avoid during <strong>pregnancy</strong>, pending further study Excreted during <strong>lactation</strong>. Use in large third-world populations shows no identifiable problems for infants [26,27]</td>
<td>C</td>
<td>Unrated</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Lindane</td>
<td>Controversial, with both discouraging [178,179] and encouraging [180,181] reports Adverse occurrences are thought to arise from misuse or use on traumatized or abnormal skin [182] Briggs: because of potential toxicity, suggests pyrethrins (such as permethrin) as alternative [183] USP DI: if used during <strong>pregnancy</strong>, best not to exceed recommended dose [184] Controversial during <strong>lactation</strong> USP DI: avoid <strong>nursing</strong> for 24 hours after use [184] Briggs: amount delivered to infant from <strong>lactation</strong> may be clinically insignificant [183]</td>
<td>B</td>
<td>Undetermined</td>
<td>Limited</td>
<td>High risk is unlikely; substantial risk in doses high enough to be toxic to pregnant women</td>
<td></td>
</tr>
<tr>
<td>Malathion</td>
<td>A pediculocide Has not been associated with teratogenicity</td>
<td>B</td>
<td>Unlikely</td>
<td>Fair</td>
<td>TERIS warning: if teratogenic, risk is likely larger at greater exposure or maternal toxicity; feta risk may rise if maternal red blood cell cholinesterase activity is noted</td>
<td></td>
</tr>
</tbody>
</table>
Physicians may also wish to consult Reproductive Toxicology Service, which provides a computer-based software or on-line program available by subscription (see www.reprotox.org). References on the effects of drugs and physical agents on human fertility, pregnancy, and fetal development are updated regularly. No rating system is included. Finally, the World Health Organization publishes a book on lactation, available through libraries [96].

TERIS provides information on the relative teratogenicity of agents and reports “permanent abnormality of structure or function in an organism exposed during embryonic or fetal life” [28]. Comprehensive summaries implement a rating system that includes none, unlikely, minimal, moderate, high, and undetermined. Qualifying these risks is an evaluation of data on which these risks have been based: none, poor, limited, fair, good, and excellent.

### Antiviral agents in pregnancy and lactation

<table>
<thead>
<tr>
<th>Class</th>
<th>Data [Ref.]</th>
<th>FDA pregnancy category</th>
<th>TERIS Risk</th>
<th>Data rating</th>
<th>Notes when applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Not teratogenic in animals but causes fetal death, growth retardation, malformations in rats at maternotoxic doses [193,194] Has not been associated with adverse fetal effects during human pregnancy [195] Briggs: insufficient data to establish safety [196] Briggs: helpful in reducing mortality from disseminated herpes simplex virus infections (HSV); however, use in recurring HSV infections is not as convincing [196] Not necessary during pregnancy, except near term or in cases of severe systemic viral involvement Manufacturer: use with caution during lactation [197] AAP, Briggs: compatible with lactation [6,196]</td>
<td>B</td>
<td>Topical form: undetermined</td>
<td>Topical form: limited to fair</td>
<td>—</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>No teratogenicity shown in animals. Causes benign tumors in rats [198] Manufacturer: during pregnancy, use only when potential benefit to patient clearly exceeds potential risk to fetus [199] Briggs: given rat tumorigenicity, advises discontinuation during lactation [198]</td>
<td>B</td>
<td>Unrated</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>The pro-drug of acyclovir Has not been associated with animal teratogenicity Manufacturer reports uneventful use during pregnancy, but recommends only if potential benefit to patient outweighs potential risk to infant [200] Guidelines for use of acyclovir should be followed Manufacturer: use with caution during lactation [200] AAP: no rating Briggs: compatible with lactation [196]</td>
<td>B</td>
<td>Unrated</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
The FDA's rating system (Table 5), developed out of a 1996 task force, is the most well known and followed [97]. Physicians should note that no drugs listed in this article have been assigned the rating A.

The FDA also provides two lactation drug risk categories: discontinue and caution. “Discontinue” points out that a “decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.” The category “Caution is advised if the drug is used during lactation” is used if the drug is absorbed and excreted into human breast milk but does not have known adverse reactions or tumorigenic potential.

Most physicians are aware of the FDA pregnancy categories, but other ratings are also used in the tables.

Table 12
Biologic agents in pregnancy and lactation

<table>
<thead>
<tr>
<th>Class</th>
<th>Data [Ref.]</th>
<th>FDA pregnancy category</th>
<th>TERIS Risk</th>
<th>Data rating</th>
<th>Notes when applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>No human studies have been conducted</td>
<td>B</td>
<td>Undetermined</td>
<td>None</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>No apparent evidence of embryotoxicity, teratogenicity, or increased pregnancy loss [201]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A pregnancy registry has been established</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Briggs: potential maternal benefits appear to be great and probably outweigh the unknown fetal risk; treatment during first trimester should be discussed with patient [202]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No data available for use during lactation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Manufacturer: citing potential for adverse reaction, suggests discontinuation during lactation [201]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Briggs: probably compatible with lactation [202]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AAP: unrated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>No evidence of adverse effects on humans, but is very new</td>
<td>B</td>
<td>Undetermined</td>
<td>Very limited</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>A pregnancy registry has been established</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Manufacturer: recommends discontinuation of breastfeeding during use given potential adverse reaction in infants [203]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Briggs: probably compatible with lactation [204]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>Has not been studied in animals given difference of mechanism of action in humans; has not been studied in humans</td>
<td>B</td>
<td>Undetermined</td>
<td>None</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Manufacturer has established a pregnancy registry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Briggs: real risk is unknown, given similar mechanism of action as thalidomide; potential for serious maternal reactions in some patients; limited human data [205]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Manufacturer: advises against breastfeeding during use [206]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Briggs: probably compatible with lactation [205]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AAP: unrated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 13
Corticosteroids in pregnancy and lactation

<table>
<thead>
<tr>
<th>Class</th>
<th>Data [Ref.]</th>
<th>FDA pregnancy category</th>
<th>TERIS Risk</th>
<th>Data rating</th>
<th>Notes when applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids, systemic, general</td>
<td>Animal studies show use during pregnancy to be associated with increased risk of cleft palate, placental insufficiency, spontaneous abortion, and growth retardation in utero [207,208]. USP DI, low dose: no teratogenic effect or serious problem observed in humans [209]; high dose: use during human pregnancy is associated with potential risk of placental insufficiency, decreased birth weight, or stillbirth [209]. Oral clefts were found to be three times more common in infants of women treated with oral steroids than in controls in a prospective study [210]. Low birth weight associated with 10 mg/d doses throughout pregnancy [211,212]; may be linked to later development of hypertension and cardiovascular mortality [213]. To minimize infant exposure, delay nursing 3–4 h after dose [214]. Use during lactation has been called “safe” [215]. AAP: use is compatible with lactation [6].</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Unlikely</td>
<td>Fair to good</td>
<td>While therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk, data are insufficient to claim no risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids, topical, general</td>
<td>Use during pregnancy is not thought to be associated with significant risk to fetus. Limited-time use has not been associated with congenital anomalies, in general. Use of large amounts over extensive parts of the body during pregnancy may be associated with low birth weight. Should not be applied to breasts until nursing ceases. Hypertension is reported in an infant whose mother applied topical steroids to the nipple [216].</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Unlikely</td>
<td>Poor to fair</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Briggs: poses a small risk of orofacial clefts to developing fetus [217]. Congenital cataracts were reported in an infant of a mother treated throughout pregnancy [218]. Use of 40–80 mg/d doses for short periods of time has not increased risk of congenital anomalies, except when antiphospholipid abnormalities presented a confounding factor [219]. During lactation: a 5 mg/d systemic dose appears not to affect blood chemistry or infection rate of nursing infants [218]. During lactation: if therapy is long-term or requires doses exceeding 20 mg/d, prednisolone should be substituted [214].</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C, D&lt;sup&gt;b&lt;/sup&gt;</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Briggs: Poses a small risk of orofacial clefts to developing fetus [217]. To be preferred during lactation to prednisone if therapy is long-term or requires doses exceeding 20 mg/d [214].</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C, D&lt;sup&gt;b&lt;/sup&gt;</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triamcinolone&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Intraterine growth retardation was reported in an infant of a mother who used the equivalent of 40 mg/d through topical application [220].</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>—</td>
<td>—</td>
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<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> See also Corticosteroids, systemic, general above.
<sup>b</sup> Briggs: during first trimester [198].
<sup>c</sup> See also Corticosteroids, topical, general above.
## Immunomodulators in pregnancy and lactation

<table>
<thead>
<tr>
<th>Class</th>
<th>Data [Ref.]</th>
<th>FDA pregnancy category</th>
<th>TERIS Risk</th>
<th>Data rating</th>
<th>Notes when applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine USP DI</td>
<td>Systemic use is not teratogenic, but embryotoxic, fetotoxic, and carcinogenic in some animal studies [221] Briggs: studies show use during pregnancy poses no risk to developing fetus, but very limited data [222] Use during lactation is not recommended by manufacturers, given risk of nephrotoxicity, hypertension, and malignancy in infants [223,224] AAP recommends against use during lactation, citing possible immunosuppression, unknown effect on growth, or association with carcinogenesis [6] Briggs: use during lactation poses potential toxicity for infant [222]</td>
<td>C</td>
<td>Malformations: minimal</td>
<td>Malformations: fair</td>
<td>—</td>
</tr>
<tr>
<td>Imiquimod USP DI</td>
<td>Maternotoxic doses, topical form has been shown to produce reduced pup weights and delayed ossification in rats [225] Not shown to be distributed in human milk [226] AAP has no rating</td>
<td>C</td>
<td>Not listed</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Not recommended for use during pregnancy Manufacturer: effective contraceptive must be used before, during, and six weeks after use [227] Manufacturer, Briggs: contraindicated during lactation [228] AAP has no listing</td>
<td>C</td>
<td>Undetermined</td>
<td>Limited</td>
<td>Not recommended during pregnancy, given possibly substantial interference with DNA and RNA synthesis in fetus</td>
</tr>
<tr>
<td>Pimecrolimus</td>
<td>No problems during pregnancy reported Manufacturer: use during lactation is contradicted [229,230] AAP, Briggs: no rating FDA issued Public Health Advisory, March 2005, citing unknown risk of lymphoma after topical use</td>
<td>C</td>
<td>Unrated</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>No problems during pregnancy reported. Manufacturer: use during lactation is contraindicated [230] Briggs: data are limited on human lactation. Given potential toxicity, advises against use of oral form [231] AAP: no rating FDA issued Public Health Advisory, March 2005, citing unknown risk of lymphoma after topical use</td>
<td>C</td>
<td>Undetermined</td>
<td>Limited</td>
<td>Neonatal hyperkalemia reported in infants of mothers treated with oral form after transplant</td>
</tr>
</tbody>
</table>
that may or may not be entirely consistent with those listed by the manufacturer. For example, Briggs and coworkers [98] have modified the rating somewhat, based on evaluation of human and animal data, route of administration, and risk of maternal disease among other distinctions. Revisions of FDA pregnancy categories may be forthcoming, because the categories are found to be confusing and sparse with helpful data.

Revisions may not always come in the form of a new category. In 2006, the FDA will implement its plan to restrict the use of isotretinoin, already a category X drug, by requiring prescribers and patients to be registered before they can dispense or take the drug. In August 2005, the FDA approved that plan, known as iPledge “to make sure females do not become pregnant while taking this medicine. Isotretinoin causes birth defects” [61].

The example of isotretinoin marks the importance of staying up-to-date with pregnancy and breast-feeding ratings. Advances in knowledge of

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Table 15
Miscellaneous drugs in pregnancy and lactation

<table>
<thead>
<tr>
<th>Class</th>
<th>Data [Ref.]</th>
<th>FDA pregnancy category</th>
<th>TERIS Risk</th>
<th>Data rating</th>
<th>Notes when applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcipotriene</td>
<td>A vitamin D analog. High oral doses of vitamin D show skeletal abnormalities in animal studies; similar findings not confirmed in human studies [232] A pregnancy registry has been established. Topical use shows no fetal toxicity until maternal toxicity has been approached  No problems identified with use during lactation. Manufacturer does not contraindicate such use [233] Briggs: vitamin D use is compatible with lactation [232]</td>
<td>C</td>
<td>Undetermined</td>
<td>Very limited</td>
<td>High risk, in recommended doses, is unlikely Risk of congenital abnormalities may be higher in infants of mothers with hypervitaminosis D</td>
</tr>
<tr>
<td>Coal tar</td>
<td>A known carcinogen and mutagen [234] Use of shampoo is associated with uptake of coal tar [235] No human studies have been conducted. No information is available on use during lactation</td>
<td>C</td>
<td>Undetermined</td>
<td>None</td>
<td>High risk is unlikely</td>
</tr>
<tr>
<td>Precipitated sulfur</td>
<td>Applied to abraded skin, associated with fatalities after use in animals and humans in one report [236] During pregnancy, use of alternatives is preferable given relative ineffectiveness No information germane to lactation</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Box 1. Pregnancy category X: avoid in pregnancy and lactation

- Acitretin
- Estrogens
- Etretinate
- Finasteride
- Fluorouracil
- Flutamide
- Isotretinoin
- Methotrexate
- Stanozolol
- Tazarotene
- Thalidomide

* Both men and women should avoid if pregnancy is anticipated.
the effects of drugs on fetuses and nursing infants are continuous.

Tables 6–15 group drugs by their ratings and are included for further ease of reference [1–4,6,26,27,29–31,45,49–51,55,82,84–92,99–236]. Boxes 2 and 3 list drugs of minimal risk to mother and fetus

Box 2. Drugs with minimal risk to mother and fetus during pregnancy

**Analgesics**

- Acetaminophen
- Aspirin (low-dose; avoid preconception and third trimester)
- Codeine (low-dose)
- Ibuprofen (low-dose; avoid preconception and third trimester)
- Meperidine (low-dose)
- Oxycodone (low-dose)
- Propoxyphene (low-dose)

**Anesthetics**

- Lidocaine
- Lidocaine with epinephrine
- Lidocaine-prilocaine

**Antibacterial agents**

- Bacitracin (topical)
- Clindamycin (topical)
- Erythromycin (except estolate)
- Erythromycin (topical)
- Metronidazole (topical)
- Mupirocin (topical)
- Neomycin (topical)
- Penicillins
- Polymyxin B (topical)
- Sulfonamides (except third trimester)
- Sulfur (topical)
- Sulfur with resorcinol (topical)

**Antifungal agents**

- Butaconazole (topical)
- Ciclopinox (topical)
- Clotrimazole (topical; except first trimester)
- Econazole (topical; except first trimester)
- Fluconazole single dose
- Ketoconazole (topical)
- Miconazole (topical; except first trimester)
- Naftifine (topical)
- Nystatin (oral and topical)
- Oxiconazole (topical)
- Sulconazole (topical)
- Terbinafine (topical)

**Antihistamines**

- Cetirizine (except first trimester)
- Cyproheptadine
- Diphenhydramine
- Fexofenadine
- Hydroxyzine (except first trimester)
- Loratadine

**Antiscabetic and antipediculocidal agents**

- Crotamiton (topical)
- Malathion (topical)
- Permethrin (topical)
- Precipitated sulfur (topical)

**Antiviral agents**

- Acyclovir
- Famciclovir
- Valacyclovir

**Corticosteroids**

- Oral (avoid high doses first trimester)
- Topical (avoid high doses long term)

**Miscellaneous: topical antiacne products**

- Benzoyl peroxide
- Clindamycin
- Erythromycin

**Miscellaneous: other drugs**

- Calcipotriene (topical; low doses)

- Avoid vaginal use after membrane rupture.
- Avoid last 2 weeks of pregnancy if fetus is premature.
- Restrict use to treatment of severe herpes virus infections.
during pregnancy and to mother and infant during lactation, respectively.

Summary of cautions in treating women of childbearing age

Given the importance of the possible phases of pregnancy of any woman of childbearing age, the physician should determine whether the patient is using contraception, attempting to become pregnant, is already pregnant, or is lactating before any dermatologic treatment is recommended. Subtle distinctions within the three trimesters of pregnancy must also be considered. In sum:

- If the patient is attempting to avoid conception through the use of contraceptive drugs or devices, the physician should determine the possible interaction of dermatologic drugs and the contraception used before prescribing dermatologic therapy. Contraceptive failure presents a risk to the patient.
- If the patient is currently not pregnant but is trying to conceive, she should be asked to disclose her pregnancy as soon as possible after conception because of possible risk to herself or her fetus. The physician also should educate the

<table>
<thead>
<tr>
<th>Box 3. Drugs with minimal risk to mother and infant during lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analgesics</strong></td>
</tr>
<tr>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Codeine (low-dose)</td>
</tr>
<tr>
<td>Meperidine (low-dose)</td>
</tr>
<tr>
<td>Morphine (low-dose)</td>
</tr>
<tr>
<td>Oxycodone (low-dose)</td>
</tr>
<tr>
<td>Propoxyphene (low-dose)</td>
</tr>
<tr>
<td><strong>Anesthetics</strong></td>
</tr>
<tr>
<td>Lidocaine</td>
</tr>
<tr>
<td>Lidocaine with epinephrine</td>
</tr>
<tr>
<td>Lidocaine-prilocaine</td>
</tr>
<tr>
<td><strong>Antibacterial agents</strong></td>
</tr>
<tr>
<td>Bacitracin (topical)</td>
</tr>
<tr>
<td>Cephalosporins</td>
</tr>
<tr>
<td>Erythromycins</td>
</tr>
<tr>
<td>Erythromycin (topical)</td>
</tr>
<tr>
<td>Penicillins</td>
</tr>
<tr>
<td>Sulfur (topical)</td>
</tr>
<tr>
<td>Sulfur with resorcinol (topical)</td>
</tr>
<tr>
<td>Tetracycline (topical)</td>
</tr>
<tr>
<td><strong>Antifungal agents</strong></td>
</tr>
<tr>
<td>Ciclopirox (topical)</td>
</tr>
<tr>
<td>Clotrimazol (topical)</td>
</tr>
<tr>
<td>Econazole (topical)</td>
</tr>
<tr>
<td>Miconazole (topical)</td>
</tr>
<tr>
<td>Naftifine (topical)</td>
</tr>
<tr>
<td>Nystatin (oral and topical)</td>
</tr>
<tr>
<td>Oxiconazole (topical)</td>
</tr>
<tr>
<td>Sulconazole (topical)</td>
</tr>
<tr>
<td>Terbinafine (topical; not on nipple)</td>
</tr>
<tr>
<td><strong>Antihistamines</strong></td>
</tr>
<tr>
<td>Loratadine</td>
</tr>
<tr>
<td>Fexofenadine</td>
</tr>
<tr>
<td><strong>Antiviral agents</strong></td>
</tr>
<tr>
<td>Acyclovir</td>
</tr>
<tr>
<td>Valacyclovir</td>
</tr>
<tr>
<td><strong>Antiscabetic agents</strong></td>
</tr>
<tr>
<td>Crotamiton (topical)</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
</tr>
<tr>
<td>Oral: use prednisolone; avoid nursing for 4 hours after use</td>
</tr>
<tr>
<td>Topical: avoid use on nipple or areola</td>
</tr>
<tr>
<td><strong>Miscellaneous: topical antiacne products</strong></td>
</tr>
<tr>
<td>Azelaic acid</td>
</tr>
<tr>
<td>Benzoyl peroxide</td>
</tr>
<tr>
<td>Retinoids</td>
</tr>
<tr>
<td>Adapalene</td>
</tr>
<tr>
<td>Tretinoin</td>
</tr>
<tr>
<td><strong>Miscellaneous: other drugs</strong></td>
</tr>
<tr>
<td>Calcipotriene (topical)</td>
</tr>
</tbody>
</table>
patient about the possible risks of drug therapies used at the time of conception.

If a woman is not pregnant and is taking a medication that places her at high risk for problems during early pregnancy (eg, methotrexate, isotretinoin, thalidomide), she should be extensively counseled about the risk to her and her fetus. In addition, she should have regular pregnancy testing before and during her treatment course and use an effective form of birth control throughout the treatment.

If a woman is pregnant, her physician should determine her estimated date of conception and current trimester of pregnancy. Risks of drugs vary depending on the trimester of pregnancy.

If the patient is pregnant and has urgent need of a medication that places her or her fetus at risk, her physician should review her actual risk from the previously mentioned sources, especially TERIS and Drugs in Pregnancy and Lactation [94]. It is recommended that the physician document the discussion of risk with the patient.

If a patient is very near term, the physician should take careful note of those dermatologic drugs that are contraindicated in the last 2 weeks of pregnancy. Table 2 provides a prime example on antihistamines.

When an optional drug poses minimal risk, discussion of the options with the patient and her obstetrician, pediatrician, and primary care physician is advised. The dermatologist should anticipate that the patient’s other health care providers may be inclined toward or against the use of certain drugs during pregnancy or lactation.

If a drug therapy is optional and the manufacturer publishes a contraindication of use during pregnancy or breast-feeding, the drug should be prescribed only under exceptional clinical circumstances: if the patient’s overall health is at significant risk, and after discussing the risks and benefits with the patient, the father, and their obstetrician or pediatrician. Documentation of the risk-benefit conversation is strongly advised.

Because breast-feeding affects the proper choice of drug therapy, the physician treating a pregnant patient should determine if she plans to nurse. If a female patient is not pregnant, the physician should ask if she is nursing. Drugs of minimal risk in pregnancy may present greater risk during lactation, whereas drugs that are contraindicated during pregnancy may be safe during lactation. Two choices present themselves in treating a nursing patient. A drug treatment can be avoided or suspended until after nursing ceases or nursing can be avoided or suspending during treatment.

Controversy among sources over the use of drugs during lactation may complicate the physician’s choice of treatment. The best sources for information on risk during lactation include Drugs in Pregnancy and Lactation [94], the AAP [6], and the World Health Organization [96].

References


Jick H, Holmes LB, Hunter JR, et al. First trimester...


Nevi and Melanoma in Pregnancy

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The influence of pregnancy on melanocytic nevi and malignant melanoma (MM) continues to be a controversial issue. This topic takes on more importance in the twenty-first century, as more women delay childbearing into their 30s and 40s, and possibly result in a rising incidence of MM during pregnancy. Over the past 50 years, case reports and uncontrolled studies have suggested that nevi are more likely to become malignant during pregnancy, and MM diagnosed during pregnancy has a poor prognosis. Clinical and laboratory observations suggested that pregnancy-associated hormones may influence nevi and MM. Recent clinical and laboratory evidence suggests, however, that pregnancy does not influence the prognosis of MM, nor does it seem to cause significant changes in nevi. A clear link between hormones and MM has not been established. An analysis of this evidence is presented along with practical recommendations for the patient.

**Historical review**

The origin of this controversy began with multiple case reports [1–5] and observations published since the 1950s. Pack and Scharnagel [1] reviewed 1050 cases of MM: of 10 patients diagnosed during pregnancy, 5 died within 30 months of diagnosis. Eleven patients reported changes in their nevi during pregnancy and were subsequently diagnosed with MM in the postpartum period. These investigators suggested that hormonal influences may cause melanocytic nevi to undergo malignant change during pregnancy, and that these MMs may grow and rapidly metastasize. These reports, along with the observation of hyperpigmentation as a normal occurrence in multiple cutaneous sites during pregnancy, have led to the suggestion that pregnant women are more likely to have worrisome changes in nevi and poor prognosis if diagnosed with MM.

**Melanocytic nevi and pregnancy**

Several studies have reported that women diagnosed with MM during pregnancy have had a significantly greater tumor thickness compared with nonpregnant age-matched controls [6–8]. It has been proposed that hormonal influences normally cause melanocytic nevi to darken or enlarge during pregnancy, and diagnosis may be delayed. Few studies, however, have investigated changes in nevi during pregnancy.

In two studies that addressed this issue, enlargement or color change in nevi was self-reported by pregnant women [9,10]. In the study by Foucar and coworkers [9], of 86 pregnant patients, approximately one third reported some enlargement or change in color of nevi. On further examination, these investigators stated that most of these changes represented skin tags; dermatofibromas; or in one case, an attached tick. Histologic examination of 128 nevi removed from these patients showed a slightly higher mean melanocytic atypia score in the pregnant patients compared with nonpregnant age-matched controls; these atypia scores were based on nine histologic features [9]. In the study by Sanchez and coworkers [10], approximately 10% of 389 pregnant

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women reported some change in their pigmented lesions. Twenty-six lesions were biopsied from the pregnant patients; 20 of these were from women who had reported lesion changes. Overall, 22 of the 26 specimens were melanocytic nevi, and these showed no significant histologic differences compared with nevi biopsied from age-matched nonpregnant controls [10].

Two prospective studies evaluated changes in nevi over the course of pregnancy [11,12]. When 17 women with the atypical mole syndrome were followed during their pregnancy, Ellis [11] observed changes in the size and color of nevi. Only one study [12], however, has prospectively studied whether or not normal nevi change in size during pregnancy. The authors examined nevi located on the back of pregnant women, both through clinical examination and photography. Of the 129 nevi studied, only 8 (6.2%) changed from the first to third trimester: four increased by 1 mm and four decreased by 1 mm [12]. Although larger prospective studies are needed to confirm these findings, one should not assume that changes in nevi during pregnancy are physiologic. Biopsy of a changing nevus in pregnancy should not be delayed.

Melanoma and pregnancy

The influence of pregnancy on the prognosis of MM raises three separate issues for the woman of childbearing age with MM: (1) if diagnosed during pregnancy, what is the effect on prognosis of MM; (2) if diagnosed in the postpartum years, what effect do prior pregnancies have on the development and prognosis of MM; and (3) if diagnosed before becoming pregnant, what effect will a subsequent pregnancy have on the prognosis of MM?

Diagnosis of malignant melanoma during pregnancy

Six well-controlled studies have addressed survival rates or disease-free interval (DFI) in women diagnosed with localized MM (American Joint Committee on Cancer stage I or II) during pregnancy compared with matched, nonpregnant controls [6,7,13–16]. With the exception of the most recent study [16], the authors have described these studies in detail in a previous review [17] and all are summarized in Table 1. All six case-control studies observed no significant difference in survival rates between the two groups. Of the five studies that performed statistical comparisons of DFI, Reintgen and coworkers [13] and Slingluff and coworkers [6] observed a significantly shorter DFI in pregnant patients compared with controls; a third study observed a trend toward a shorter DFI, but the difference was not statistically significant [16]. Various explanations have been offered for the shortened DFI despite unchanged survival rate. Some of the investigators suggested that a longer follow-up period may be needed to observe an effect on survival [13]. Adami and coworkers [18] questioned whether or not there is sufficient statistical power to observe an effect on survival because the frequency of metastasis is low in patients with localized MM.

Two recent case-control studies evaluated the prognosis of MM diagnosed during pregnancy by analyzing larger populations: O’Meara and coworkers [19] used records from the California Cancer Registry from 1991 to 1999, and Lens and coworkers [20] used data from Swedish National and Regional Registries from 1958 to 1999. The former study showed no difference in survival between 303 women who had “pregnancy-associated melanoma” (patients diagnosed with MM during pregnancy or within 1 year after pregnancy) and 1799 age-matched nonpregnant controls [19]. Tumor thickness data were missing, however, from approximately 20% of both the study and control groups. Likewise, the latter study found no significant difference in survival between 159 patients diagnosed with MM during pregnancy and 4385 nonpregnant controls, but tumor thickness data were missing for approximately 26% of the study patients and 60% of the controls [20].

A noteworthy observation made in two [6,7] of the six case-controlled studies and one additional study by Travers and coworkers [8] was the significantly greater tumor thickness reported in pregnant patients. It is possible that changes in nevi during pregnancy are considered physiologic and diagnosis of early MMs is delayed. Only the authors’ own small prospective study [12] has shown no significant changes in the size of nevi over the course of pregnancy; a larger number of patients need to be studied for both changes in size and color to confirm these results.

Effect of prior pregnancies on the prognosis of malignant melanoma

Only two controlled studies [7,21] have addressed the effect of prior pregnancies on the prognosis of MM. Bork and Bräuninger [21] observed no difference in survival between women who had been pregnant either once or twice before the diagnosis of MM compared with nulliparous controls. Likewise,
Table 1
Controlled studies: malignant melanoma during pregnancy

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of patients</th>
<th>Number of controls</th>
<th>AJCC stage of disease</th>
<th>Mean thickness of primary lesion (mm)</th>
<th>Effect of pregnancy on survival</th>
<th>Effect of pregnancy on DFI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reintgen et al [13]</td>
<td>58</td>
<td>585</td>
<td>I or II</td>
<td>Study group: 1.90 Controls: 1.51 SD not stated</td>
<td>No</td>
<td>Yes (shorter DFI in study group, SD, <em>P</em> = .04)</td>
</tr>
<tr>
<td>McManamny et al [14]</td>
<td>23</td>
<td>243</td>
<td>I or II</td>
<td>Study group: 1.62 (survived), 2.62 (died) Controls: 1.72 (survived), 3.96 (died)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Wong et al [15]</td>
<td>66</td>
<td>619</td>
<td>I or II</td>
<td>Study group: 1.24 Controls: 1.28 Matched controls: 1.06 SD not stated</td>
<td>No</td>
<td>Actuarial DFI curves not generated Study group: 37.7 months Matched controls: 27.3 months SD not stated</td>
</tr>
<tr>
<td>Slingluff et al [6]</td>
<td>88</td>
<td>79</td>
<td>I or II</td>
<td>Study group: 1.87 Controls: 1.45 SD not stated</td>
<td>No</td>
<td>Yes (shorter DFI in study group, SD, <em>P</em> = .039)</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>86</td>
<td>All stages</td>
<td>Study group: 2.17 Controls: 1.52 SD, <em>P</em> = .052</td>
<td>No</td>
<td>Yes (shorter DFI in study group, SD, <em>P</em> = .028)</td>
</tr>
<tr>
<td>MacKie et al [7]</td>
<td>92</td>
<td>143</td>
<td>I or II</td>
<td>Study group: 2.38 Controls: 1.96 SD, <em>P</em> = .002</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Daryanani et al [16]</td>
<td>46</td>
<td>368</td>
<td>I or II</td>
<td>Study group: 2 Controls: 1.7 NS</td>
<td>No</td>
<td>No, but trend toward longer DFI in controls</td>
</tr>
</tbody>
</table>

*Abbreviations:* AJCC, American Joint Committee on Cancer; DFI, disease-free interval; SD, significant difference.
MacKie and coworkers [7] found no significant difference in either survival or DFI between women with pregnancies before diagnosis with MM compared with controls.

Effect of subsequent pregnancy on the prognosis of malignant melanoma

Only two controlled studies [7,13] analyzed the effect of subsequent pregnancies on the prognosis of MM. There was no significant difference in survival or DFI in women who became pregnant after being diagnosed with MM compared with women who did not have a subsequent pregnancy.

Influence of hormones on malignant melanoma

In addition to early case reports that implied that the hormonal milieu of pregnancy could cause MM to metastasize, various early observations led many to hypothesize that there may be a link between hormones and MM. Some of these observations included the rare occurrence of MM before puberty [22], the presence of receptors for estrogen and progesterone in some MMs [23,24], and the increased growth rate of MMs in mice after administration of estrogen [25]. In recent years most of these observations have come into question.

It has been hypothesized that there may be some hormone or other factor associated with pregnancy that could influence MM. A hormone that specifically affects MM cell proliferation and the induction of angiogenesis has not been identified. Numerous investigators have studied the binding of estrogen, progesterone, androgens, and glucocorticoids to MM in tissue culture using various techniques. If binding was observed, it was at a low level and most of the binding seen in MM was not to true receptors [26]. Laboratory studies that have used monoclonal antibody techniques, which are likely to have greater specificity than earlier studies, did not detect estrogen receptors in benign nevi, primary MM, metastatic MM, or pregnancy-associated MM [27–29]. The effect of placenta growth factor, a member of the platelet-derived growth factor family, has recently been studied for its effects on human melanoma cell lines [30,31]. Although both groups found that human melanoma cell lines secrete placenta growth factor, only one group [30] observed MM cell proliferation in response to placenta growth factor.

A recent case report [32] of a melanocytic nevus that changed in size during pregnancy describes other interesting laboratory observations. A benign nevus that enlarged during pregnancy showed rapid postpartum regression; biopsies were taken during and after pregnancy. No evidence of malignancy was seen on histologic examination. Consistent with the previously mentioned findings, there was no evidence of estrogen or progesterone receptors using monoclonal antibody techniques. The nevus cells were examined for apoptosis using Tdt-mediated dUTP-biotin nick end labeling assay. During pregnancy there was only focal weak reactivity in the upper dermis, whereas the postpartum lesion revealed strong staining of apoptotic nevus cells throughout the lesion. The expression of Bcl-2, an oncoprotein involved in tumorigenesis by blocking apoptosis, showed the opposite pattern of reactivity: loss of bcl-2 expression in the postpartum lesion. Evidence of decreased apoptosis and enhanced bcl-2 expression has been observed in MMs [33], but this observation during pregnancy did not coincide with malignant transformation. Further study is needed to confirm decreased apoptotic activity of nevus cells during pregnancy and its clinical significance, if any.

In addition to laboratory investigations, other evidence has failed to link hormones and MM. Endocrine manipulation with antiestrogens, such as tamoxifen, has been ineffective in the treatment of MM [34]. Likewise, epidemiologic studies have consistently demonstrated that there is no increased risk for MM in women who have taken oral contraceptive pills [35].

Summary and recommendations for the patient

Although early case reports suggested a grave prognosis for the pregnant woman diagnosed with MM, multiple controlled studies of women with localized MM diagnosed during pregnancy have not revealed an effect on survival. Likewise, pregnancy before or after a diagnosis of localized MM has not been shown to influence overall survival. Laboratory investigations have not consistently identified a specific pregnancy-related hormone that induces proliferation of melanoma cell lines. Epidemiologic evidence has not demonstrated an adverse effect of exogenous hormones (ie, oral contraceptive pills) on the risk for MM. The widely held belief that changes in nevi during pregnancy are physiologic has not been firmly established.

Based on the knowledge to date, recommendations for women concerning melanoma and pregnancy are as follows. First, for the pregnant patient with localized MM, recommendations for prognosis
should be based on the same prognostic factors established for the nonpregnant patient. Second, when advising a woman diagnosed with MM whether or not to become pregnant, the primary consideration is how the established prognosis for that given MM affects the life expectancy of the mother. If the tumor is an early, thin MM, there is no reason to delay a subsequent pregnancy. If the tumor has a high risk for recurrence, it is reasonable to delay pregnancy for a period of 2 to 3 years, because most recurrences are observed during this time. Third, based on limited data, pregnancies before a diagnosis of localized MM does not affect prognosis.

Recommendations for the management of changes in nevi during pregnancy are identical to those for the nonpregnant patient: biopsy should not be delayed. Further prospective study needs to be performed on whether or not changes in size and color of nevi occur during pregnancy, but for now such changes should not be assumed to be hormonally driven, physiologic changes.

References


Performing dermatologic surgery in any patient requires a thoughtful and careful approach to provide optimal patient care. One must consider the risks and benefits specifically related to each individual carefully before the procedure is planned and performed. This concept is especially important when considering dermatologic surgery in a pregnant patient. The surgeon must keep not only the health of the woman in mind, but also the health of the fetus. The goal of this article is to outline some of the perioperative issues that are related specifically to performing dermatologic procedures in a pregnant woman.

Physiologic changes

A pregnant woman’s body is changing constantly throughout the 40 weeks of gestation. Although a complete review of physiologic changes is outside the scope of this article, it is important to highlight those changes that could directly affect the planning and execution of surgical procedures.

The uterus is a nurturing environment from the initial crucial stages of organogenesis to the final stages of fetal growth and maturity. Changes occur in several organ systems during pregnancy to meet increasing demands of the fetus. Hemodynamically, cardiac output and stroke volume increase to meet oxygenation demands of mother and fetus as maternal peripheral vascular resistance decreases. Venous blood return to the heart slows as the gravid uterus compresses vessels [1,2]. Because maternal hypotension could quickly compromise uterine blood flow, a pregnant patient’s blood pressure should be monitored closely during surgical procedures. Decreased vascular resistance in combination with increased production of circulating coagulation factors may heighten the risk for thromboembolic events, especially during late pregnancy and the puerperium as platelets aggregate [3]. Patients who have additional risk factors (such as personal or family history of thrombosis or clotting factor deficiencies) may need thromboprophylaxis, such as subcutaneous heparin and pneumatic leg compression, if undergoing lengthy or complex procedures [2,3].

Respiratory tidal volume and minute respiration increase to meet fetal oxygen requirements causing a pregnant woman to be in a state of compensated respiratory alkalosis and sensitive to potential decreases in arterial $P_{O_2}$ [2,3]. During long or complicated procedures, a pregnant patient should be placed in a comfortable position (see following discussion) to maximize oxygenated blood flow to the fetus. Aortocaval compression by the gravid uterus causes arterial $P_{O_2}$ to decrease.

Changes in the renal, gastrointestinal, and musculoskeletal systems may stimulate a pregnant patient to request frequent breaks during long surgical procedures. Increased renal blood flow, glomerular filtration rate, and collecting system volume aids disposal of maternal and fetal metabolic waste and causes frequent urination [2,3]. Likewise, bladder pressure increases as the gravid uterus enlarges contributing to urinary frequency. Supine positioning may worsen acid reflux symptoms, because progesterone decreases gastroesophageal sphincter tone [3]. Fasting blood sugar levels are typically lower than normal during pregnancy because of the continuous

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glucose demands of the fetus. Frequent snacking may help to alleviate hypoglycemic symptoms and prevent potential ketosis [2,3]. Repositioning breaks may relieve muscle cramps and pelvic or lower back discomfort associated with hormonally induced ligamentous laxity [2,3].

The peripheral white blood cell count progressively increases during pregnancy [3]. This should not be misinterpreted as a marker of occult infection in the absence of clinical signs or symptoms (eg, wound infection after surgery). Platelets may aggregate in late pregnancy and the puerperium causing an increased incidence of cerebrovascular disease [3].

**Timing of surgery**

The correct timing for performing a surgical procedure on a pregnant woman is an important and individualized issue. The first 12 weeks of gestation are critical for organogenesis and carry a higher risk for spontaneous abortion. Surgery performed during the third trimester may increase the risk for preterm labor. Most authorities agree that non-emergent surgery should not be performed on a pregnant woman during the first or third trimesters and recommend scheduling necessary dermatologic procedures on a pregnant woman during the second trimester (13–28 weeks) or the postpartum period to minimize risk to patient and fetus.

What if a pregnant woman presents with a lesion suspicious for malignancy or even a benign but bleeding tumor? In this situation, most dermatologists agree that an expeditious biopsy or excision is mandated. The risk of not performing a procedure, even an excisional biopsy, far outweighs the potential harm incurred by leaving such a lesion on the skin. In addition, the surgeon is better prepared to discuss management issues once the histologic diagnosis is known. A patient in her first trimester of pregnancy with a superficial basal cell carcinoma on her chest or abdomen may be able to wait until the postpartum period to undergo treatment. Alternatively, a patient who has an aggressive squamous cell carcinoma on the nose during her first trimester of pregnancy may require immediate Mohs micrographic surgery as definitive treatment.

A difficult decision arises when the biopsy reveals a malignant melanoma, particularly in the first or early third trimester of pregnancy. Increasing rates of melanoma in the general population and an increase in the average age of the pregnant woman have raised concerns that the incidence of melanoma in pregnancy may increase [4]. There also has been controversy as to whether elevated hormone levels associated with pregnancy could lead to an increased incidence of melanoma or a worse outcome for the mother and fetus [5–9]. Fortunately recent studies suggest that the clinical course, prognosis, and outcome for pregnant women who have melanoma (stage I-II) are comparable to those seen in non-pregnant women [10–13]. Future pregnancies do not seem to affect recurrence or survival risks for patients who have melanoma [2]. Tumor thickness and presence or absence of ulceration are still the most important prognostic factors. It is somewhat unclear whether greater tumor thickness occurs in pregnant patients, as suggested by previous studies [7,14]. Benign nevi are believed to darken or enlarge during pregnancy [6]. This fact in combination with hesitance to perform a biopsy or procedure during pregnancy could lead to a delay in diagnosis. Because aggressive or more advanced melanomas carry higher maternal and fetal morbidity and mortality risks, suspicious lesions must be biopsied in an expeditious manner to prevent a delay in diagnosis [15].

Sentinel lymph node biopsy can be performed safely in pregnancy [11,16,17]. A preoperative intradermal injection of a radiocolloid (99mTcTechnetium radioactive isotope) around the tumor site is followed by an intraoperative intradermal injection of isosulfan blue dye. Lymphatic mapping then is performed using a hand-held gamma counter and direct visualization of the blue dye in draining lymph nodes [19]. The dose used for this lymphatic mapping is small, less than 5 mGy of radiation (<100 mGy do not increase incidence of fetal malformation) [11,17,20]. Most of the injected radioactivity remains at the injection site or moves to the sentinel nodes that are removed. Some may choose to perform the sentinel lymph node biopsy after the first trimester to minimize risk to the developing fetus [17]. Small quantities of radioactivity may be excreted in breast milk [17]. The reported incidence of allergic reactions to the isosulfan blue dye is as high as 2.5% [19]. This includes risk for anaphylaxis (1.1%) [11,18,19], which can be avoided by using radiocolloid alone. Alternatively, a woman in her third trimester of pregnancy may elect to have a narrow excision followed by a sentinel lymph node biopsy and wide excision during the postpartum period. A tumor of 1 mm or greater thickness, however, is best addressed immediately for long-term survival.

Although unusual, melanoma is the most common type of cancer to metastasize to the placenta and the fetus [4,11,21,22]. Prognostic features of the mother, placenta, or fetus remain unclear because of a paucity of reported cases in the literature. Placental metastasis
from melanoma, however, seems to be associated with concurrent maternal visceral metastases (stage IV disease). Likewise, fetal metastasis almost always has been associated with evidence of placental metastasis [4]. The timing of the wide excision, sentinel node biopsy, and other treatments is guided by an individualized treatment plan that considers potential risks to mother and fetus. This treatment plan likely will be the result of a multidisciplinary approach to provide optimal monitoring of mother and fetus. It is imperative, however, that all pregnant women who have melanoma have the placenta sent to histopathology for careful gross and microscopic examination. Placental metastasis indicates stage IV disease and directly impacts treatment of the mother and prognosis of the fetus.

Positioning the patient

As the uterus expands, a pregnant woman may find it difficult to lie in a comfortable position. Supine positioning, commonly used for patients undergoing surgical procedures, may lead to aortocaval compression syndrome with symptoms of lightheadedness, headache, nausea, vomiting, diaphoresis, hypotension, and tachycardia [2]. Symptoms may occur suddenly without warning but typically are relieved by positioning the patient in a left lateral tilt with a wedge or pillow under the right hip or between the knees (Fig. 1). Using this position during particularly long or difficult procedures may prevent the onset of symptoms. If the patient cannot be placed in the left lateral position, she may be positioned on her right side to allow the uterus to fall forward and improve venous return [1].

Planning the procedure

Once the decision is made to schedule a surgical procedure the surgeon must consider various issues such as choice of anesthetic, choice of suture and duration in skin, wound care, and risk for infection. As in any surgical procedure, it is important that a thorough medical history of the patient is elicited to uncover any additional risk factors such as history of diabetes, hypertension, or cardiac disease. In particular, it is imperative that a pregnant patient’s medical status is reviewed carefully on the day of surgery. A history of recent contractions, vaginal bleeding, increasing edema, or other concerning symptoms may necessitate consultation with the patient’s obstetrician and possible rescheduling of the procedure. The patient’s vital signs, including blood pressure, should be recorded accurately to screen for occult signs of pre-eclampsia or other medical problems. In some instances, fetal heart rate monitoring may be needed to identify fetal stressors during a procedure. If this is required, the procedure might best be moved to an operating setting where an anesthesiologist is available for patient and fetal monitoring.

Emotional and physical stressors associated with pregnancy coupled with concerns about an impending surgical procedure can heighten the level of anxiety in a pregnant patient. Most patients respond favorably to various techniques such as education, acknowledgment of fears and concerns, and reassurance by the surgical staff [1]. Highly anxious patients or those who have a history of severe anxiety may require preoperative sedation. The patient’s obstetrician and primary medical provider may be useful resources when considering this issue.

Antiseptics

Alcohol and chlorhexidine do not have any increased risk for the pregnant patient but do have some risks. Alcohol-based preparations must be allowed to dry completely to achieve a bacteriocidal effect. This also prevents any risk for ignition with use of electrocautery or lasers. Chlorhexidine gluconate should be used with caution around the eyes

Fig. 1. Left lateral position.
because of a risk for conjunctival irritation, keratitis, or corneal ulceration [2]. Likewise, it can cause ototoxicity if the patient has a perforated tympanic membrane. Povidone-iodine and hexachlorophene do have potential risks during pregnancy. Povidone-iodine absorption through mucous membranes has been linked to fetal hypothyroidism [1,2,23]. Hexachlorophene is not recommended because of reports of central nervous system toxicity in the fetus [1,2].

Anesthesia

The use of anesthesia during pregnancy has raised concerns about potential ill effects to the developing fetus. Each anesthetic has the potential to be teratogenic to some species under the right conditions and definitive human studies are lacking [24]. The American College of Obstetrics and Gynecologists’ Committee on Obstetric Practice acknowledges that “not enough data exists to make specific recommendations on the issue of non-obstetric surgery and anesthesia in pregnancy” [25]. They do, however, recognize that each case presents varied risks and the surgeon should obtain obstetric consultation as needed to protect the mother and child.

A pregnant woman requiring an extensive surgical procedure may need general anesthesia. Nitrous oxide frequently has been used to achieve this purpose, but concerns have arisen regarding its teratogenicity. Nitrous oxide can impair DNA production by oxidizing cobalamin (vitamin B12) and inhibiting methionine synthase activity [2,24]. This impairment could have a profound effect on fetal organogenesis during early pregnancy. Some studies suggest that this risk may be avoided by pretreating the patient with folic or folinic acid, but adequate clinical studies are needed [24]. Avoiding the use of general anesthesia during the first trimester can minimize potential risks.

Regional anesthesia may be an alternative to general anesthesia in some patients. Spinal anesthesia can achieve good pain control while minimizing placental drug transfer to the fetus. Alternatively, an epidural or brachial plexus block may cause increased placental transfer with higher local anesthetic blood levels [24]. In all cases, hypotension, hypoxia, and acidosis need to be identified and treated quickly.

Most procedures that would occur in the dermatologic surgical suite likely would use local anesthetics. These medications can be used safely, but dermatologic surgeons must become familiar with potential side effects. The US Food and Drug Administration has categorized the teratogenic risk of medications (Box 1) [26]. In general, medications in category A or B are considered safe in pregnancy; those in category C lack adequate human studies; category D medications have benefits that outweigh

<table>
<thead>
<tr>
<th>Box 1. Categories for drug use in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category A</strong></td>
</tr>
<tr>
<td>Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.</td>
</tr>
<tr>
<td><strong>Category B</strong></td>
</tr>
<tr>
<td>Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women.</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.</td>
</tr>
<tr>
<td><strong>Category C</strong></td>
</tr>
<tr>
<td>Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women.</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.</td>
</tr>
<tr>
<td><strong>Category D</strong></td>
</tr>
<tr>
<td>Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus. The benefits of therapy, however, may outweigh the potential risk.</td>
</tr>
<tr>
<td><strong>Category X</strong></td>
</tr>
<tr>
<td>Adequate well-controlled or observational studies in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.</td>
</tr>
</tbody>
</table>
risks to fetus noted in studies; those in category X are contraindicated in pregnancy.

**Local anesthetics**

The teratogenic risk of medications as characterized by the US Food and Drug Administration can guide the choice of anesthetics. For most dermatologic surgical procedures, lidocaine and prilocaine are considered safe as category B medications [2,27,28]. Studies have shown that use of lidocaine during pregnancy has no increase in adverse events to the fetus [1,2,29,30]. Local anesthetics can cross the placental barrier [28]. In certain situations, such as inadvertent arterial injection or large volumes of anesthesia, this may expose the fetus to cardiac or central nervous system toxicity [2,30]. Bupivacaine and mepivacaine have been associated with an increased risk for fetal bradycardia [30]. Signs of early local anesthetic systemic toxicity in the mother may mimic signs of aortocaval compression: lightheadedness, tachycardia, diaphoresis, and headache. Proper positioning of the patient in combination with accurate recording of total doses of local anesthetic should help to identify the problem quickly. Local anesthetics can be excreted in breast milk [27]. The total amount of local anesthetic exposure to the fetus must be carefully monitored to prevent fetal toxicity [2,31].

Epinephrine is often added to local anesthetics to decrease bleeding at the operative site and slow absorption of the anesthetic, enhancing efficacy. A category C medication, epinephrine generally is considered safe if used cautiously. Concerns regarding use of epinephrine in pregnancy developed when it was shown to decrease uterine blood flow in animal experiments [27]. Uterine artery spasm from high levels could induce premature labor because of poor placental perfusion [1]. If one considers the dilution used in dermatologic surgery and the small controlled amounts, however, the benefit of local vasoconstriction during surgery seems to outweigh potential risk. As with all medications during pregnancy, judicious use of epinephrine is the preferred tactic.

**Benzocaine**

Benzocaine, an ester anesthetic, is available as an aerosol spray, gel, ointment, or solution for use on mucosal surfaces. It is a para-aminobenzoic acid (PABA) derivative, and can cause contact sensitization [32]. As a pregnancy category C medication, insufficient data exists regarding the risks to human fetuses during gestation. Benzocaine-containing products carry a potential risk for methemoglobinemia, especially in infants [32–34].

**Lidocaine**

A pregnancy category B medication, lidocaine is generally thought to be safe in pregnancy. It is available in 2% to 5% gel, topical, and viscous solutions that are great for mucosal surfaces but do not adequately penetrate intact skin. Some topical preparations have been compounded to include higher concentrations of lidocaine to enhance penetration. The risk for greater absorption and potential side effects increases with use of this type of product, however. Fortunately, other topical anesthetics containing lidocaine in more effective delivery systems have been developed to address this problem. Lidocaine and prilocaine creams are probably the most widely studied topical anesthetics marketed for intact skin.

**Lidocaine and prilocaine creams**

Lidocaine 2.5% and prilocaine 2.5% cream is an emulsion comprised of a eutectic mixture of amide local anesthetics in a liquid oil phase at room temperature [32]. Nonabsorbent occlusive dressings are used when applying the cream to intact skin to enhance dermal penetration and duration of application (protects site), factors that directly affect depth and duration of local analgesia. Dermal analgesia is achieved approximately 1 hour after application, reaches maximum level at 2 to 3 hours, and persists up to 2 hours after removal. Analgesia is achieved more rapidly on mucosal surfaces, in 5 to 10 minutes, and occlusion may not be required [35].

A pregnancy category B medication, lidocaine-prilocaine cream should be used only as needed in pregnant patients because total doses of lidocaine or prilocaine must be considered if using concomitant topical and injectable local anesthetics. Potential side effects include transient local blanching or erythema, edema, and allergic contact dermatitis (prilocaine) [33]. Alkaline chemical injuries to the cornea (eg, abrasions, ulcerations) can occur with use of lidocaine-prilocaine cream near the eyes and require immediate ophthalmology referral [36]. Some patients may develop purpura or petechiae at the application sites, likely because of injury to capillary endothelial cells [33]. Lidocaine-prilocaine cream also carries a risk for methemoglobinemia, particularly to the fetus. Fetal red blood cells are more susceptible to oxidative stressors because of lower levels of erythrocyte methemoglobin reductase [33]. Lidocaine and possibly
prilocaine are excreted in breast milk. Caution should be used in determining when to schedule postpartum procedures if the patient is breastfeeding. The area and duration of lidocaine-prilocaine cream application and methemoglobin levels must be monitored closely in neonates, making its use problematic during pregnancy.

Liposome-encapsulated lidocaine cream

Liposome-encapsulated lidocaine cream containing either 4% or 5% (anorectal cream) lidocaine encapsulated in a liposomal delivery system to facilitate penetration and duration of anesthesia. This cream does not contain prilocaine and thus does not carry a risk for methemoglobinemia. It seems to have a faster onset of action with dermal analgesia occurring in 30 minutes, an advantage for unplanned procedures that occur in the office setting. Occlusive dressings seem to enhance performance, yet it has been successfully used without occlusion in more superficial procedures [33,35]. It is not recommended for use on conjunctival or mucosal surfaces because of risk for corneal irritation and higher levels of absorption [31,32]. It is categorized as a pregnancy category B medication.

Studies indicate that liposome-encapsulated lidocaine cream is as effective as lidocaine-prilocaine cream in reducing pain for superficial surgical procedures [33]. Yet anecdotal experiences by these investigators suggest that lidocaine-prilocaine cream provides better analgesia after a 60 minute application under occlusion. Both creams seem to work better with occlusion especially for more invasive surgical procedures. Liposome-encapsulated lidocaine cream can be purchased without a prescription.

Lidocaine gel

Topical lidocaine is also available over the counter as a gel containing 4% lidocaine in a microemulsion vehicle [35]. It should be applied for 30 to 60 minutes under occlusion for maximum effect, lasting about one hour. Lidocaine gel demonstrated a rapid onset and long duration of action in a study comparing lidocaine-prilocaine, liposome-encapsulated lidocaine cream, and lidocaine gel [36–38]. It is a pregnancy category B medication and is excreted in breast milk.

Tetracaine

Tetracaine, a long-acting ester anesthetic, is available in a 0.5% solution. It is more commonly recognized as a component of TAC, a compounded formulation of tetracaine, adrenaline (epinephrine), and cocaine [31]. Because of limited absorption on intact skin, it has been used more commonly for anesthesia for laceration suturing or ophthalmic procedures (penetrates mucous membranes) [31,32]. Amethocaine 4% gel, a preparation of 4% tetracaine, may have a more rapid onset, a longer duration of action, and be more efficacious than lidocaine-prilocaine cream [33,35,38]. There is no specific information regarding the safety of amethocaine in pregnancy or breastfeeding infants. It is not recommended, however, for use in neonates younger than 1 month old. Local side effects include erythema, edema, pruritus, and allergic reactions [27,33]. It should be applied under an occlusive dressing [32].

Some of the topical anesthetics mentioned previously may be compounded into more elegant vehicles. For example, BLT is a combination of benzocaine, lidocaine, and tetracaine. Because increasing the number of medications in one formulation may increase the number of potential risks or side effects, a better studied and more easily available topical anesthetic may be the logical choice for use on a pregnant woman.

Bupivacaine and mepivacaine

Bupivacaine and mepivacaine are relatively contraindicated in pregnancy. They are amide anesthetics that are listed as pregnancy category C medications because of a risk for fetal bradycardia [2]. Bupivacaine carries a risk for cardiac toxicity by inducing reentrant arrhythmias that are refractory to treatment [32]. This risk may be more severe during pregnancy, possibly because of a combination of increased progesterone levels and inefficient venous return during resuscitation (aortocaval compression) [39,40].

If a patient claims an allergy to local anesthetics, it probably warrants further investigation before deciding to postpone surgery or use general anesthetics. A history of allergic reactions to local anesthetics is uncommon [41] and usually because of a sensitivity to ester anesthetics [27]. Some patients’ symptoms are not a true allergy but are due to anxiety or the effects of epinephrine mixed with the anesthetic. Fortunately, intradermal skin testing and progressive challenge testing have been used safely in pregnant women [41] to avoid life-threatening sequelae that could occur with true allergies (usually to esters). Multiple-use vials of amide local anesthetics may contain ester-based preservatives [27,41]. Alternatives to true anesthetic allergy include the use of diphenhydramine and normal saline solution to achieve anesthesia [1,2]. These provide superficial short-term analgesia for a rapidly performed biopsy
but are inadequate for excisional surgery. Although less than ideal, they can be used safely in pregnancy.

**Design of procedure**

As with any surgery, the procedure should be carefully designed to account for variables such as location, risk for infection, and risk for bleeding. The incision should allow for the least tension possible. How do you follow relaxed tension lines on a pregnant woman’s abdomen? In areas in which there is any question about the vector of least tension, lesion excision should be circular. The wound then should be undermined adequately. At this point, the vector of least tension is usually clear. Placement of the central suture allows identification of the size and placement of standing cone repair.

**Electrocautery**

Electrocautery is believed to be a safe procedure in pregnant patients because no current flows through the patient. Concerns have been raised as to whether the fetus is at risk for exposure to harmful or mutagenic airborne particles from electrocautery smoke [2,42]. Techniques to minimize exposure to cautery smoke should be used, but this is the case for all patients and caregivers. Certainly placing a mask on the patient may help minimize exposure when extensive cautery plume is present.

**Suture choice**

For the most part, choice of suture in a pregnant patient reflects the same principles used in choosing suture for any patient. If the surgical procedure occurs on the abdomen, for example, one might decide to use a slowly absorbing buried suture with increased strength and knot security. Sutures may need to remain in the skin longer because of slower wound healing associated with pregnancy. A staged suture removal may help to alleviate concerns of dehiscence in high-tension areas such as the expanding abdomen.

**Use of antibiotics**

When faced with the use of oral or topical antibiotics perioperatively or postoperatively, medications considered safe in pregnancy (category A and B) should be used. In the dermatologic surgery world, penicillin-based derivatives and cephalaxin are commonly prescribed. Erythromycin and azithromycin are safe alternatives in penicillin-allergic patients. Erythromycin estolate has been associated with an increased risk for cholestatic jaundice in some pregnant patients [29,43]. Clindamycin may cause liver function test abnormalities on rare occasions [2]. Sulfonamides may cause neonatal hyperbilirubinemia with kernicterus, particularly if taken during the third trimester close to delivery [2]. Fluoroquinolones, tetracyclines, and aminoglycosides are relatively contraindicated; fluoroquinolones have been associated with cartilage defects in immature animals, tetracycline carries a risk for tooth enamel staining, and aminoglycosides have a risk for fetal ototoxicity [2,44]. Chloramphenicol is contraindicated because of reports of gray baby syndrome and neonatal death (Box 2) [2]. Antibiotic prophylaxis should be discussed carefully before the procedure is planned because it may require input from the obstetrician or another care provider.

**Analgesia**

Acetaminophen, as a category B medication, should be used for analgesia as needed. It crosses the placenta but is safe if used in recommended doses for limited duration. Consistent use of high dose acetaminophen has been associated with maternal

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**Box 2. Oral antibiotics used in dermatologic surgery**

**Safe in pregnancy**

- Penicillins
- Cephalosporins
- Erythromycin (non-estolate)
- Azithromycin
- Clindamycin
- Sulfonamides

**Relatively contraindicated**

- Fluoroquinolones
- Tetracyclines
- Aminoglycosides

**Contraindicated**

- Chloramphenicol
and fetal hemolytic anemia and renal toxicity [1]. Ibuprofen and salicylates interfere with platelet function and increase the risk for potential bleeding. These should be avoided in the third trimester of pregnancy to prevent postpartum hemorrhage. In addition, these medications can prolong pregnancy or cause constriction of the ductus arteriosus in the fetus by blocking prostaglandin synthesis [2]. Salicylates also may be teratogenic or retard fetal growth [1]. Severe pain management issues should be discussed with the patient’s obstetrician as long-term use of opiates can harm the mother and fetus [1,2]. Short-term use, however, may be appropriate.

Complications

Complications can occur in any patient undergoing a surgical procedure. Although a full discussion of potential surgical complications is outside the scope of this paper, it is important to review some of the more common or potentially serious complications that could arise in a pregnant patient (Box 3).

Healing and scar formation

Pregnant women seem to be more susceptible to slow healing, postinflammatory hyperpigmentation, and worsening of keloid scars. Literature adequately describing scars after dermatologic surgery in pregnant women is scarce. There are limited data on skin closure techniques of cesarean delivery that provide some insight into skin healing in a changing hormonal milieu. Frishman and colleagues [45], for example, compared staples versus subcuticular suture in closure of Pfannenstiel skin incision (cesarean section closure) and noted a better cosmetic outcome of the scar with subcuticular sutures. There are no conclusive studies indicating the best method to use in closing the skin after cesarean section [46]. Hypertrophic scar or keloids can be treated safely with intralesional steroids or laser during pregnancy to reduce symptoms of pruritus or erythema. Alternatively, the scar can be treated with various modalities after delivery to minimize risk to mother and fetus. All cosmetic or elective procedures should be postponed until the postpartum period to promote normal healing and scar formation. Postinflammatory hyperpigmentation, scar widening, and delayed healing associated with pregnancy may alter significantly the desired results of any procedure. Cosmetic procedures, including cosmetic laser procedures, should be delayed until the postpartum period. Patients who are breastfeeding may require a longer delay because of persistently elevated hormone levels. Laser treatments for symptomatic lesions, such as a bleeding pyogenic granuloma, can be performed safely as needed [2].

Bleeding

Postoperative bleeding in a pregnant woman could be a potentially dangerous situation. A pregnant woman undergoes a physiologic hemodilution with plasma volume increasing more than the red blood cell volume and mass [1–3]. This hemodilution in combination with the cardiovascular changes described previously makes a pregnant woman more vulnerable to episodes of acute bleeding because uterine perfusion can be affected. Early blood transfusion may be required to maintain adequate uterine perfusion in the face of significant acute surgical blood loss [2,3].

Infection

Some women may have a higher risk for wound infection because of immunosuppression associated with pregnancy. The procedures used in dermatologic surgery are probably at low risk, however, because of the use of clean or sterile techniques. When postoperative infections occur, there are several antibiotics that can be used safely in pregnancy to treat wound infection, as described previously.

Summary

The physiologic changes of pregnancy and risks to the fetus require attention during dermatologic
surgery. Elective surgery should be performed in the second trimester or the postpartum period. Cosmetic work should occur after delivery to avoid hypertrophic or hyperpigmented scars. Care in patient positioning prevents pressure on the vena cava that could impede venous return. Skin preparatory agents and anesthetics may have fetal implications and should be chosen with care. Antibiotic selection for any infections must take into account possible maternal and fetal risks. Attention to detail and awareness of the changes in pregnancy should lead to safe surgery in the pregnant patient.

References

[33] Chen BK, Eichenfield LF. Pediatric anesthesia in der-


Allergic Contact Dermatitis to Cosmetics

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The US Food and Drug Administration defines the term “cosmetic” as “articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and articles intended for use as a component of any such articles; except that such term shall not include soap” [1]. The broad category of cosmetics includes skin care products, facial makeups, personal cleanliness products, nail and hair care products, perfumes, and shaving preparations. It has been estimated that over $800 million is spent on over-the-counter moisturizers alone [2]. Precautions have been taken to ensure the safety of the ingredients used. The Cosmetic Ingredient Review was established in 1976 by the Cosmetic, Toiletry and Fragrance Association to document the safety of ingredients used in cosmetics [3]. The Cosmetic Ingredient Review Expert Panel reviews ingredients that are used in at least 20 or more cosmetic formulations that are not otherwise regulated by the Food and Drug Administration [4].

Given the widespread use of cosmetics, it is important to monitor their adverse effects. DeGroot and coworkers [5] interviewed female clients of beauticians and found that 254 (26%) of 982 women interviewed claimed to have experienced adverse reactions to cosmetics and toiletries in the preceding 5 years. It has been estimated that adverse reactions to cosmetics occur, on average, once every 13.3 years per person [6]. Adverse effects are most commonly irritant reactions [7]. The prevalence of allergic reactions to cosmetics in the general population is relatively low but, nevertheless, is significant because the diagnosis is often not suspected [8–10]. Skin care products have been responsible for most cases of cosmetic allergy followed by hair care preparations or nail cosmetics [8,10–13]. The most common responsible allergens are fragrances and preservatives [8,10–14]. This article specifically focuses on allergic contact dermatitis to skin care products and facial makeup. Medline was used to search published articles in English using the terms “allergy,” “cosmetics,” and “contact dermatitis.” In addition, hand searching of published manuscripts was performed.

Spectrum of adverse cutaneous reactions

Cosmetics may cause many types of adverse reactions. Most reactions are irritant in nature, but cosmetics also cause contact urticaria; delayed-type hypersensitivity; photosensitization (either phototoxic or photoallergic); pigmentary disorders; damage of hair and nails; paronychia; aceneiform eruptions; folliculitis; and worsening of pre-existing dermatoses [15]. The primary differential diagnoses for allergic contact dermatitis include irritant contact dermatitis, photoallergic reactions, and contact urticaria. There are two types of irritation: subjective and objective. Subjective irritation consists of the sensation of burning or stinging on the application of cosmetics that is not accompanied by visible changes [15,16]. Often, patients do not seek medical care for such reactions, yet they may be the most common source of dissatisfaction with cosmetics [17]. Objective irritation is defined as nonimmunologically mediated skin in-
flammation with visible changes [17]. Both contact urticaria (type I or immediate hypersensitivity) and allergic contact dermatitis (type IV or delayed hypersensitivity) are immunologically mediated reactions [16]. Allergic contact dermatitis is much less common than irritant reactions to cosmetics [12,18]. The development of sensitization depends on several factors: product composition and concentration of ingredients, application site, skin barrier integrity, contact time, and frequency of application [19,20]. Sensitization often occurs after repeated applications or application to damaged skin. Photoallergy is a type of delayed hypersensitivity in which ultraviolet radiation converts a chemical into an allergen and evokes dermatitis on sun-exposed skin [17]. In the past, most cases of photoallergy caused by cosmetics were the result of halogenated salicylanilides in soaps [21] and musk ambrette, a fragrance ingredient often found in men’s after-shave products [22]. Currently, most cases of photoallergy are caused by sunscreen ingredients [18].

**Epidemiology**

Despite the widespread use of cosmetic products, the rates of allergic reactions to cosmetic ingredients are relatively low. Several studies in Europe and the United States have found a prevalence of cosmetic allergy of less than 1% in the general population, as shown in Table 1 [8–11,14,23–25]. The actual rate of allergic reactions to cosmetics is likely higher, however, because most people do not seek medical care for mild reactions and simply discontinue the offending product [17]. Of 30,207 patients patch tested for suspected contact dermatitis in seven different studies, the pooled prevalence rate of allergic contact dermatitis to cosmetics was 9.8% (see Table 1) [8–11,14,24,25]. Rates of cosmetic allergy vary with time and geographic location [18]. Nielsen and coworkers [25] patch tested patients in Denmark in both 1990 and 1998 and reported that contact sensitization to cosmetic-related allergens had doubled. The increased prevalence of cosmetic allergy may be caused by increased consumer use of cosmetics, use of more allergenic ingredients, or enhanced accessibility of allergens for patch testing [14]. Risk factors for allergic contact dermatitis seem to be related to populations with increased exposure to cosmetic products. Most patients with cosmetic sensitivity are between the ages of 20 and 55 [1,8–10] and are female [8,10,11,14,26].

### Clinical features of allergic contact dermatitis

Allergic contact dermatitis occurs at the site of contact with an allergen. It may acutely present with pruritic papules, vesicles, or bullae [16]. Chronic exposure may result in eczematous dermatitis. Because most cosmetic ingredients are relatively weak allergens, chronic eczematous dermatitis is more common than acute vesicular eruptions [27]. More than half of the reported cases of cosmetic sensitivity occur on the face and the periocular area [8,11,12,14]. It is possible that a product applied to the entire face may only affect the eyelids because this thin skin is very vulnerable [19]. The site of eruption usually indicates the causative agent. The offending product may not be obvious, however, because surfaces con-

<table>
<thead>
<tr>
<th>Investigators</th>
<th>No. with cosmetic ACD (% of patch tested)</th>
<th>Total No. patients evaluated</th>
<th>No. with cosmetic ACD (% of patch tested)</th>
<th>No. patients patch tested</th>
</tr>
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<tbody>
<tr>
<td>Europe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skog 1980</td>
<td>—</td>
<td>70,126</td>
<td>41 (0.06)</td>
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<tr>
<td>Romaguera et al 1983</td>
<td>460 (8.3)</td>
<td>58,128</td>
<td>460 (0.8)</td>
<td>5539</td>
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<tr>
<td>DeGroot 1987</td>
<td>75 (4.2)</td>
<td>18,747</td>
<td>75 (0.4)</td>
<td>1781</td>
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<tr>
<td>Nielsen and Menné 1992</td>
<td>7a (2.4)</td>
<td>—</td>
<td>—</td>
<td>290</td>
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<tr>
<td>Nielsen et al 2001</td>
<td>27a (5.8)</td>
<td>—</td>
<td>—</td>
<td>469</td>
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<tr>
<td>Kohl 2002</td>
<td>297 (36.3)</td>
<td>—</td>
<td>—</td>
<td>819</td>
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<td>United States</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Eiermann et al 1982</td>
<td>487 (6)</td>
<td>179,800</td>
<td>487 (0.3)</td>
<td>8093</td>
</tr>
<tr>
<td>Adams and Maibach 1985</td>
<td>713 (5.4)</td>
<td>281,100</td>
<td>713 (0.3)</td>
<td>13,216</td>
</tr>
</tbody>
</table>

Pooled prevalence 9.8% 607,901 0.4% 30,207

ACD, allergic contact dermatitis.

* Estimated numbers of patients calculated from reported percentages.
Table 2
Allergens recommended for patch testing in suspected cosmetic contact dermatitis (excluding hair and nail cosmetics)

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Function</th>
<th>Patch test concentration and vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard series&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
</tr>
<tr>
<td>Alpha tocopherol</td>
<td>Antioxidant</td>
<td>100%</td>
</tr>
<tr>
<td>Amidoamine</td>
<td>Surfactant</td>
<td>0.1% aq</td>
</tr>
<tr>
<td>Balsam of Peru, &lt;i&gt;Mycroxylon pereira&lt;/i&gt;&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Fragrance</td>
<td>25% pet</td>
</tr>
<tr>
<td>Benzalkonium chloride</td>
<td>Preservative, disinfectant</td>
<td>0.1% aq</td>
</tr>
<tr>
<td>Benzophenone-3, oxybenzone</td>
<td>Ultraviolet absorber</td>
<td>3% pet</td>
</tr>
<tr>
<td>2-Bromo-2-nitropropane-1,3-diol</td>
<td>Preservative</td>
<td>0.5% pet</td>
</tr>
<tr>
<td>Chloroxylenol</td>
<td>Preservative</td>
<td>1% pet</td>
</tr>
<tr>
<td>Cocamidopropyl betaine</td>
<td>Surfactant</td>
<td>0.5% pet, 1% aq</td>
</tr>
<tr>
<td>Colophony, rosin</td>
<td>Plasticizer</td>
<td>20% pet</td>
</tr>
<tr>
<td>Compositae mix</td>
<td>Fragrance</td>
<td>6% pet</td>
</tr>
<tr>
<td>Diazolidinyl urea</td>
<td>Preservative</td>
<td>1% pet, 1% aq</td>
</tr>
<tr>
<td>DMDM hydantoin</td>
<td>Preservative</td>
<td>1% pet, 1% aq</td>
</tr>
<tr>
<td>Ethylenediamine dihydrochloride&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Emulsifier</td>
<td>1% pet</td>
</tr>
<tr>
<td>Formaldehyde&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Preservative</td>
<td>1% aq</td>
</tr>
<tr>
<td>Fragrance mix&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Fragrance</td>
<td>8% pet</td>
</tr>
<tr>
<td>Glutaraldehyde</td>
<td>Preservative</td>
<td>1% pet</td>
</tr>
<tr>
<td>Imidazolidinyl urea</td>
<td>Preservative</td>
<td>2% pet, 2% aq</td>
</tr>
<tr>
<td>Iodopropynyl butylcarbamate</td>
<td>Preservative</td>
<td>0.1% pet</td>
</tr>
<tr>
<td>Jasmine absolute</td>
<td>Fragrance</td>
<td>2% pet</td>
</tr>
<tr>
<td>Lanolin alcohol&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Emollient, emulsifier</td>
<td>30% pet</td>
</tr>
<tr>
<td>Methylchloroisothiazolizone, methylisothiazolizone&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Preservative</td>
<td>100 ppm aq</td>
</tr>
<tr>
<td>Methylidibromoglutaronitrile, phenoxyethanol</td>
<td>Preservative</td>
<td>4% pet</td>
</tr>
<tr>
<td>Paraben mix&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Preservative</td>
<td>1% pet</td>
</tr>
<tr>
<td>Phenoxethanol</td>
<td>Preservative</td>
<td>1% pet</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>Solvent, humectant, preservative</td>
<td>30% aq</td>
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<tr>
<td>Quaternium-15&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Preservative</td>
<td>2% pet</td>
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<tr>
<td>Sesquiterpene lactone mix</td>
<td>Fragrance, botanical</td>
<td>0.1% pet</td>
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<tr>
<td>Thimerosal&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Preservative</td>
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<tr>
<td>Ylang-ylang oil</td>
<td>Fragrance</td>
<td>2% pet</td>
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Other antigens

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Function</th>
<th>Patch test concentration and vehicle</th>
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<tr>
<td>Abietic acid</td>
<td>Plasticizer</td>
<td>5% pet</td>
</tr>
<tr>
<td>Abitol (dihydroabietyl alcohol)</td>
<td>Plasticizer</td>
<td>10% pet</td>
</tr>
<tr>
<td>Amerchol L-101</td>
<td>Emollient, emulsifier</td>
<td>50% pet</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>Preservative, fragrance</td>
<td>1% pet</td>
</tr>
<tr>
<td>Butylated hydroxyanisole</td>
<td>Antioxidant</td>
<td>2% pet</td>
</tr>
<tr>
<td>Butylated hydroxytoluene</td>
<td>Antioxidant</td>
<td>2% pet</td>
</tr>
<tr>
<td>Captan</td>
<td>Preservative</td>
<td>0.1% pet</td>
</tr>
<tr>
<td>Castor oil</td>
<td>Emollient</td>
<td>100%</td>
</tr>
<tr>
<td>Cetylslearyl alcohol</td>
<td>Emulsifier</td>
<td>20% pet</td>
</tr>
<tr>
<td>2-Chloracetamide</td>
<td>Preservative</td>
<td>0.2% pet</td>
</tr>
<tr>
<td>4-Chloro-3-cresol</td>
<td>Preservative</td>
<td>1% pet</td>
</tr>
<tr>
<td>Cinnamic aldehyde</td>
<td>Fragrance</td>
<td>1% pet</td>
</tr>
<tr>
<td>Cocamide DEA</td>
<td>Emulsifier</td>
<td>0.5% pet</td>
</tr>
<tr>
<td>3-(Dimethylamino) propylamine</td>
<td></td>
<td>1% aq</td>
</tr>
<tr>
<td>Dodecyl gallate</td>
<td>Antioxidant</td>
<td>0.25% pet</td>
</tr>
<tr>
<td>Ethylenediaminetetraacetic acid</td>
<td>Antioxidant</td>
<td>1% pet</td>
</tr>
<tr>
<td>Hydroquinone</td>
<td>Antioxidant, bleaching agent</td>
<td>1% pet</td>
</tr>
<tr>
<td>Isopropyl myristate</td>
<td>Emulsifier</td>
<td>20% pet</td>
</tr>
<tr>
<td>Lemon grass oil</td>
<td>Fragrance/ botanical</td>
<td>2% pet</td>
</tr>
<tr>
<td>Octyl gallate</td>
<td>Antioxidant</td>
<td>1% pet</td>
</tr>
<tr>
<td>Oleamidopropyl dimethylamine</td>
<td>Emulsifier</td>
<td>0.1% aq</td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td>Solvent</td>
<td>100%</td>
</tr>
<tr>
<td>Propolis</td>
<td>Emulsifier</td>
<td>10% pet</td>
</tr>
<tr>
<td>Propyl gallate</td>
<td>Antioxidant</td>
<td>1% pet</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td>Preservative</td>
<td>5% pet</td>
</tr>
<tr>
<td>Sorbic acid</td>
<td>Preservative</td>
<td>2% pet</td>
</tr>
<tr>
<td>Sorbitan sesquioleate</td>
<td>Emulsifier</td>
<td>20% pet</td>
</tr>
<tr>
<td>Tea tree oil</td>
<td>Fragrance/ botanical</td>
<td>1% pet</td>
</tr>
<tr>
<td>Triclosan</td>
<td>Preservative</td>
<td>2% pet</td>
</tr>
<tr>
<td>Triethanolamine</td>
<td>Emulsifier</td>
<td>2.5% pet</td>
</tr>
<tr>
<td>Vanillin</td>
<td>Fragrance</td>
<td>10% pet</td>
</tr>
</tbody>
</table>

Abbreviations: Aq, aqueous; pet, petrolatum.

<sup>a</sup> Selected cosmetic-related allergens from the 65 allergens of the 2006 NACDG Standard Screening Series [33].

<sup>b</sup> Allergens present on TRUE test (Allerderm, Petaluma, California).
Allergens may even be transmitted by sexual partners, friends, or coworkers causing “connubial” dermatitis [28] or “consort” dermatitis [30]. The diagnosis of allergic contact dermatitis is made by a thorough history and physical examination and patch testing to commercial allergens and personal products. For most leave-on cosmetic products, such as creams and foundation makeup, patch testing can be performed with the product as is. Some products must be allowed to dry before occlusion. These include mascara, liquid eyeliner, and nail polish [31]. For rinse-off products, such as facial cleansers, dilutions of 1% should be used for patch testing [31]. Recommended allergens and the appropriate concentrations and vehicles for patch testing in patients with suspected cosmetic-related facial contact dermatitis are listed in Table 2 [32–35].

### Responsible allergens

**Fragrances**

In patch-tested patients, the frequency of positive reactions to fragrance mix (8% petrolatum) is high. Recent European studies have found relatively constant rates of fragrance sensitivity in patch-tested patients: 6.2% from 1988 to 1992 in Denmark [36], 6.7% in males and 8.5% in females from 1980 to 1996 in the United Kingdom [37], and 7% from 1995 to 2002 in Finland [38]. The North American Contact Dermatitis Group (NACDG) has reported higher, but decreasing, rates in the United States: 14% during 1994 to 1996 [39] and 10.4% during 2001 to 2002 (relevance rates are much lower) [33].

Fragrances have consistently proved to be the most common cause of cosmetic allergic contact dermatitis [8,10,12,14]. Positive reactions to fragrances were found in 42% to 54% of patch-tested patients with suspected cosmetic dermatitis [11,14,40]. The high frequency of sensitization to fragrance ingredients relates to the widespread presence of fragrances in commercial products. Besides perfumes and colognes, fragrance allergens are encountered in cosmetics, soaps, toothpastes, household cleaning products, medications, and even perfumed products worn by other people [37,41–43]. Additionally, products marketed as “unscented” are not “fragrance-free” and may contain a masking fragrance [17,44]. Most reactions occur from sensitization to fragranced skin care products. Actual fragrance products, such as perfumes, toilet water, and colognes, rarely cause allergy [8]. Aromatic compounds can also be used as flavorings in cosmetics. Taylor and coworkers [45] reported a case of perioral eczema caused by maltol, a flavor enhancer and component of the strawberry flavor present in the patient’s lip salve. Buckley and coworkers [37] found that females were 1.3 times more likely to be allergic to fragrance than males ($P < .001$, 95% confidence interval 1.17–1.41). This likely reflects the more frequent exposure of women to fragrances in cosmetics and household products [17].

Determining the optimal patch testing method for detecting fragrance allergy has been debated. In 1976, Larsen [46] designed a fragrance mixture to screen for fragrance allergy. The 16% fragrance mix consisted of a concentration of 2% each of eugenol, isoeugenol, cinnamic aldehyde, cinnamic alcohol, oak moss, geraniol, hydroxycitronella, and α-amylcinnamic aldehyde. Later, the concentration of the constituents was decreased to 1% each and the emulsifier sorbitan sesquioleate was added at 5%, creating the 8% fragrance mix that is currently widely used [36,37]. This mix commonly results in irritant reactions, so patch test results must be interpreted with caution.

Initial studies indicated that the fragrance mix was a good reflection of exposure because up to six constituents of the fragrance mix were detected in most perfumes and scented cosmetic products investigated [17,47–49]. Larsen’s 8% fragrance mix was estimated to identify 70% to 80% of fragrance-sensitive patients [42]. In the early 1990s, however, DeGroot and coworkers [50] found that 6.2% of 65 patients allergic to fragrances had false-negative reactions to the 8% mix. The percentage of false-negative reactions to fragrance mix may be increasing with time because exposure to fragrances is changing. It has been shown that, as compared with older perfumes, newer perfumes contain fewer of the compounds included in the 8% mix [51]. Also, with the popularity of “natural” products, there has been increased use of plant extracts as fragrance ingredients [52]. Many investigators have evaluated other screening allergens to enhance the detection of fragrance allergy. In a multicenter study, Larsen and coworkers [53] reviewed the patch test results of 167 fragrance-sensitive patients and found that the 8% fragrance mix correlated with 85.6% of positive responses to fragrance ingredients. This was improved by simultaneously testing with ylang-ylang oil, narcissus oil, sandalwood oil, and balsam of Peru, the combination of which detected 96% of fragrance-sensitive patients. A new fragrance mix, fragrance mix II, was shown to have a lower number of false-positive reactions and to detect additional patients sensitive to
fragrances missed by Larsen’s 8% mix [54]. Fragrance mix II consists of 2.5% hydroxyisohexyl 3-cyclohexene carboxaldehyde, 1% citral, 2.5% farnesol, 2.5% coumarin, 0.5% citronellol, and 5% α-hexylcinnamic aldehyde [54]. Although sensitivity rates to fragrance mix in Europe have stabilized, there has been an increase in the rate of sensitivity to another marker of fragrance allergy, balsam of Peru. This may indicate changing compositions of fragrances and the resulting insufficiency of fragrance mix to reveal fragrance sensitivity [38]. Balsam of Peru is a natural mixture of aromatic chemicals produced from the Myroxylon pereirae tree in Central America [43] and contains the following chemicals: cinnamic acid, cinnamic aldehyde, methyl cinnamate, benzyl cinnamate, benzyl benzoate, benzoic acid, benzyl alcohol, and vanilllin [55]. It is used as a screening agent for detection of fragrance allergy but is not as sensitive as the fragrance mix. It has been estimated that balsam of Peru detects approximately 50% of fragrance-sensitive patients [12,18]. The prevalence of allergy to balsam of Peru has recently exceeded that of fragrance mix. In the NACDG report from 1994 to 1996 evaluating the patch test results of approximately 3000 patients, 10.4% reacted to balsam of Peru, whereas 14% reacted to the 8% fragrance mix [39]. From 2001 to 2002 close to 5000 patients were evaluated and 11.6% reacted to balsam of Peru compared with 10.4% reacting to the 8% fragrance mix [33].

Preservatives

Preservatives are used in cosmetics to prevent the overgrowth of microorganisms. Prevention of contamination is essential because many cosmetics are designed as multiuse products and come into repeated contact with the environment and human skin [18,56]. Preservatives fall into three categories: (1) antimicrobials, (2) antioxidants, and (3) ultraviolet light absorbers [15,57]. The antimicrobials can be further categorized as formaldehyde, formaldehyde-releasers, and non–formaldehyde-releasing preservatives. Of the antimicrobials, it has been reported that the most frequently used preservatives in cosmetics and toiletries include parabens, imidazolidinyl urea, quaternium-15, formaldehyde, and isothiazolinones [17,58]. Studies have repeatedly shown preservatives to be one of the two most common classes of cosmetic allergens [10–13,26]. A 1-year study (1989–1990) by the Swiss Contact Dermatitis Research Group involving 2295 patch test patients found that formaldehyde, benzalkonium chloride, methylchloroisothiazolinone-methylisothiazolinone (MCI-MI), and thimerosal had the highest sensitization rates of 13 preservatives tested [59]. The chemicals with the lowest rates of sensitization included three formaldehyde-releasers: (1) quaternium-15, (2) imidazolidinyl urea, and (3) 2-bromo-2-nitropropane-1,3-diol [59]. Wilkinson and coworkers [60] studied patch test results of over 70,000 patients evaluated at 16 different centers in 11 countries in the European Union from 1991 to 2000 and found the highest rates of sensitization to formaldehyde and MCI-MI and the lowest rates of sensitization to parabens.

**Formaldehyde**

Formaldehyde is an inexpensive preservative with good antimicrobial activity [61], yet it is rarely used in cosmetics because it is a frequent sensitizer. Despite decreased use in cosmetics, formaldehyde sensitivity levels remain high because of continued use of formaldehyde in cleaning products and from exposure to formaldehyde-releasing biocides [60]. NACDG patch test results show an increasing rate of allergic reactions to formaldehyde 1% aqueous ranging from 6.8% of 3290 patients in the late 1980s to 9.2% of 5830 patients in the late 1990s and 8.4% of 4909 patients tested from 2000 to 2001 [33,62]. Wilkinson and coworkers [60] found lower and stable levels of sensitivity to formaldehyde 1% aqueous in Europe, between 2% and 2.5% from 1991 to 2000.

Formaldehyde is one of the most ubiquitous contact allergens [18,58]. The presence of formaldehyde in a product may not always be documented because of the presence of formaldehyde-releasers, the degradation of other ingredients to formaldehyde during storage and use, or because of its unidentified presence in raw materials [19,63]. Agner and coworkers [63] evaluated 57 patients with formaldehyde allergy several years after initial diagnosis and found that 77% were still exposed to formaldehyde. Because 65% of the formaldehyde-allergic patients reported avoidance behavior, it was concluded that the avoidance of formaldehyde is difficult. Thus, formaldehyde-sensitive patients often have chronic contact dermatitis [64]. Agner and coworkers [63] also found, however, that patients with formaldehyde allergy who actively engaged in avoidance practices had statistically significantly fewer eruptions than those who did not engage in avoidance practices [63].

**Formaldehyde releasers**

Formaldehyde-releasing preservatives include 2-bromo-2-nitropropane-1,3-diol, DMDM hydantoin, diazolidinyl urea, imidazolidinyl urea, and quaternium-15. These preservatives are inherently antibacterial and antifungal but also act by formaldehyde
release because of an easily detachable formaldehyde moiety [17,19,65]. The amount of formaldehyde produced by these chemicals depends on temperature and pH [65]. Allergic reactions to formaldehyde releasers may be caused by the preservative, formaldehyde, or both [65,66].

The rate of cross-reactivity between formaldehyde releasers and formaldehyde varies. Herbert and Rietschel [67] reviewed patch test reactions of 219 patients who reacted to either formaldehyde or five different formaldehyde-releasing preservatives from 1996 to 2002. Of these patients, over half only reacted to one or two of these allergens and less than 1% reacted to all six [67]. Allergy to one formaldehyde-releasing preservative may not necessitate a restriction of the entire class [67].

2-Bromo-2-nitropropane-1,3-diol

The preservative 2-bromo-2-nitropropane-1,3-diol has been used in a wide variety of cosmetic and pharmaceutical preparations including shampoos, creams, lotions, cleansers, and eye makeup [68]. It is water soluble with antimicrobial activity against bacteria, fungi, and yeast [61,68]. Since the early 1980s, however, its use has declined [15,57]. This is because at alkaline pHs it breaks down into formaldehyde and bromo compounds, which develop a yellow or brown color on exposure to light [61]. Additionally, it can react with amines or amides to produce potentially carcinogenic nitrosamines or nitrosamides [57]. 2-Bromo-2-nitropropane-1,3-diol can be allergenic itself or can cause allergy by its formaldehyde-releasing properties [69,70]. Also, it is a frequent cause of irritant reactions at concentrations as low as 0.25% aqueous and 1% in petrolatum [68]. Studies have shown that 2-bromo-2-nitropropane-1,3-diol is a relatively rare sensitizer with positive patch tests rates as low as 0.47% of 8149 patients in Europe [70]. In the early 1980s, Adams and Maibach [10] found that 2-bromo-2-nitropropane-1,3-diol was the fourth most common implicated preservative in 713 cases of cosmetic allergy in the United States. The NACDG has reported increasing sensitivity rates ranging from 0.7% in the late 1980s to approximately 3% of 3000 to 5000 patients tested during the late 1990s and first few years of this decade [33,39,71]. 2-Bromo-2-nitropropane-1,3-diol was responsible for numerous cases of allergic contact dermatitis caused by Eucerin cream (Beiersdorf, Wilton, Connecticut) in the early 1980s until it was replaced by a different preservative [68].

DMDM hydantoin

DMDM hydantoin is active against fungi, yeast, gram-positive bacteria, and gram-negative bacteria [72]. It is found in many cosmetic products, most frequently in shampoos, followed by skin care preparations, hair conditioners, makeup foundations and bases, and personal cleanliness products [72]. The NACDG reported increasing sensitivity rates from 0.5% of approximately 3000 patients in 1985 to 1990 to 3.3% of almost 5000 patients in 2001 to 2002 [33,39]. Rates seem lower in Europe and may be related to less exposure to this preservative [73]. In a study of patch test results of 67,915 patients in Germany from 1995 to 2000 the proportion of positive reactions ranged from 0.39% to 0.65% [73].

Diazolidinyl urea

Diazolidinyl urea was first introduced in 1982 (Sutton Labs, Chatham, New Jersey) [66,74]. It is a colorless, odorless, stable, and water-soluble preservative [74,75]. It is reported to have a wider antimicrobial spectrum than imidazolidinyl urea [75], to which it is structurally related. It is effective against gram-negative and gram-positive bacteria, molds, and yeast, but has limited activity against fungi [74]. Allergy to diazolidinyl urea was first reported in 1985 in a study of patch test results of 67,915 patients in Germany from 1995 to 2000 the proportion of positive reactions ranged from 0.39% to 0.65% [73].

Imidazolidinyl urea

Imidazolidinyl urea is a widely used preservative in cosmetics because of several desirable features. It is compatible with almost all cosmetic ingredients and is colorless, odorless, tasteless, and not pH-dependent [61]. It is more active against bacteria than against yeast and molds [61]. An important feature of this preservative is that it acts synergistically with other preservatives, especially parabens [61]. It is not surprising that imidazolidinyl urea has been reported to be the second most commonly used preservative in cosmetics, after parabens [17,57].
In 1974, the first case of cosmetic allergy caused by imidazolidinyl urea was described in a woman with facial dermatitis proven by patch testing to be caused by imidazolidinyl urea in her facial moisturizing lotion and liquid eyeliner [77]. Adams and Maibach [10] subsequently found that imidazolidinyl urea was the second most common preservative responsible for cases of cosmetic allergy in 13,216 patients evaluated from 1977 to 1983. The role of imidazolidinyl urea in allergy to cosmetics seems, however, to have decreased. More recent studies have shown that it ranks fifth or lower as a cause of cosmetic allergy [12,14,38].

Despite its frequency of use, imidazolidinyl urea seems to be the least common sensitizer of the formaldehyde-releasing preservatives [18]. Guinea pig sensitization tests showed that the lowest concentration that induced contact hypersensitivity was 10 times higher than concentrations used in cosmetic preparations (0.02%–0.5%) [78]. Human patch test results parallel the low rate of sensitivity found in animal testing. A Belgian study detected only three allergic reactions to 2% aqueous imidazolidinyl urea in 279 patients with cosmetic allergy of a total of 1175 patients patch tested [79]. Wilkinson and co-workers [60] found that levels of sensitivity of European patients to imidazolidinyl urea remained stable at around 1% during the 1990s. Sensitivity rates have been higher in the United States according to the NACDG, who reported reactions in 2.5% to 3.2% of patients patch tested [33,62].

Quaternium-15

Quaternium-15 is an odorless, colorless, water-soluble, antimicrobial agent that is active against bacteria more so than yeast and molds [61,67]. It is a widely used preservative in cosmetics and toiletries and has been shown to be the most common cosmetic preservative allergen [8,10]. Positive patch test reactions have increased from 6.2% of 3994 patients to 9.3% of 4910 patients according to NACDG results from 1985 to 2002 [33,62]. Compared with the NACDG results, European studies have found lower rates of sensitivity to quaternium-15 [11,12,14,38]. Wilkinson and coworkers [60] found that rates of sensitivity in the European Union were stable during the 1990s, at about 1%. Quaternium-15 has proved to be more than eight times as sensitizing as imidazolidinyl urea [61]. Most sensitization to quaternium-15 is caused by formaldehyde release. Most patients who are allergic to quaternium-15 are also allergic to formaldehyde [39,80]. Conversely, it is the most common coallergen in formaldehyde-sensitive patients [80].

Nonformaldehyde preservatives

Parabens. Parabens are esters of 4-hydroxy benzoic acid. The five commonly used parabens are: (1) methylparaben, (2) ethylparaben, (3) propylparaben, (4) butylparaben, and (5) benzylparaben [58,81,82]. Parabens have a broad spectrum of activity against yeasts and molds but are less active against bacteria [61]. Two or more parabens are often combined because they have a synergistic preservative effect [81]. Parabens are also usually combined with other preservatives, such as formaldehyde releasers [56,61]. Parabens are popular because of their broad antimicrobial activity; low rate of allergenicity; effectiveness over a wide pH range; and because they are colorless, odorless, nontoxic, and inexpensive [82–84]. Because of these characteristics, they are the most widely used preservatives. It has been reported that 87% to 93% of investigated cosmetic products contain one or more of the parabens [58,83]. They are found in facial makeup (especially mascara and eye shadow); skin care products; and medicinal creams and lotions [81].

Despite the widespread use of parabens in cosmetics, these compounds are rare causes of allergic contact dermatitis. Mowad [84] reported a case of a 76-year-old woman with an extremely pruritic face and neck dermatitis that coincided with usage of an increased number of cosmetic products. Patch testing with an expanded series, including preservatives, vehicles, and corticosteroids revealed a positive reaction to paraben mix, which was found in her cosmetics. Wilkinson’s and coworkers [60] analysis of a decade of patch test results (1991–2000) in the European Union found that the parabens had the lowest level of sensitivity, approximately 0.5% to 1%. Similarly, the NACDG reported that only 0.6% of 4898 patients patch tested reacted to parabens [33,62]. Patch testing is performed with a paraben mix (methylparaben, ethylparaben, propylparaben, and butylparaben) in petrolatum with subsequent testing of the individual esters if there is a positive reaction to the mix [82].

Fisher [85] first described a “parabens paradox” in 1973, referring to observations that paraben-sensitive patients can often tolerate paraben-containing products on normal skin. Several hypotheses for this phenomenon have been suggested [85], including the “esterase” and “microbial metabolism” hypotheses [82]. Although parabens have generally been regarded as safe in cosmetics, the Cosmetic Ingredient Review Expert Panel recently elected to review data suggesting that parabens may act as reproductive toxins and disruptors of endocrine function [86].
Methylchloroisothiazolinone-methylisothiazolinone. MCI-MI is the active ingredient of a commonly used preservative system. It consists of a mixture of two isothiazolones, 1.15% MCI and 0.35% MI, in water with 23% magnesium chloride and nitrate as stabilizers [66,87,88]. It is a broad-spectrum antimicrobial active against bacteria, yeasts, and fungi, and is effective in low concentrations [88–92]. It was introduced in Europe in the mid-1970s and into the United States in the early 1980s [87,88]. MCI-MI can be found in many cosmetic products, including rinse-off and leave-on products [88–90].

The first cases of allergic contact dermatitis to MCI-MI were reported in Europe [88] and many resulted from the use of moisturizing creams on compromised skin [93]. MCI-MI was the most important cosmetic allergen in a study from The Netherlands in 1986 to 1987, causing reactions in 27.7% of 119 patients with cosmetic allergy [12]. Hannuksela [85] reported that the proportion of positive patch tests to MCI-MI 100 ppm in 167 unselected eczema patients increased from 0% in 1983 to 0.7% in the first half of 1985 and to 4.6% in late 1985 and early 1986 [94]. Because of the rapidly increasing sensitivity, the use of MCI-MI in Europe, and later in the United States, was limited to concentrations of 7.5 ppm in leave-on products and 15 ppm in rinse-off products [38,88].

Subsequently, throughout the 1990s, the frequency of MCI-MI sensitivity in the European Union remained high, but stable, around 2% to 2.5% [59,60]. In 2005, Hasan and coworkers [38] reported that sensitivity rates to MCI-MI in Finland had fallen from 2.4% in 1995 to 1.3% in 2000 to 2002. The decrease is likely due to the restriction of MCI-MI use and the replacement with newer, more popular preservatives, such as MDBGN [38,59]. In the United States, sensitivity patterns have followed that of Europe. NACDG patch testing results show that positive patch test reactions to 100 ppm MCI-MI increased from 1.8% in the late 1980s to 2.9% to 3% in the mid-1990s but then decreased in the first part of this decade to 2.3% [33,62]. MCI-MI is patch tested at 100 ppm aqueous but the amount actually used in products is much lower. Patients sensitized to MCI-MI may often have false-negative reactions to MCI-MI–containing products [12,19,95].

Methyldibromoglutaronitrile-phenoxyethanol. The methyldibromoglutaronitrile-phenoxyethanol (MDBGN-PE) preservative system is a combination of two active ingredients, 2-phenoxyethanol and 1,2-dibromo-2, 4-dicyanobutane, in a ratio of 4:1 [17,66]. Manufacturers began using this preservative system in cosmetics because guinea pig testing showed no sensitizing potential and a substitute for MCI-MI was needed [96]. It was introduced in Europe in 1985 [66,97,98] and in the United States approximately 5 years later [98]. It is equally effective against bacteria, yeasts, and fungi at a low concentration of 0.1% [66,97]. MDBGN-PE is used as a preservative in cosmetics, predominantly in creams and lotions [98–100]. It is commonly referred to in the literature as Euxyl K400 [101].

Contrary to the initial animal studies, MDBGN-PE has shown to be a sensitizing agent in humans, predominantly in Europe where it was first introduced [98,100]. The principal allergen has been shown to be MDBGN [97,102]. Before its use in cosmetics, there were numerous cases of perianal allergic contact dermatitis reported from this preservative in moist toilet tissue [100]. The first case of cosmetic allergy was reported in 1989 caused by MDBGN in an antiwrinkle cream [103]. Now, most reported cases of MDBGN allergy result from exposure to cosmetics [98,104]. As the rate of allergy to MCI-MI has decreased [99], the rate of allergy to MDBGN has increased, corresponding to the replacement of the former by the latter as a preferred preservative system. In The Netherlands, 0.3% of 281 patch-tested patients were found to be positive to MDBGN during the first half of 1993. Prevalence rapidly increased to 3.2% of 281 patients in the second half of 1993 and 2.4% of 247 patients in the first half of 1994 [100]. In 1996, DeGroot and coworkers [105] reported that MDGBN was the most common preservative allergen in The Netherlands, surpassing MCI-MI (4% versus 3.2%). The frequency of MDBGN allergy increased in the United Kingdom in the late 1990s and in Finland in the late 1990s to 2002 [38,104]. Wilkinson’s and coworkers [60] multicountry study in the European Union from 1991 to 2000 reported that reactions to MDBGN increased from 0.7% in 1991 to 3.5% in 2001. Two recent studies in Denmark showed that MDBGN was the third most common allergen, after nickel and fragrance allergy [99,106]. In the United States, MDBGN allergy is also increasing [62,71,107] albeit at a slower rate and with lower prevalence than in Europe, likely because of its later introduction into the American market.

Interpretation of sensitivity rates is affected by a debate over proper patch test concentrations for MDBGN [38,60,101,108]. Additionally, patch tests with the incriminated products often give false-negative reactions because of the low concentration of the preservative in the product [98]. Nevertheless, because of the rapidly increasing sensitization, its use in Europe in leave-on products was banned in 2003 [108]. A recent study aimed at determining the maxi-
Iodopropynyl butylcarbamate. Iodopropynyl butylcarbamate is a relatively new preservative in cosmetics. It is used in shampoos, lotions, powders, makeup, and creams [109–111]. Iodopropynyl butylcarbamate is a known irritant at concentrations of 0.5% but was not recognized as a cosmetic allergen until this past decade [109]. It is permitted for use in cosmetics in the European Union in concentrations up to 0.1% [109,110]. Interestingly, industrial products in Europe containing a concentration greater than 0.01% are labeled as “irritant” but this same requirement does not apply to cosmetics [109].

There have only been three case reports of iodopropynyl butylcarbamate allergy related to cosmetics [109,110]. In 1999, the first case described a 29-year-old woman with a recurrent, pruritic, papular facial dermatitis that was determined by patch testing to be caused by iodopropynyl butylcarbamate in her facial cosmetic cream [112]. Subsequently, Bryld and co-workers [110] reported two cases in 2001 caused by a moisturizer, which caused severe contact dermatitis, necessitating one of the patients to be hospitalized with erythroderma. The data on sensitivity to iodopropynyl butylcarbamate are limited because it has not routinely been evaluated in the past. Reported rates have been low: 0.02% of 3168 [110], 0.3% of approximately 5000 [33,113], and 0.32% of 312 patch-tested patients, respectively.

The sensitivity rates of iodopropynyl butylcarbamate must be interpreted carefully because the proper patch test concentration has not been determined. Most studies have used a concentration of 0.1% iodopropynyl butylcarbamate [109–113], although the Information Network of Departments of Dermatology in Germany recently suggested 0.2% may be the optimal patch test concentration [113,114]. The difficulty in determining proper patch test concentration results from the scarcity of patients with proven and clinically relevant contact allergy to this allergen [114]. Also, it is a newer preservative in cosmetics and may have lower rates of usage and exposure. The experiences with MCI-MI and then with MDBGN-PE have shown there is often a lag time between introduction of a new preservative and overt clinical problems [114].

Antioxidants
Antioxidants protect products from the deterioration of unsaturated fatty acids, which can cause a rancid odor and oxidation-based discoloration [15,18,34,57,115]. The most commonly used antioxidants include butylhydroxyanisole; butylated hydroxytoluene; tertiary butylhydroquinone; the gallate esters (propylgallate, octylgallate, and dodecylgallate); norhydroguaiaretic acid; α-tocopherol (vitamin E); and ascorbic acid (vitamin C). Allergic contact dermatitis has been reported to butylhydroxyanisole, butylated hydroxytoluene, and tertiary butylhydroquinone, which often cross-react with each other because of structural similarity [115,116]. Norhydroguaiaretic acid has also been reported as a sensitizer, most often in creams [115]. There are numerous reports of sensitization to gallate esters. These antioxidants are frequently used in lip products, such as lipsticks, lip balm, and salves, but are also present in creams and lotions [117]. Most cases of cosmetic allergy caused by gallates result in cheilitis from lip care products [117–119]. The first case of lipstick dermatitis from propylgallate was reported by Cronin in 1980 [120]. Although other topical products contain gallate esters, the concentration may be too low to induce sensitization [115]. α-Tocopherol has caused relatively frequent cases of allergic contact dermatitis [121,122]. In contrast, ascorbic acid is a rare cause of cosmetic allergy [123].

UV absorbers
Chemicals that absorb ultraviolet radiation are added to cosmetics to prevent deterioration of the product and to function as a sunscreen. Sunscreens can cause both photocontact and contact allergy [34]. In cosmetics, benzophenones have replaced the use of p-aminobenzoic acid, which was a commonly reported sensitizer in the past [43,124]. Because of its increased usage, oxybenzone, or benzophenone-3, has become the most commonly reported sunscreen sensitizer, present in 0.6% of NACDG patients patch tested [71].

Vehicles, emulsifier, and other base ingredients
Vehicles of topically applied preparations used to be considered inert ingredients [125]. They are potential sensitizers, however, and have been reported to cause allergic contact dermatitis [125,126]. Even petrolatum, which has classically been considered harmless [126], has been reported to cause allergic contact dermatitis [127], although this is rare. Surface active agents can also cause cosmetic contact dermatitis [128]. Emulsifiers are present in creams and lotions to facilitate the combination of water and ole-
aginous materials [57]. They are analogous to surfactants present in soaps and detergents, which build viscosity and foaming of cleansing products [15,129]. Emulsifiers can be mild irritants but are infrequent sensitzers [57].

Glycerin and glycols
Glycerin is a nonirritating humectant that is stable, nontoxic, and imparts smoothness to cosmetics [130]. It is a rare sensitizer [131], especially when compared with other vehicles, such as propylene glycol [130]. Preston and Finch [131] reported a 29-year-old woman with a 7-month history of patchy eyelid, facial, neck, scalp, and axillary eczema. Patch testing showed a positive reaction to a hand cream and, subsequently, to glycerin that was present in this hand cream. Despite its desirable nonirritating and nonallergic qualities, glycerin has largely been replaced by the glycols (propylene, 1,3-butylene, hexylene, pentylene, and polyethylene glycol) because it is an inferior solvent [131].

Of the glycols, propylene glycol and 1,3-butylene glycol are most frequently discussed in cases of cosmetic contact dermatitis. Propylene glycol has been widely used in cosmetics. It is a solvent and humectant, and has antimicrobial properties [57]. Propylene glycol is a frequent cause of irritant and allergic contact dermatitis, with irritation being particularly common [126,131]. The NACDG found that sensitivity to 30% propylene glycol aqueous was 1.1% in 3077 patients from 1994 to 1996 and increased to 4.2% of 4899 patients tested from 2001 to 2002 [33]. 1,3-Butylene glycol is also widely used in cosmetics because it has desirable humectant and antibacterial effects, good solubility, and low irritant potential [132]. Unfortunately, there are frequent cases of cosmetic allergy caused by this vehicle, many occurring in Japan [133]. Suguira and Hayakawa [133] reported a patient with a history of cosmetic dermatitis who presented with facial erythema that appeared 1 day after using a foundation cream containing 1,3-butylene glycol. These investigators subsequently evaluated 18 “hypoirritant” cosmetics marketed for sensitive skin and found that 1,3-butylene glycol was present in all the investigated products. Diegenant and coworkers [132] reported two Belgian patients with generalized dermatitis who, on patch testing, had positive reactions to a “supertanner” cream and one of its ingredients, 1,3-butylene glycol.

Lanolin
Lanolin is a variable mixture of fatty acids esterified with monohydric alcohols derived from sheep’s wool [18,134,135]. It is used in cosmetic products as an emollient and emulsifier [18]. Sensitization rates to lanolin are high from topical therapeutics used on patients with stasis dermatitis but it is rarely a sensitizer in cosmetics [18]. Analogous to the “parabens paradoxes” described by Fisher [85], Wolf [135] described two paradoxes related to the use of lanolin. Lanolin in topical therapeutic agents sensitizes a high proportion of patients [134] but is relatively safe in cosmetics; patients with lanolin-allergy can often use lanolin-containing cosmetics [135].

The allergenic component of lanolin is thought to be wool-wax alcohols [19,43,135–137]. Sensitization rates to lanolin alcohol in patients with suspected contact dermatitis were 1.2% to 3.3% [62,71,126]. From 1977 to 1983, Adams and Maibach [10] reported that allergy to lanolin was the fourth most common allergen causing cosmetic reactions (after fragrances, preservatives, and p-phenylenediamine). DeGroot [11] reported that lanolin derivatives were responsible for 6.1% of 82 reactions to cosmetic allergens in 75 patients with allergic contact dermatitis to cosmetics.

Castor oil—ricinoleic acid
Castor oil is extracted from the seeds of Ricinus communis and used in cosmetics as an emollient in lipsticks, makeup removers, and moisturizers [138,139]. Allergic contact dermatitis to castor oil has been reported, most commonly from lipsticks [139,140]. Brandle and coworkers [141] reported a case of acute facial dermatitis in a 23-year-old woman caused by castor oil in a makeup remover. Ricinoleic acid is the sensitizer in castor oil [140] and metal salts of ricinoleic acid, known as rincinoleates, are also common causes of allergic cosmetic cheilitis [139].

Cocamidopropyl betaine
Cocamidopropyl betaine is a surfactant that is widely used in cosmetics, especially in shampoos, but also in liquid soaps; skin care products (moisturizers and cleansers); deodorants; shower gels; and bath foams [129,142,143]. Of the numerous case reports of allergy to cocamidopropyl betaine, most are caused by cocamidopropyl betaine in shampoos and shower gels [129,143]. Ross and White [142], however, reported a 60-year-old woman with a 2-month history of eyelid eczema, which was caused by an oil-free lotion makeup remover containing cocamidopropyl betaine. It is broadly accepted that cocamidopropyl betaine itself is not allergenic [144]. Rather, impurities remaining from the synthesis of cocamidopropyl betaine are thought to be the actual allergens.
Cocamidopropyl betaine is formed by reacting fatty acids extracted from coconut oil with dimethyl-aminopropylamine, yielding cocamidopropyl dimethylamine (also known as “amidoamine” or “cocamidoamine”), which then reacts with sodium monochloroacetate to produce cocamidopropyl betaine [143,144]. Amdioamine[145–147] and dimethyl-aminopropylamine are thought to be the primary allergens [147–149].

**Other cosmetic allergens**

**Propolis**

Propolis, also known as “bee-glue” [27], is made by bees from the resinous exudates of plants, especially poplar trees [150,151]. It can be found in many natural cosmetics, such as lotions, lip care products, and shampoos, and pharmaceutical and dental products [27,152]. Rates of sensitization vary from 1.2% to 6.2% [38,152]. A Finnish study of cosmetic allergens found a significant increase in the rate of patch test sensitivity to propolis, rising from 1.4% of 3885 patients during 1995 to 1997 to 6.2% of 5130 patients during 2000 to 2002 [38]. The authors hypothesized that one reason for the drastic increase in propolis sensitivity is the popularity of natural cosmetics containing this substance [38]. The main allergen in propolis is LB-1, which consists primarily of 3-methyl-2-butenyl caffeate and phenylethyl caffeate [27,150,152,153]. One interesting case report of cosmetic propolis allergy described erosive dermatitis of the lips and oral mucosa, which mimicked pemphigus vulgaris but was determined by patch testing to be allergic contact dermatitis to propolis in a lip balm [151].

**Colophony**

Colophony, or rosin, is obtained from the tree species Pinaceae and consists of resin acids and neutral matter [15,154,155]. In cosmetics, it is used primarily in lipsticks and eye makeups, including mascaras, eye shadow, and eyeliners [15,156]. Sensitization is not common, but has been reported in cases of eyelid and periorbital dermatitis [154,157] and with cheilitis and perioral dermatitis [158]. Two substances from colophony have been determined to be allergens: abietic acid and dihydroabietyl alcohol. Abietic acid is a major component of colophony and it, or its oxidation products, has been considered to be the main allergen [15,155]. It serves as a binder or plasticizer in cosmetics [15]. Dihydroabietyl alcohol is produced from rosin acids and is used as a resinous plasticizer and as a pigment-grinding medium in cosmetics [154].

**Pigments**

Agents used to impart colors to cosmetics can also be responsible for allergic cosmetic reactions. They are referred to as “D&C” colors, indicating usage in drugs and cosmetics [57], and are carefully monitored by the federal government. In the 1950s, D&C red 21 (eosin) used in lipsticks caused many adverse reactions and was reported to be the most common cause of cosmetic allergy at that time [27]. The allergen was thought to result from an impurity, and the incidence of sensitivity decreased with improved purification processes [27]. Several other D&C pigments have been reported to be sensitizers including D&C red 7 [159], D&C red 36 [160], and D&C yellow 11 [161,162]. Iron oxides are pigments used in eye makeup and lipsticks that have rarely been reported to cause allergic contact dermatitis [163,164]. Saxena and coworkers [164] reported a 44-year-old woman with chronic periorbital and eyelid dermatitis that was determined by patch testing to be caused by black iron oxide in the patient’s mascara.

**Other**

Case reports of cosmetic allergy have been reported to many other chemicals used in cosmetics. These include, but are not limited to, the allergens listed in Table 3 [138,165–194].

**Pertinent noncosmetic allergens**

In the evaluation of suspected allergic reactions to cosmetics, it is important to consider three major noncosmetic allergens that may mimic cosmetic allergy: (1) gold, (2) nickel, and (3) rubber. Gold is a common allergen that often presents as a patchy facial or eyelid dermatitis in sensitized patients [195,196]. Nickel has been reported as a contaminant in eye cosmetics, such as eye shadow and eyeliner, possibly because of container leaching [197,198]. Also, it has been reported to cause eyelid dermatitis from nickel-plated eyelash curlers [199]. Rubber used in cosmetic applicators and sponges can produce an eczematous reaction in the same distribution in which the associated makeup product is used. Fisher [200] described a 29-year-old woman with facial dermatitis who did not react to any cosmetics or standard allergens on patch testing but did react to tetramethyl-
thiuram, an accelerator present in the rubber sponge used for applying her cosmetics.

Management

The key tenet in management of allergic contact dermatitis is avoidance of the offending allergen. The prevalence of the allergen and availability of substitutes are important for successful avoidance. The first step in facilitating avoidance was taken in 1976 when the US Food and Drug Administration required ingredients be listed on all direct consumer cosmetics [201]. This allowed consumers to avoid allergens by reading cosmetic labels. The individual components of fragrances are rarely listed, however, because these are regarded as trade secrets [201]. Fragrances are also very difficult to avoid given their ubiquitous presence in many common products and because of the presence of unlabeled fragrances in some products, even in products labeled as “fragrance-free” [44]. Fragrances that have more than one function, such as those that act as preservatives or fixatives, can be included in but not listed as an ingredient of fragrance-free cosmetics [17]. Additionally, natural products, such as essential oils and botanical ex-

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Product</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Preservatives</td>
<td></td>
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<tr>
<td>Chlorophenesin</td>
<td>Face cream, foundation make-up</td>
<td>Wakelin and White [165],</td>
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<td></td>
<td></td>
<td>Brown and Orton [166]</td>
</tr>
<tr>
<td>Potassium sorbate</td>
<td>Face powder</td>
<td>Fisher [167]</td>
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<tr>
<td>Vehicles, active ingredients</td>
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<td></td>
</tr>
<tr>
<td>C12–16 (medium chain) triglyceride</td>
<td>Face cream</td>
<td>Laube et al [168]</td>
</tr>
<tr>
<td>C18–36 acid triglyceride</td>
<td>Lip gloss</td>
<td>Kimura et al [169]</td>
</tr>
<tr>
<td>C18 aliphatic compounds</td>
<td>Lipstick</td>
<td>Hayakawa et al [170]</td>
</tr>
<tr>
<td>DEA-dihydroxypalmityl phosphate,</td>
<td>Face lotion</td>
<td>Dooms-Goossens et al [171]</td>
</tr>
<tr>
<td>isopropyl hydroxypalmityl ether mixture</td>
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<tr>
<td>Di-isostearyl malate</td>
<td>Lipstick</td>
<td>Guin [172]</td>
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<tr>
<td>Glyceryl monoisonoate monomyristate</td>
<td>Lipstick</td>
<td>Asai et al [173]</td>
</tr>
<tr>
<td>2-Hexyldecanoic acid</td>
<td>Lipstick</td>
<td>Kimura and Kawada [174]</td>
</tr>
<tr>
<td>Hydroxy stearic acid</td>
<td>Lip gloss</td>
<td>Kimura et al [169]</td>
</tr>
<tr>
<td>Isohexadecane</td>
<td>Sunscreen lotion</td>
<td>Bharati and King [175]</td>
</tr>
<tr>
<td>Isopalmityl diglyceryl sebacate</td>
<td>Lipstick</td>
<td>Suzuki et al [176], Shono [177]</td>
</tr>
<tr>
<td>Isopropyl myristate</td>
<td>Sunscreen</td>
<td>Bharati and King [175]</td>
</tr>
<tr>
<td>Lanpol 5</td>
<td>Lipstick</td>
<td>Rademaker et al [178]</td>
</tr>
<tr>
<td>Monotertiary butyl hydroquinone</td>
<td>Lipstick</td>
<td>Calnan [179]</td>
</tr>
<tr>
<td>Oleyl alcohol</td>
<td>Face cleanser, lipstick</td>
<td>Guidetti et al [180], Tan et al [138]</td>
</tr>
<tr>
<td>Polyoxyethylene lauryl ether</td>
<td>Foundation make-up</td>
<td>Kimura and Kawada [181]</td>
</tr>
<tr>
<td>Sodium dihydroxycetyl phosphate</td>
<td>Face cream</td>
<td>Lomholt et al [182]</td>
</tr>
<tr>
<td>Sodium myristoyl sarcosinate, sodium</td>
<td>Face cleanser</td>
<td>Malanin [183]</td>
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<tr>
<td>myristoate</td>
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<tr>
<td>Stearic acid</td>
<td>Face cream</td>
<td>De Groot et al [184]</td>
</tr>
<tr>
<td>Other</td>
<td></td>
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<tr>
<td>Coathylene</td>
<td>Mascara</td>
<td>Chowdhury [185]</td>
</tr>
<tr>
<td>Ethylenediaminetetraacetic acid</td>
<td>Face lotion, face cream</td>
<td>Kimura and Kawada [186], Soga et al [187]</td>
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<tr>
<td>Para-tertiary-butylphenol</td>
<td>Lip liner</td>
<td>Angelini et al [188]</td>
</tr>
<tr>
<td>Prime yellow carnauba wax</td>
<td>Mascara</td>
<td>Chowdhury [185]</td>
</tr>
<tr>
<td>Pyrocatechol</td>
<td>Eyelash, eyebrow cream dye</td>
<td>Andersen and Carlsen [189]</td>
</tr>
<tr>
<td>Sesquiterpene lactone</td>
<td>Facial make-up</td>
<td>Bernedo et al [190]</td>
</tr>
<tr>
<td>Shellac</td>
<td>Lipstick, mascara</td>
<td>Rademaker et al [178], Orton et al [191],</td>
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<tr>
<td></td>
<td></td>
<td>LeCoz et al [192]</td>
</tr>
<tr>
<td>Tetrahydrocurcumin</td>
<td>Sunblock cream</td>
<td>Lamb and Wilkinson [193]</td>
</tr>
<tr>
<td>Vanilla</td>
<td>Lipsalve</td>
<td>Ferguson and Beck [194]</td>
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</tbody>
</table>
Allergic contact dermatitis to cosmetics is an important cause of facial dermatitis. The list of cosmetic allergens is extensive, but primarily consists of fragrances and preservatives. More studies are needed to evaluate the appropriate patch test concentrations and vehicles for newer allergens and the prevalence of sensitization to known allergens. As older cosmetic ingredients are replaced with newer chemicals, these substances also need to be monitored for the development of sensitivity.

Summary

Allergic contact dermatitis to cosmetics and traditional Chinese medicine may cause problems for the fragrance-allergic patient and should be avoided. Similarly, avoidance of formaldehyde-containing products can also be very difficult. Rastogi found that 23% to 33% of investigated products were incorrectly labeled with respect to formaldehyde content. Paraben-sensitive and lanolin-sensitive patients may tolerate cosmetics containing these substances, provided they are applied to undamaged skin that has not been subjected to dermatitis in the past.

An essential tool in facilitating avoidance is the Contact Allergen Replacement Database, available online from the American Contact Dermatitis Society. This is a computerized database containing thousands of cosmetics and personal-care products, which physicians can use to generate a patient-friendly list of products that do not contain offending allergens.

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Nail Diseases Related to Nail Cosmetics

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Fashion is a visual extension of one’s person and fashion statements, be they in the form of hairstyle, clothing, body painting, or extravagant accessories, are elements of an image that are projected to the outside world. In society’s complex arena, what might seem like a trivial appendage to some is often a powerful means of self-expression to others. This fact has fueled the nail adornment industry over past decades. According to Nails Big Book 2004–2005, women and men (who now make up >6% of customers) visited nail salons by the thousands and spent an estimated $6.84 billion on nail services alone in 2004 [1]. The list of services offered is ever expanding and includes nail jewelry, aromatherapy, and even reflexology in some salons. The persons providing these services are referred to as “nail technicians” rather than “manicurists” and traditional manicures (Box 1) are no longer the most requested service. The most frequently requested service is “artificial nail” application (Box 2), specifically acrylics, making up close to 35% of the total procedures provided.

Unfortunately, the main focus of this multibillion dollar industry is the nail plate (NP), the “dead” part of the nail unit. The quest to beautify this structure often happens at the expense of the regenerating and supporting components of the nail unit. It is damage incurred by these elements that leads to unhealthy nails and such conditions as paronychia and onycholysis, which are presented in the following sections. Also to be discussed are conditions affecting the NP itself, such as onychoschizia, onychorrhexis, and brittle nails. These are defects commonly seen by dermatologists and often linked to the use of nail products and nail salon procedures. The focus here is on the pathogenesis of each entity and its relationship, if any, to the use of nail cosmetics.

The nail unit

The nail unit has several components in addition to the NP (Fig. 1). These include the proximal and lateral nail folds, the bed, the hyponychium, and the matrix. The nail folds are collectively known as the “perionychium” and frame the proximal and lateral aspects of the dorsal NP, whereas the ventral NP is supported by the nail bed. The stratum corneum of the ventral aspect of the nail folds grows out a short way onto the dorsal surface of the NP forming the true cuticle. It is a colorless but closely adhering structure that can be seen as a fine white line as it lifts off the NP before being shed. The end of the nail bed and the beginning of the volar epidermis is marked by the hyponychium. The cuticle and the hyponychium are waterproof and seal off potential dead spaces above and below the NP, respectively (see Fig. 1). These spaces only become apparent in diseased nails. The dorsal portion of the nail folds gives rise to the eponychium, a thick rim of white keratinous material at the free margin of the nail folds. The word “cuticle” is commonly used to refer to the eponychium rather than the true cuticle [2].

Paronychia

Paronychia is inflammation of periungual soft tissues and is more often than not accompanied by
yeast or bacterial infection. Patients present with erythematous swollen nail folds that may be tender and ooze pus on palpation. Chronic paronychia, by definition, is a paronychia that lasts for more than 6 weeks. Chronic paronychia may be secondary to a skin condition (eg, psoriasis); systemic disease (eg, lupus erythematosus); or even drugs (eg, retinoids) [3]. The focus here is on primary paronychia that is not related to diseases or drugs and is almost always precipitated by an insult to the cuticle or its source, the nail folds.

Nail artists and patients consider the eponychium unsightly and use various means at their disposal to remove it. Removing the eponychium and cuticle allows for an even application of nail lacquer, acrylic, and gel films. Several nail salon practices may damage the nail folds and the cuticles leading to paronychia. They are divided into mechanical trauma, irritant, and allergic reactions.

### Mechanical trauma

Although removing the eponychium per se probably does not affect the nail unit, the mechanical manipulations using V-shaped sharp trimmers or nippers, when overly aggressive, lead to abrasion and inflammation of the nail folds. Wooden or metal spatulas used to push back the true cuticle destroy the seal it creates. Electric grinding drills used on the surface of the NP during the application of prosthetic nails can also damage the true cuticle and cause abrasion of the nail folds when they come in contact with these structures.

### Irritant reactions

Irritant paronychia may be caused by several nail care products including enamel removers, cuticle removers, primers, and nail hardeners.

- **Enamel removers.** Routinely used solvents for polish removal include acetone, ethyl acetate, or butyl acetate. Acetone is also used for the removal of acrylic nails but has no effect on photo-bonded gels. Although these irritants only come in brief contact with perionychial tissues, their frequent use combined with vigorous rubbing irritates the nail folds and can lead to paronychia.

- **Nail cuticle removers.** These products usually contain alkaline substances, most commonly sodium and potassium hydroxide, which dissolve keratin by attacking disulfide bonds. When left in place too long or used frequently they cause irritation of the nail folds.

- **Primers.** Methacrylic acid used as a primer in the application of acrylic nails is a very strong irritant that when spilled onto the cuticles can produce a third-degree burn. Soap of baking soda with water neutralizes methacrylic acid [4,5].

- **Nail hardeners.** Applied as a base coat, nail hardeners may contain a wide array of ingredients that presumably improve the resiliency of the NP. Examples include polytuf, nylon, titanium-silicon-zirconium polymers, calcium, and biotin. Although not in common use anymore, nail hardeners containing formaldehyde are very powerful irritants and can cause paronychia [6]. Under current regulations, their application is limited to the free edge of the NP and free formaldehyde concentration of 2%.

<table>
<thead>
<tr>
<th><strong>Box 1. The process of a manicure</strong></th>
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<tbody>
<tr>
<td>1. Nail polish is removed with nail polish remover</td>
</tr>
<tr>
<td>2. The nails are soaked to soften the nail and cuticle</td>
</tr>
<tr>
<td>3. The nails are cleaned with a brush and an orange stick</td>
</tr>
<tr>
<td>4. Cuticle remover is applied and the cuticles are removed using nippers and pushers</td>
</tr>
<tr>
<td>5. Stained nails are bleached with a solution of 6% hydrogen peroxide</td>
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<tr>
<td>6. The nails may be buffed at this point</td>
</tr>
<tr>
<td>7. Cuticle oil is applied and massaged into the cuticle</td>
</tr>
<tr>
<td>8. The nails are shaped and beveled by filing the undersurface of the free edge</td>
</tr>
<tr>
<td>9. The nail plate is cleaned to remove oil</td>
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<tr>
<td>10. Nail basecoat, nail polish, and topcoat are applied</td>
</tr>
</tbody>
</table>

Allergic reactions

Up to 3% of the general population has nail polish allergy, the main allergen being toluene sulfonamide formaldehyde resin [6]. Other allergens encountered in nail salons include acrylate monomers and cyanoacrylates used in artificial fingernail application. Acrylates are sensitizers in their monomeric forms and may result in allergic eczematous contact dermatitis and paronychia when they come in contact with perionychial skin before the rapid polymerization process. The allergic reaction can occur as long as 16 months after the first application and the allergic paronychia is associated with severe pain and sometimes paresthesia. Ethyl cyanoacrylate is glue used to fix artificial nails onto the natural NP; it can also cause allergic sensitization. Cyanoacrylate allergy does not usually cross-react with the other acrylate monomers used in nail sculpture [4].

Regardless of the nature of the insult, the end result is damage to the true cuticle itself or the nail folds creating portals of entry for yeast (*Candida* species); gram-negative bacteria (*Escherichia coli*, *Proteus*, *Klebsiella*, more frequently in adults than children); gram-positive bacteria (group A streptococci, *Staphylococcus aureus*, *Eikenella corrodens*, more frequently in children than adults); and anaerobes (*Bacteroides*, *Fusobacterium nucleatum*, gram-positive cocci, more frequently in children than adults). Bacterial infections are thought to exacerbate paronychia rather than play a role in its pathogenesis. The role of yeast is questionable. Although *Candida* species are consistently isolated in most patients with chronic paronychia, many authorities consider their presence to be secondary. Some authors regard *Candida* as a primary pathogen in patients with underlying predisposing conditions, such as Raynaud’s disease or peripheral vascular disease [3,7].

Preventative measures should be followed by any patient presenting with chronic paronychia. In addi-
tion to the usual recommendation of double gloving for wet work and when handling citrus and raw food, patients should be instructed to avoid nail cosmetics until their paronychia resolves. After that they should limit the use of nail enamel remover to once per week and consider switching to acetone-free products and avoiding cuticle removers and manipulation of the cuticle. Cuticle care should be limited to the use of softeners and gently pushing it back using a piece of fabric after soaking. Careful trimming of the eponymchium is acceptable as long as it does not injure the nail folds. For patients using sculptured nails and suffering from allergic paronychia, patch testing using a recently recommended panel of 10 acrylates may provide them with alternative products to use [8]. When ethyl cyanoacrylate allergy is not a problem, silk nails (nail wraps) are an excellent, although more tedious, alternative for these patients [4]. Finally, nail salons do pose a risk of transmission of yeast and bacteria from a customer carrying these organisms to another when instruments are inadequately sterilized or disposable items, such as files, are improperly reused. Taking one’s personal instruments to the nail salon and making sure fresh water is used for soaking substantially decrease that risk.

Concerning treatment of chronic paronychia, some studies have shown that topical steroids when used alone are effective [9]. Nonetheless, the usual treatment consists of a topical or systemic azole in combination with a topical steroid.

**Onycholysis**

Onycholysis is the separation of the NP from the nail bed. Tight adhesion of plate to bed is ensured by a nail bed epithelium that has a stronger attachment to the NP than to the mesenchyme of the nail bed. The nail bed epithelium is derived from the matrix and onycholysis can result from a direct injury to the nail bed or from injuring the matrix, which is the source of the nail bed epithelium.

Patients present with whitish discoloration of the NP secondary to a creation of a solid-gas interface caused by uplifting of the NP and air creeping in below the ventral surface of the NP. This leads to changes in light refraction making the NP appear as opaque or white-yellow in color [2]. If the newly created space is colonized by *Pseudomonas* or *Aspergillus*, a bluish green tint is noticeable.

Here the focus is simple onycholysis that is unrelated to disease or drugs and commonly occurs in a similar setting to paronychia. This happens because mechanical trauma, irritants, and allergens that affect the periungual tissues leading to paronychia can also affect the subungual nail bed and matrix and cause onycholysis. In most patients who present with simple onycholysis, history reveals exposure to strong irritants [10]. Although relatively well protected from irritants and allergens, the nail bed and matrix can still be reached by strong irritants, such as methacrylic acid primer, which permeates thin NPs soaking the nail bed and leading to onycholysis [4]. Formaldehyde-containing nail hardeners are other irritants associated with painful onycholysis [6]. Allergens, such as acrylate monomers and toluene sulfonamide formaldehyde resin, have also been associated with onycholysis. Excessively long nails, whether artificial or natural, can cause excessive mechanical forces on the nail bed even after minor trauma because of the lever effect, which sometimes results in onycholysis.

As with paronychia, the role of *Candida* in the pathogenesis of onycholysis remains uncertain. Despite various studies showing that more than 85% of patients with simple onycholysis have positive yeast cultures, whether or not *Candida* is acting as a primary pathogen is still a subject of debate. Most authors agree, however, that *Candida* should be treated for onycholysis to resolve [10].

Treatment should not be delayed because with prolonged onycholysis, the nail bed undergoes cornification, markedly decreasing the chances of NP reattachment [10]. Patients with onycholysis should follow the preventative measures discussed under paronychia, with special attention to strictly avoid strong irritants. In addition, patients should keep the nails to a short trim to decrease the likelihood of mechanical onycholysis. Topical antifungals are the treatment of choice.

**Onychoschizia and brittle nails**

Onychoschizia, also referred to as lamellar dystrophy, is the horizontal splitting and peeling of the NP; it is a feature of the brittle nail syndrome. Patients present with cracks that run transversely along the NP. Longitudinal splitting and ridging (onychorhaxis) is also often present [11].

Ultrastructural studies of the NP using scanning electron microscopy have shown that it is made up of three layers: thin dorsal and ventral layers where slanted cells are stacked like overlapping tiles and a thick intermediate layer composed of long narrow interdigitating cells oriented laterally parallel to the nail’s free edge like long fibers [12]. Within these
cells, keratin fibrils stabilized by extensive disulfide bonding are arranged in a similar orientation [13]. The intermediate layer makes up the bulk of the NP and dominates its fracture properties. In such a structure cracks are more prone to occur in a transverse orientation because the energy needed to propagate a crack transversely in the intermediate layer (where a mere separation of the cells arranged in fibers is needed) is one quarter of the energy needed to propagate it longitudinally (which would necessitate cutting through the cells). Fractures in the dorsal layer are propagated more haphazardly but the tile-like arrangement of cells in this layer adds some waterproofing to the NP that protects the intermediate section on onychoschizia apply.

In all three layers, the cells are held together by an intercellular cement substance the nature of which is still poorly defined. Some think the intercellular material contributes to the hardness of the NP and that excessive exposure to detergents, nail polish removers, and other organic solvents with powerful lipid extraction properties and lytic action on the cement substance weaken the NP making it susceptible to splitting after minor trauma [14]. This theory was challenged by a study in which nail clippings were exposed to various solvents (water, lactic acid, acetone, and sodium hydroxide) both continuously and with alternate periods of drying. The results showed that nails that developed horizontal lamellar separation similar to what is seen with onychoschizia were the ones exposed to water with alternate periods of hydration and dehydration. Acetone and potassium hydroxide solutions caused minimal changes in the NP. The authors concluded that expansion and contraction between NP layers caused by hydration and dehydration are critical in the induction of lamellar cracks. In contrast, the same study showed that continuous hydration of the NP had little effect. In fact, the modulus of elasticity and flexibility both increase when the NP is hydrated [15].

The brittle nail syndrome is a diagnosis used to label patients who suffer from NPs with onychoschizia in addition to onychorrhexis (longitudinal splitting) and NP surface degranulation. It is a condition that affects 20% of the population with a twofold higher incidence among women [13]. These patients complain of soft, dry, weak, and easily breakable nails. Most cases of brittle nails are idiopathic but dehydration of the NP is thought to be a major causative factor and the same factors discussed in the section on onychoschizia apply.

Other predisposing factors include hapalonychia, female gender, and advancing age [11]:

- Hapalonychia is thinning of the NP caused by a decrease in length of the nail matrix. A study that looked at nail matrix parameters in several nail disorders by using a 20-MHz ultrasound found that the patients with brittle nails (four patients) showed thinning of the NP and a decrease in the nail matrix volume. Patients with thin NPs seem to be more at risk of developing brittle nail disease [16].
- The same study showed the NP and the matrix volumes to be higher in men than in women independent of age. The decreased thickness of the NP in women might explain in part their twofold higher incidence of brittle nails. Other reasons why gender might be a predisposing factor for brittle nails include increased exposure to detergents, chemicals, and cosmetics in the female population, plus a slower nail growth rate compared with men.
- The elderly also show a higher prevalence of brittle nails. Nail growth rate starts to decline after the second decade of life and slow-growing NPs have an increased predisposition to become brittle because faster growing nails are younger, more flexible, and better water retaining. Any treatment that stimulates nail growth is beneficial in the treatment of brittle nails [11].

A recently proposed semiquantitative grading system for the severity of brittle nails allows the calculation of an average score that reflects the severity of brittleness. This score gives the treating physician an objective means of following the progress of brittle nails because, in many patients, changes are mostly subjective [13].

In the treatment of onychoschizia and brittle nails, avoiding frequent exposure to water seems to be a crucial, albeit not always practical, step in the management. The use of an emollient immediately after hand washing is a good alternative. Because continuous hydration has little effect on the NP, the use of an occlusive topical agent promoting water retention helps avoid constant fluctuation between wetting and drying. The application of an emollient to the NP should be repeated several times per day, preferably using a preparation that contains urea or alpha hydroxy acids.

Nail cosmetics are thought to exacerbate brittle nails. Although some authors believe that a coat of nail polish beneficially increases water retention within the NP, the drying effect of enamel removers
Potential hazards

The American Association of Poison Control Centers reported 224,792 exposures to cosmetics and personal care products in 2004. These products represented the third most commonly involved culprits in human exposure after analgesics and cleaning substances. They ranked first in the pediatric population. Nail products made up more than 12% of exposures. Although polish and polish removers constituted the bulk of nail products involved in accidental human exposure, “artificial nail” adhesives and primers did account for close to 7% of the total [19]. This reflects the trend of increasing artificial nail popularity and the shift from professional salons to home application of nail sculptures with salon-like results but at a fraction of the cost.

Almost 85% of childhood exposure to artificial nail products reported to poison control centers occurred at home. Home use primers are designed to minimize exposure by selecting rapidly polymerizing formulations. The Consumer Product Safety Commission requires child-resistant packaging for liquid household products containing more than 5% methacrylic acid; yet, products intended for professional use with much higher percentages and very low pH are widely available. Wholesale cosmetics supply houses or retail pharmacies often do not ask for identification or a beautician’s license. Moreover, when looking at the adequacy of labeling of nail primer cosmetics, the product information was found to be incomplete and inadequate in its warning and first aid instructions [20].

Nail technicians, constantly exposed to solvents, methacrylates, and low-levels of neurotoxins common to nail studios, have been found to experience small but significant cognitive and neurologic symptoms [21].

Another health-related concern is the tendency of artificial nails harboring harmful bacteria that are difficult to eliminate with hand cleansing using antimicrobial soaps or alcohol-based gels. This makes their use by health care workers potentially hazardous with an increase in the likelihood of transmitting infections. The Association of Operating Nurses recommends that surgical personnel keep their nails short and unadorned [22].

Multiple-use instruments that can draw blood, such as nail clippers, cuticle nippers, and electric drills, may still harbor infectious fungi, yeasts, bacteria, and viruses even after cleaning with Environmental Protection Agency–registered disinfectants, such as benzalkonium chloride, which is commonly used in nail salons [23]. These equipments should be labeled as “critical items” according to the terminology that is used by the Centers for Disease Control and Prevention to refer to objects used in health care facilities that enter sterile tissue or the vascular system. Critical items are associated with a high risk of infection if contaminated with any microorganism. Their sterilization by heat is best (autoclaving) but immersion in liquid chemical sterilants or high-level disinfectants, such as 7.5% stabilized hydrogen peroxide and ≥2.4% glutaraldehyde-based formulations, is an acceptable alternative. To destroy all microorganisms including bacterial spores, however, liquid immersion of instruments should last for 6 and 10 hours when using hydrogen peroxide and glutaraldehyde, respectively. Other approved sterilants have contact times ranging between 3 and 12 hours [24].

Unfortunately, most states allow the use of low-level Environmental Protection Agency–registered hospital disinfectants, such as chlorine and quaternary ammonium–based products, for cleaning the instruments in nail salons. Furthermore, an immersion time of 10 minutes between customers is often the only requirement [25]. Clients are encouraged to use their own nail instruments when receiving manicure and pedicure services [23].
Summary

Whether performed at home or in professional nail salons, nail care procedures and the use of nail cosmetics can potentially cause problems. The requirements for state licensure of technicians vary significantly from state to state and with more than 250,000 salons in the United States, it is very difficult to standardize and regularly inspect sanitation practices. Nevertheless, by following a few relatively simple guidelines, consumers can limit the risk of damaging their nails significantly. For the millions of women and men who visit nail salons and use nail cosmetics every year, the shortcomings of nail adornments seem to be forgivable as long as they get their fashionable nails.

As the French artist and writer Jean Cocteau (1889–1963) once wrote: “fashion dies very young: so we must forgive it everything.” Perhaps nowhere does this apply more, than in the world of nail fashion.

References

Osteoporosis is a common condition that affects more than 75 million people in the United States, Asia, and Europe [1]. According to the International Osteoporosis Foundation, approximately one in three women and one in eight men suffer from osteoporosis worldwide. Osteoporosis results from a combination of genetic and environmental factors that contribute to peak bone mass and the rate of bone loss. These factors include medications, diet, race, sex, lifestyle, and physical activity. The management of osteoporosis can be complicated by simultaneous treatment of other diseases. For dermatologists, the use of long-term oral corticosteroids for the management of immunobullous and blistering diseases is of particular importance. Although these treatment modalities are potentially lifesaving for patients, the side effects can be dangerous. This article examines the pathophysiology, clinical course, and treatments for osteoporosis and the special considerations that arise when managing patients using corticosteroids.

Osteoporosis: clinical definition

A Consensus Development Conference defined osteoporosis as a “systemic skeletal disease characterized by low bone mass and microarchitectural deterioration with a consequent increase in bone fragility and susceptibility to fracture” [2]. Both men and women lose bone mass with advancing age, but in some the loss is so great that the skeleton is unable to maintain optimal structural integrity, and the result is susceptibility to fractures, particularly of the hip and spine. Osteoporosis also can be defined operationally as a bone mineral density that is 2.5 standard deviations below the mean peak value in young adults (T-score) [3]. This technical definition has many limitations because this criterion does not include the measurements that are useful for diagnostic evaluation or the other factors that influence bone mineral density. In particular, it does not consider the site or the procedure that should be used in assessing bone mineral density. Bone mineral density also can be compared with the mean value in normal subjects of the same age and sex (known as the Z-score). A Z-score less than –1 at either the lumbar spine or the proximal femur would indicate a value in the lowest 25% of the reference range. At this value the risk for fracture is approximately doubled. A Z-score less than –2 would indicate a value in the lowest 2.5% of the reference range, a level associated with a considerably larger increase in the risk for fracture. Without further study, however, the definition established by the World Health Organization for osteoporosis cannot be used for other populations, such as premenopausal women [4].

Osteoporosis can be divided into two main classifications: primary (senile and postmenopausal) and secondary. Most cases of osteoporosis are primary,
yet physicians who prescribe long-term corticosteroids must be particularly cautious, because corticosteroid-induced osteoporosis is the most common cause of secondary osteoporosis [5]. Studies demonstrate bone densities that range from 10% to 30% less than normal because of glucocorticoid (GC)-induced osteoporosis. In addition, the risk for fractures in patients receiving chronic corticosteroids has been shown in observational studies to range from 30% to 50% [6,7]. Other clinical risk factors such as body weight, age, sex, and concomitant diseases are reviewed in this article. In addition, the duration and dosage of GC treatment have a large effect on fracture risk.

**Genetics**

Peak bone mass in humans usually is attained between the ages of 25 and 30 years [8]. Its magnitude is determined largely by hereditary factors, especially the allele for the vitamin D receptor molecule. The type of vitamin D receptor molecule that is inherited accounts for approximately 75% of the maximal peak mass achieved [9]. Polymorphism in the vitamin D receptor molecule is associated with either a higher or lower maximal bone mass. Increased parathyroid hormone (PTH) levels or insufficient intake of vitamin D do not play a major role in the development of senile and postmenopausal osteoporosis. Physical activity, muscle strength, diet, and hormonal state, however, all contribute [10]. Once maximal skeletal mass is attained, a small deficit in bone formation accrues with every resorption and formation cycle because each sequence is not completely effective. Accordingly, age-related bone loss, which may average 0.7% per year, is a normal and predictable biologic phenomenon [2,9]. Although much remains unknown, discoveries in the molecular biology of bone have provided intriguing new hypotheses in the pathogenesis of osteoporosis.

**Age-related changes**

Age-related changes in bone cells and matrix have a strong impact on bone metabolism. Osteoblasts from elderly individuals have reduced reproductive and biosynthetic potential when compared with osteoblasts from younger individuals [11]. Also, proteins bound to the extracellular matrix, such as growth factors, which are mitogenic to osteoprogenitor cells and stimulate osteoblastic synthetic activity, lose their biologic effect over time. The end result is a skeleton populated by bone-forming cells that have a diminished capacity to make bone. This is the main explanation for primary senile osteoporosis.

**Reduced physical activity**

Reduced physical activity increases the rate of bone loss in experimental animals and humans because mechanical forces are important stimuli for normal bone remodeling. The type of exercise is important because load magnitude influences bone density more than the number of load cycles. Resistance exercises such as weight training are more effective stimuli for increasing bone mass than repetitive endurance activities such as jogging [11].

**Hormonal influences**

In the decade after menopause, yearly reductions in bone mass may reach up to 2% of cortical bone and 9% of cancellous bone. Women may lose as much as 35% of their cortical bone and 50% of their trabecular bone in 30 to 40 years of life after menopause [12]. The effects of estrogen on bone mass are mediated by cytokines. Decreased estrogen levels result in increased secretion of IL-1, IL-6, and TNF-alpha by blood monocytes and bone marrow cells [13]. These cytokines are potent stimulators of osteoclast activity. Osteoblast activity occurs, but it does not keep pace, leading to what is classified as a high turnover form of osteoporosis. The entire skeleton is affected in postmenopausal and senile osteoporosis, but certain regions tend to be involved more severely than others [14]. In postmenopausal osteoporosis, the increase in osteoclast activity affects mainly bones or portions of bones that have increased surface area, such as the cancellous compartment of vertebral bodies. The osteoporotic trabeculae are thinned and lose their interconnections, leading to progressive microfractures and eventual vertebral collapse. In senile osteoporosis, the osteoporotic cortex is thinned by subperiosteal and endosteal resorption and the haversian systems are widened [9].

**Other risk factors**

In addition to the aforementioned risk factors there is an extensive list of factors that place someone at risk for primary osteoporosis and that need to
be considered before initiating treatment with corticosteroids. The National Osteoporosis Foundation identified the following as the most common and easily ascertained risk factors for osteoporosis: low body weight (<58 kg), smoking, first-degree relative with low-trauma fracture, and personal history of low-trauma fracture [9]. Physicians strongly recommend smoking cessation to patients concerned about osteoporosis, because smoking cigarettes is known to accelerate bone loss. For example, the results of one study suggested that women who smoke one pack per day throughout adulthood have on average a 5% to 10% reduction in bone density by menopause, resulting in an increased risk for fracture. Physicians also may recommend that patients limit alcohol consumption because high alcohol intake may increase the risk for fracture for several reasons, such as an increased susceptibility to falling, poor nutrition, and so on. Although it has been suggested that women at risk for osteoporosis should avoid salt and caffeine, many experts do not advise caffeine or salt restriction because these measures have not been proven to prevent bone loss in those who have a sufficient intake of calcium.

Clinical course

The clinical manifestations of structural failure of the skeleton depend on which bones are involved. Vertebral fractures that occur frequently in the thoracic and lumbar regions are painful [15]. Multiple-level fractures can cause significant loss of height and various deformities, including lumbar lordosis and kyphoscoliosis. Complications of overt fractures of the femoral neck, pelvis, or spine, such as pulmonary embolism and pneumonia, are frequent and result in 40,000 to 50,000 deaths per year [16]. Osteoporosis cannot be detected reliably in plain radiographs until 30% to 40% of the bone mass is lost, and measurement of blood levels of calcium, phosphorus, and alkaline phosphatase are not diagnostic [3,15]. Osteoporosis in thus a difficult condition to diagnose accurately because it remains asymptomatic until skeletal fragility is well advanced. Currently the best procedures that accurately estimate the amount of bone loss, aside from biopsy, are specialized radiographic imaging techniques, such as single energy photon absorptiometry, dual-energy absorptiometry, and quantitative computed tomography, which measure bone density. Among the most useful in clinical practice is dual-energy x-ray absorptiometry. With these techniques, measurement of the density of the proximal femur is the most useful for predicting fractures, and measurement of lumbar spine density is the most useful for monitoring therapy [17].

Pathophysiology of corticosteroid-induced osteoporosis

GC-induced bone loss is produced by stimulating osteoclast-mediated bone resorption and reducing osteoblast-mediated bone formation, and through indirect or systemic effects on calcium metabolism and sex hormones [18,19]. The decline in bone formation may be mediated by a direct inhibitory effect on osteoblasts [19], inhibition of insulin-like growth factor-I production [20,21] and testosterone [19], and an increase in osteoblast and osteocyte apoptosis. This apoptosis also may explain the tendency of GCs to cause osteonecrosis [20].

GCs affect the osteoclasts primarily through transcriptional control. Osteoclast function is increased by upregulating expression of the receptor activator of nuclear factor-(kappa) B ligand (RANKL), which acts on an osteoclast receptor to induce osteoclastogenesis. GCs simultaneously downregulate expression of osteoprotegerin, which is a competitive inhibitor at the RANKL site. GCs do not affect the bone-resorbing activity of mature osteoclasts, because these cells do not have functional GC receptors [22]. Although there is little evidence to suggest secondary hyperparathyroidism in patients who take GCs [23], PTH secretion may be directly and indirectly stimulated, the latter by way of the following effects. GCs decrease intestinal calcium absorption [24,25], an effect that is not mediated by inhibition of the synthesis of calcitriol (1,25-dihydroxyvitamin D, the most active metabolite of vitamin D) [25–27]. GCs increase renal calcium excretion because of the increase in calcium mobilization from bone and a direct effect on the kidney [26,28]. The urinary excretion of other indicators of bone resorption, such as hydroxyproline, is also increased [29].

GCs also exert multiple growth-suppressing effects, decreasing endogenous growth hormone secretion, bone formation, nitrogen retention, and collagen formation. As a result, growth impairment is common in children receiving GC therapy. The mechanism of increased bone loss (ie, increased bone resorption relative to bone formation associated with decreasing levels of estrogen or testosterone) is similar to that seen in postmenopausal osteoporosis [30]. Treatment strategies that have been shown to increase bone mass and reduce fractures in postmenopausal women
who have osteoporosis therefore have been applied to GC-induced bone loss.

Clinical course of GC-induced osteoporosis

The risk for GC-induced bone loss is correlated roughly with both the dose and duration of treatment [31–33]. The risk for subsequent fracture is related more closely to daily dosage than cumulative dose. Recent evidence has suggested that dosages of prednisone as low as 2.5 mg/d increase the risk for bone loss and fracture, with the bone loss occurring within the first 3 months of initiating oral corticosteroids. The total lifetime cumulative dose may also affect the extent of bone loss, although threshold values above which osteopenia occurs have not been established clearly. When comparing dosages of less than 2.5 mg/d, 2.5 to 7.5 mg/d, and greater than 7.5 mg/d, relative risk for vertebral fracture and risk for hip fracture increased [34]. Alternate-day therapy has been shown to be as detrimental to bone homeostasis as daily therapy.

Most agents that increase bone loss, such as thyroxine or sustained elevation of PTH, accelerate not only bone resorption but also bone formation, albeit to a lesser extent [35]. Because GCs accelerate resorption while inhibiting formation, their use is associated with especially rapid bone loss [36,37]. A prospective longitudinal study, for example, found that patients beginning high-dose GC therapy (mean dose of prednisone 21 mg/d) lost a mean of 27% of their lumbar spine bone mineral density during the first year of therapy [36]. Fortunately the rate of loss slows substantially thereafter [38,39]. There is a substantial increase in fracture risk in patients receiving GC therapy that appears within 3 to 6 months of initiating treatment. Fracture risk seems to be related to the dose and duration of therapy, but is independent of bone mineral density [34,40,41].

Management of GC-induced osteoporosis

The ultimate goal is to prevent GC-induced osteoporosis. Epidemiologic evidence has shown that at any one time 0.5% to 2.5% of the population is taking GCs [41]. Guidelines for the prevention and management of patients using long-term GCs have been available since the mid-1990s (Figs. 1 and 2) [42–44]. In a recent retrospective study, Curtis and colleagues compared rates of screening and preven-

Starting long-term steroid therapy or
On long-term steroid therapy with abnormal BMD
  • Engage in weight bearing exercises
  • Quit smoking/avoid smoking
  • Decrease alcohol consumption (if excessive)
  • Receive supplementation with Calcium/Vitamin D (800 IU)

Contraindication to bisphosphonates?

Yes
  • Receive a bisphosphonate
  • If premenopausal or male
    • Consider calcitonin
  • If post menopausal
    • Consider HRT or SERM

No
  • For males already on long-term steroid therapy, consider testosterone replacement if deficient

Fig. 1. Recommendation guidelines. Long-term steroid therapy refers to ≥ 5 mg/day prednisone (or equivalent) for ≥ 3 months. BMD, bone mineral density; HRT, hormone replacement therapy; SERM, selective estrogen receptor modulator.
tion of GC-induced osteoporosis in groups of patients from a national managed care organization from 1995–1998 and 2001–2003. This study showed that the frequency of bone mass measurement among GC-treated patients in 2001–2003 increased threefold compared with 1995–1998, and the use of prescription antiresorptive medication increased approximately twofold [45]. Unfortunately, rates of screening and preventive treatment in the 2001–2003 cohort were less than 50%. This brings us to what can be done to prevent osteoporosis in patients who require long-term GC treatment. Preventive steps are available that may help to maintain or increase bone density. In addition, for those already affected by osteoporosis, prompt diagnosis and assessment of bone loss and associated fracture risk are essential, because therapies are available that may slow further loss of bone or increase bone density, reversing the progression of osteoporosis.

Nonpharmacologic therapies

The primary nonpharmacologic therapies for GC-induced osteoporosis include three major components: diet, exercise, and smoking cessation. If possible, prolonged therapy with or high doses of systemic GCs should be avoided. An optimal diet includes an adequate intake of calories and calcium and vitamin D, which are essential in helping to maintain proper bone formation and density.

Calcium and vitamin D intake

Although the optimal level of calcium intake has not been established clearly, it is recommended that daily calcium intake be at least 1000 mg in premenopausal women and in men and 1500 mg in postmenopausal women who do not take estrogen. The total daily calcium intake should not routinely exceed 2000 mg, however, because of the possibility of adverse effects. Although calcium supplements are recommended as an adjuvant therapy for all patients starting GC therapy, they are insufficient if used alone [46]. Calcium carbonate should be taken with meals to help ensure optimal absorption. Calcium supplementation in excess of 500 mg/d should be taken in divided doses. In addition, patients must be aware that the daily intake recommendations given here apply to elemental calcium. For example, calcium carbonate is 40% elemental calcium; therefore, 500 mg of calcium carbonate contains 200 mg of elemental calcium [42,47].

It is recommended that patients take a total of 800 international units (IU) of vitamin D each day in combination with the calcium supplement. Such a daily dosage seems to reduce bone loss and fracture rate in older women and men. [47]. The main restrictions in prescribing calcium and vitamin D are in patients with a history of hypercalcemia or nephrolithiasis.

Although vitamin D metabolites can be prescribed in place of plain vitamin D there have been no reports to support their preference. In addition,
there is a higher incidence (25%) of patients suffering from hypercalcemia secondary to vitamin D metabolite administration.

**Bisphosphonates**

Bisphosphonates inhibit the breakdown and removal of bone by binding to hydroxyapatite on the surface of bone. They also act by increasing production and decreasing apoptosis of osteoblasts. Because they have minimal side effects, they are considered widely as the first choice treatment for the prevention and treatment of GC-induced osteoporosis.

Alendronate at a dose of 10 mg/d increases bone mass, reduces the occurrence of vertebral and non-vertebral fractures, and decreases the loss of height potentially associated with vertebral fractures [48,49]. In addition, alendronate therapy at a dose of 5 mg daily has been approved by the US Food and Drug Administration (FDA) as safe and effective in the prevention of osteoporosis. Even though side effects of bisphosphonates are minimal there remain two administration requirements that decrease compliance. Because of the gastrointestinal irritation caused by bisphosphonates, patients must remain upright for 1 hour post-administration. In addition, bisphosphonates have low bioavailability that requires them to be taken fasting in the morning with just water. Alendronate can also be given now as a single weekly pill (70 mg/wk) which has increased compliance without compromising efficacy [50].

Risedronate is also approved for prevention and treatment of osteoporosis at a dose of 5 mg/d (or as a single 35 mg once-weekly pill). Like alendronate, it reduces the risk for vertebral and hip fractures. It is possible that risedronate has fewer gastrointestinal side effects than alendronate, but this is not proven [39,51,52]. Another oral bisphosphonate, ibandronate, has been approved recently for the treatment of postmenopausal osteoporosis. Ibandronate has the advantage of being dosed orally 150 mg/mo [53]. Although there have not been any direct clinical trials of ibandronate for use in GC-induced osteoporosis, we can hypothesize that the effects will be similar to other bisphosphonates.

Other new bisphosphonates are being studied, including single yearly intravenous infusions of zoledronic acid [54]. Another intravenous bisphosphonate, pamidronate, may also be considered as an alternative to oral bisphosphates in treating GC-induced osteoporosis [55,56]. Although pamidronate is not FDA approved for treatment of GC-induced osteoporosis, it is used commonly off label. Both of these options have proved to have similar effects on bone density as oral bisphosphonates. Zoledronic acid, however, has not been proved to have these effects in GC-induced osteoporosis, but studies in this area are pending. Weekly intramuscular injection of 100 mg of the bisphosphate clodronate was shown to prevent bone loss and fractures in patients taking GCs [57]. Having nonoral options available is important when treating patients who have upper gastrointestinal motility disorders, reflux esophagitis, swallowing difficulties, or who cannot remain upright for 1 hour [44].

Several new studies have alerted physicians to an associated risk for osteonecrosis of the jaw as a previously unrecognized potential complication of bisphosphate use [58–60]. Awareness of this side effect can lead to an earlier diagnosis, which might prevent or reduce the morbidity resulting from advanced destructive lesions of the jaw bone. In addition, bisphosphonates should be used with caution in premenopausal women who are considering becoming pregnant, because they have been shown to be teratogenic in animal studies.

**Estrogen/progestin therapy**

Although information on fracture risk had been lacking for estrogen replacement compared with bisphosphonates and selective estrogen receptor modulators (SERMs), the Women’s Health Initiative (WHI) found that combined estrogen-progestin treatment reduced hip and vertebral fracture risk by 34%. A similar reduction in fracture risk was seen in the WHI trial of unopposed estrogen [61]. Although the preliminary results of the WHI were promising, they also showed some dangerous side effects. Estrogen-progestin therapy is no longer a first-line treatment for osteoporosis in postmenopausal women because of increases in the risk for breast cancer, stroke, blood clots, and perhaps coronary disease.

**Estrogen-like medications**

SERMs affect some of the same receptors as estrogen, thereby producing some estrogen-like effects. These agents, such as raloxifene and tamoxifen, may provide some protection against menopausal bone loss while having the potential to block other unwanted estrogen effects, such as those that may
lead to breast cancer. Raloxifene has been approved by the FDA for the prevention and treatment of osteoporosis, but not for GC-induced bone loss [61–63]. It may be less effective in preventing bone loss, however, than bisphosphonates or estrogen.

Although tamoxifen, a drug used for breast cancer and prevention of breast cancer in high-risk women, is not FDA approved for the prevention or treatment of osteoporosis, evidence suggests that it may be effective. Tamoxifen is not recommended solely for osteoporosis prevention or treatment, however.

Calcitonin

Calcitonin is a hormone produced by the thyroid gland that, together with PTH, helps to regulate calcium concentrations in the body. Synthetic preparations of the hormone sometimes are recommended as a treatment for osteoporosis. A meta-analysis of nine randomized controlled studies to evaluate its effect on GC-induced osteoporosis showed that it was more effective than calcium alone in maintaining spinal bone density [64]. Calcitonin may be administered by way of nasal spray or injection (subcutaneous salmon calcitonin). Nasal administration is typically preferred because of ease of use and because the injections tend to be associated with more nausea and flushing. Other drugs are usually recommended instead of calcitonin, because it is not clear whether calcitonin increases bone density and decreases the fracture rate outside the spine [65,66]. Calcitonin is thus regarded as a second-line treatment for GC-induced osteoporosis.

Parathyroid hormone

Produced by the parathyroid glands, PTH stimulates resorption and new bone formation. Fragmented recombinant parathyroid (teriparatide) hormone has been shown to increase bone mineral density in GC-induced osteoporosis [33]. Intermittent administration stimulates formation more than resorption. Clinical trials to date suggest that PTH therapy is effective in the prevention and treatment of osteoporosis, and a preparation called teriparatide, given by daily injection, is now FDA approved for the treatment of severe osteoporosis. Teriparatide is more effective at building spine bone density than any other treatment. Because it requires daily injection, and because of its expense, it is usually reserved for patients with severe spine osteoporosis (T-score <3.0) [67,68].

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Body Dysmorphic Disorder

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The American Society for Aesthetic Plastic Surgery compiles cosmetic surgery data annually by surveying cosmetic surgeons in the United States, including plastic surgeons, otolaryngologists, and dermatologists. In 2004, this organization reported that the number of cosmetic procedures performed in the last 7 years has increased nearly 400\% \cite{1}. The top five nonsurgical procedures are botulinum toxin injections, laser hair removal, chemical peels, microdermabrasion, and filler injections and account for almost 10 million procedures. Nearly 90\% of all cosmetic procedures in the United States are performed on women.

Among the millions of patients seeking physical beautification through cosmetic procedures, approximately 10\% suffer from body dysmorphic disorder (BDD). This is a disabling preoccupation with an imagined or minimal physical anomaly. Performing cosmetic procedures on those afflicted with BDD can be unrewarding for both the patient and the physician, because patients’ expectations are unrealistic. This article presents an overview of the diagnosis and management of this relatively common disorder.

History

In 1891, dysmorphophobia \cite{2} was published in the medical literature and since then BDD has had many names including beauty hypochondria \cite{3} and dermatologic hypochondriasis \cite{4}; more recent publications refer to patients as “polysurgery addicts” \cite{5} or “insatiable.” \cite{6} Finally, in 1987, BDD was given separate diagnostic status in the third edition of the \textit{Diagnostic and Statistical Manual of Mental Disorders} (DSM III) \cite{7}. One of the leading researchers of BDD, Dr. Katharine Phillips, was largely responsible for bringing this disease into public awareness with the publication of her text, \textit{The Broken Mirror; Understanding and Treating Body Dysmorphic Disorder} \cite{8}. She also provided the most succinct, but descriptive, definition: “the distress of imagined ugliness” \cite{9}.

Definition

In the most recent edition of the DSM (IV), the essential features of and primary criterion for BDD is a preoccupation with an imagined defect in appearance, and if a slight physical anomaly is present, the individual’s concern is markedly excessive \cite{10}. In addition, two other criteria must be met to receive a BDD diagnosis: the preoccupation causes significant distress or impairment in social, occupational, or other important areas of functioning; and the preoccupation is not better accounted for by another mental disorder (eg, dissatisfaction with body shape and size in anorexia nervosa). These most recent diagnostic criteria help guard against overdiagnosis because researchers suggest that some degree of body image concern may be beneficial. A normal level of concern leads to regular grooming and hygiene, which facilitate interactions in society and maintain health.
Clinical features

Preoccupation with appearance

The major feature of this disorder is usually a perceived flaw located on the face or head, but any visible body part may be the focus of concern. Most frequently, the preoccupation centers on the skin, hair, or nose. Often there is more than one problematic area and perceptions of asymmetry are common. Ruminations about the perceived defects abound. Psychologic disturbances include feelings of unworthiness, low self-esteem, embarrassment, and shame, which then lead to avoidance of social and occupational activities in nearly all of these patients [11].

Insight

The degree of insight a patient has is highly variable and usually dynamic. It is estimated that at least 40% of BDD patients are delusional for a period of time during their illness and during this time they are less likely to accept appropriate therapeutic intervention [12,13]. Insight may also lessen with psychologic distress and social exposure. Fortunately, treatment often improves insight and patients may eventually sympathize with their medical professionals and family for tolerating their sometimes difficult behavior.

Behavioral pathology

Repetitive behaviors are a major component of the behavior of BDD patients. Mirror gazing is the most common of these behaviors. Nearly 80% pathologically gaze at their reflection; others may avoid reflective surfaces in an exaggerated way. Most who mirror gaze are secretive about it and fear they will be perceived as vain or narcissistic. They are uniformly disgusted by their reflection. The drive to do this is so great that they use any reflective surface available to gaze into, even those that give an ambiguous reflection, such as a spoon. Table 1 summarizes differences in mirror use between BDD patients and controls from a study reported in 2001 [14]. As expected, patients feel more distress before looking in the mirror and spend an inordinate amount of time looking.

Motivation for using a mirror is also different between patients with BDD and controls. Control subjects use the mirror for functional purposes, such as shaving or combing. Patients with BDD are constantly comparing three different images: (1) what is in the mirror, (2) the ideal image of themselves, and (3) the distorted image of themselves. This leads to uncertainty about how they really look and starts the vicious cycle of more mirror gazing to rectify the images. They go to the mirror each time with a hope that they will finally look ideal and feel more comfortable. They also feel worse if they resist the impulse to look and need excessive amounts of time to perform another characteristic behavior: camouflaging.

Camouflaging, comparing, and reassurance-seeking are all behaviors that become characteristically repetitive in BDD. Camouflaging is necessary for most of these patients to endure social situations and may involve wigs, makeup, body positioning, sunglasses, hats, or clothing. They also constantly compare themselves with others, usually celebrities or models. Reassurance-seeking can frustrate family, friends, and medical professionals when the patient requires reassurance that the defect is sufficiently camouflaged. This reassurance may reduce their stress for a short time, but then further reassurance is sought. Another form of reassurance is persuading others that the perceived flaw is real and it is, indeed, unattractive.

Compulsive skin picking may be a sign of BDD. About 27% with the disorder pick at their skin to improve its appearance [15]. They report that the urge to pick is difficult to resist and some may do it for hours each day. The patients may use various implements, such as needles, razors, or knives. In one case report, a woman picked at her neck until she exposed

Table 1
Quantitative differences in mirror use between BDD patients and controls

<table>
<thead>
<tr>
<th></th>
<th>BDD patients (N=52)</th>
<th>Controls (N=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean duration of longest session (minutes)</td>
<td>73</td>
<td>21</td>
</tr>
<tr>
<td>Maximum duration spent (minutes)</td>
<td>174</td>
<td>36</td>
</tr>
<tr>
<td>Distress rating before mirror gazing (scale of 1–10; 10=most distress)</td>
<td>6.4</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Differences between both groups in all characteristics were significant at P < .05.

Abbreviation: BDD, body dysmorphic disorder.

her carotid artery [16]. These patients are also more likely to report suicidal ideation and attempts.

Psychiatric comorbidities

It is important to be aware that psychiatric comorbidities are prevalent in BDD patients. Sixty percent of BDD patients have concurrent depression and there is an 80% lifetime risk of depression. The BDD usually precedes the onset of depression and may be secondary to BDD. A third of patients have social phobia, substance abuse, or obsessive-compulsive disorder. More than 50% have avoidant personality disorder, which may explain why up to 20% of school-aged patients drop out because of BDD [17].

Pathophysiology

The cause of this complex disorder is still obscure but research in epidemiology, neurobiology, pharmacology, psychology, and sociology are all slowly contributing to its understanding. Although it is multifactorial, there seems to be a familial contribution to developing the disorder because a patient is four times more likely to have a first-degree relative with BDD than an individual without the diagnosis [17]. It is likely that a “nature” and a “nurture” component to the familial predisposition exists.

The neurobiologic literature is limited in patients with BDD. Some of what is known is gathered from imaging studies from patients with known BDD or, more commonly, other somatiform disorders. Somatiform disorders have arisen following temporal lobe dysfunction from surgery or trauma [18]. At least three cases of BDD have been reported following illness. One case resulted in left frontal temporal lobe atrophy after an acute, nonspecific inflammation of the brain [19]. BDD was reported to follow an episode of Bell’s palsy in a diabetic adolescent patient and the onset of ulcerative colitis in another (neither case reported neuroimaging) [20]. The development of BDD in these cases may be partially explained by a current area of psychoneuroimmunologic research. Studies have demonstrated that proinflammatory cytokines act on the central nervous system to trigger brain cytokines and prolonged activation of this system alters tryptophan metabolism, which can lead to various psychiatric disorders [21].

Indirectly, treatment data infer a neurochemical basis for the disorder. Antagonism of the serotonin system is known to exacerbate BDD symptoms. Based on this knowledge, it was presumed that underfunctioning, or lack of, serotonin contributed to the symptoms in BDD. Fortunately, treatment with serotonin reuptake inhibitors (SRIs) has proved beneficial to many patients and provides further evidence for the neurochemical imbalance.

Biopsychosocial models of BDD development have the greatest empirical support currently. Evolutionary theories regarding selection advantages of beauty and sexual attraction features suggest a natural biologic drive for physical perfection attenuated to the extreme in BDD. Psychologic factors, including critical incidents (eg, teasing during childhood), physical or sexual abuse, and negative affect contribute to the distorted cognitive processing that leads to, and then maintains, BDD behaviors. Sociocultural theories suggest society’s overvaluing one’s physical appearance as a primary contributor to adolescent discontent with an idealized self and development of BDD. Biologic drive and cognitive distortions, fueled by a perfection-oriented society, combine and eventually develop into BDD according to biopsychosocial models [22].

Epidemiology

Few studies have focused on the epidemiology of BDD. Prevalence and clinical features of the disorder vary depending on the population studied. The best evidence of lifetime prevalence in the general population is approximately 1% [23]. When a group of German college students was studied, however, 5.3% fit the criteria for BDD [24]; a cohort of American psychology students found a 13% BDD prevalence [25]; cosmetic surgery practices screened in two studies found 6% to 15% fit the criteria for BDD [26,27]; and in 2001, 23% of patients seeking treatment with botulinum toxin at a dermatology clinic matched the BDD profile [28]. Across these studies, the authors suggest that many of the patients in these clinical settings would benefit more from psychotherapy than from the cosmetic procedures they desire.

Even though the average age at which a BDD patient presents to a dermatologist is about 34 years old [29], the disorder usually begins in adolescence and affects an estimated 2.2% of 14 to 19 year olds [30]. Most published clinical series involve patients in their mid thirties, but those looking at adolescents have found some troubling statistics. Two thirds of adolescents with BDD report suicidal ideation, 21% have attempted suicide, 38% have engaged in violent
behavior, and 39% have been psychiatrically hospitalized [17]. As a comparison, the suicide rate in the general population in 1999 was 11 per 100,000, an estimate of attempts was just under 1% [31], and in a 1998 study of patients with psoriasis and acne the rate of suicidal ideation was 5% to 7% [32].

This disorder affects men and women equally, but there are some interesting gender-related differences in the clinical features of BDD. Women are more frequently focused on breasts, hips, thighs, and their weight, whereas men are concerned more with body build, genitalia, hair, and their height. Women perform more repetitive behaviors, such as mirror checking, camouflaging, and skin picking, and more frequently suffer from bulimia, panic disorder, and generalized anxiety disorder. Men are more likely to abuse alcohol and have bipolar affective disorder [29]. A new subtype of BDD, muscle dysmorphia, is primarily found in men [33]. Primary symptoms include fixation on muscle size and shape, camouflaging with clothing, mirror checking, and reassurance-seeking. They may also exercise and take food supplements in excess.

Implications for dermatologists

Ineffective surgery

In a cohort of patients undergoing psychiatric treatment for BDD, nearly half had sought treatment from a dermatologist and one third had requested cosmetic surgery. Approximately 20% had cosmetic surgery and two thirds of these patients reported “no change” in or worsening of their appearance [29]. Surgery may change a BDD patient’s physical appearance, but it does not alter their internal body image or mental state.

Underestimation of prevalence

Physicians may underestimate the prevalence of BDD in their practices. When patients in general dermatology practices were screened in 2000, 10% to 14% had BDD and their most frequent concerns were skin elasticity; skin coloring; and perceived imperfections, such as acne, scars, moles, and cellulite [34]. In 2001, a survey by the American Society for Aesthetic Plastic Surgery showed that their physician members who responded estimated that only 2% of the patients in their practices had symptoms of BDD [6].

Assessment

Phillips and coworkers [35] has devised a screening questionnaire, the Body Dysmorphic Disorder Questionnaire (Box 1), which practitioners may find time and cost efficient. Questionnaire items reflect the DSM-IV criteria, but are only intended as a screening tool, and are not diagnostic. As noted in Box 1, the Body Dysmorphic Disorder Questionnaire assesses preoccupation with appearance, eating disorder potential, psychologic distress, or impairment and amount of time spent thinking about appearance, all the primary features of BDD. If this simple questionnaire is offered to patients waiting for a cosmetic consultation, the results can be discussed with them in an objective manner. They are likely to have BDD (or an “altered body image”) if they are very worried about how they look; they think about their appearance more than 1 hour per day and wish they could think about it less; and their appearance has gotten in the way of work, school, or interpersonal relationships.

Box 1. Body dysmorphic disorder questionnaire

1. Are you very worried about how you look?
   a. Do you think about your appearance problems a lot and wish you could think about them less?
   b. List the body areas you don’t like

2. Is your main concern about how you look that you are not thin enough or you might get too fat?

3. How has this problem with how you look affected your life?
   a. Has it often upset you a lot?
   b. Has it often gotten in the way of doing things with friends or dating?
   c. Has it caused you any problems with school?
   d. Are there things you avoid because of how you look?

4. How much time a day do you usually spend thinking about how you look?
   a. Less than 1 hour per day
   b. One to 3 hours per day
   c. More than 3 hours per day
Treatment

Psychotherapy

The treatment of choice for patients with BDD is psychotherapy, specifically cognitive behavioral therapy [36]. Both individual and group modalities are effective. There are two components to cognitive behavioral therapy: cognitive restructuring, which involves identifying and modifying automatic thoughts of the perceived physical defects; and behavioral techniques, which are prescribed to break the repetitive and self-destructive habits that characterize this disorder. When the patient starts substituting “healthier” behaviors for the problematic ones, they may feel more distressed initially, but this lessens with time. For example, a therapeutic strategy called response prevention recommended for mirror gazing includes only looking into mirrors at a distance; abandoning the use of magnifying mirrors; limiting the amount of time spent in front of the mirror; not looking into ambiguous reflective surfaces; focusing on the whole area, not one specific part; and delaying the urge to look in the mirror until the urge diminishes. Another strategy, called planned exposure, systematically exposes the patient to anxiety-provoking situations (e.g., wearing body-accentuating clothing) until habituation, or lessening of the anxiety, occurs.

An excellent tool to diminish skin picking using a cognitive behavioral approach was developed for the internet by Mouton-Odom and coworkers [37]. The interactive web site, www.stoppicking.com, encourages participants to record details about time spent picking at their skin. The patient’s journal is then used to illustrate patterns in their picking behavior and recommend alternate behaviors and coping strategies based on their picking patterns. Details are plotted in graphs so patients can monitor their progress as they implement recommendations.

Pharmacotherapy

Although early trials with antipsychotics, tricyclic antidepressants, and electroconvulsive therapy were unsuccessful, the SRIs showed some promise. Nearly 60% of patients got a partial remission or better, meaning decreased distress and depression, less time spent on obsessional thoughts, decreased ritualistic behavior, improved social function, and improved insight. The improved insight is interesting because delusional symptoms in other disorders are usually not responsive to SRIs [38].

The first controlled pharmacologic study of BDD assessed clomipramine, a potent but nonselective SRI, and desipramine, a selective norepinephrine reuptake inhibitor [39]. Desipramine had no effect on BDD symptoms but clomipramine-treated patients showed improvement (Table 2 provides specific doses used in these trials). An open label trial of fluvoxamine, a selective SRI, demonstrated 70% of patients had “much” or “very much” improvement on the Clinical Global Impressions Scale (validated by the National Institutes of Health) [40]. Uniquely, patients reported less anger and hostility while on treatment. Another selective SRI, fluoxetine, was studied in a randomized, placebo-controlled manner [41]. Twenty percent had complete remission and 40% had partial remission. In an open label trial of the selective SRI citalopram, 80% of participants had complete or partial remission [42]. Additionally, the average time to onset of remission was shorter (4–6 weeks) than other SRIs (6–9 weeks), but no studies directly comparing different SRIs have been done.

In general, BDD often requires higher doses than those needed for depression and it is recommended the maximum, or highest tolerated, dose should be prescribed. An adequate trial is considered 12 to

Table 2
Serotonin reuptake inhibitor dosages reported in various trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug class</th>
<th>Starting daily dose (mg)</th>
<th>Dosage increase</th>
<th>Maximum daily dose (mg)</th>
<th>Mean daily dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clomipramine [41]</td>
<td>Nonselective SRI</td>
<td>25</td>
<td>Slowly increased</td>
<td>250 (highest tolerated)</td>
<td>150</td>
</tr>
<tr>
<td>Fluvoxamine [42]</td>
<td>Selective SRI</td>
<td>50</td>
<td>50 mg q 4–7 d</td>
<td>300a</td>
<td>260</td>
</tr>
<tr>
<td>Fluoxetine [43]</td>
<td>Selective SRI</td>
<td>20</td>
<td>20 mg q 10 d</td>
<td>80</td>
<td>50</td>
</tr>
<tr>
<td>Citalopram [44]</td>
<td>Selective SRI</td>
<td>20</td>
<td>20 mg q 14 d</td>
<td>60</td>
<td>50</td>
</tr>
</tbody>
</table>

Abbreviation: SRI, serotonin reuptake inhibitor.

a Doses over 100 mg/d were divided.
16 weeks once the maximum dose is achieved. The antidepressant effects occur sooner than the anti-
obsessive effects.

In treatment-resistant cases combination therapy has been suggested, although very few trials have evaluated their effectiveness. The addition of pimo-
zide to SRIs in delusional patients was thought to improve insight (not recommended with clomipra-
mine because both drugs cause QT prolongation) but a recent study showed no benefit from the addition of pimoziode [43]. The addition of buspirone or clomipramine to SRIs has been beneficial in some case reports, but monitoring of blood concentrations of clomipramine should be done because they are augmented by SRIs [17]. Because many BDD pa-
patients are delusional, augmentation with antipsychotic medications would seem appropriate. There has been one case report of successful treatment of BDD (non-
delusional type) with olanzapine monotherapy [44], but when olanzapine was added to fluoxetine in a small series of BDD patients, it had minimal or no effect in BDD symptoms [45].

Summary

Established BDD is a contraindication to cosmetic medical and surgical treatments. BDD patients may never be satisfied with treatment outcomes, which leads to patient and physician frustration. Even if a skin condition (ie, acne) improves with treatment, the BDD symptoms (ie, picking) are not likely to remit without psychiatric intervention.

If possible, incorporate the Body Dysmorphic Disorder Questionnaire into a medical history form or interview. If BDD, is suspected, keep in mind the likely comorbidities, especially depression, and also recognize the continuum of insight that exists and treat accordingly. If insight is good, referral to a psychotherapist trained in cognitive behavioral therapy may be possible early. If insight is poor and patients refuse referral, they may be amenable to treatment with SRIs to help them feel less distressed about their appearance, and if insight improves referral may be possible at a later date.

It is important to censor comments about patients’ features lest they be misinterpreted as overly critical and one must avoid cosmetic procedures in this population. Many more controlled studies are necessary assessing the cognitive and behavioral approaches with SRIs in patients with BDD, and trials comparing different SRIs. Until then, it is important to keep the patient’s best interest in mind and avoid cosmetic procedures in this population.

References

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Women’s Occupational Dermatologic Issues

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Long before the colonization of America by Europeans, Native American women were part of the workforce, and when Europeans settled the territory, the colonists and their imported servants and slaves included a large number of women. Their jobs, changed dramatically as society moved from a largely agrarian to a predominantly urban culture. Thus, women have always been a crucial component of American labor [1].

Women are entering the American workforce in record numbers, and in 2004 they accounted for 46.5% of 139.252 million workers, with their share of the labor force projected to reach 47% by 2012 [2]. Women are also projected to account for 55% of the increase in total labor force growth from 2002 to 2012. In 2004, 74% of employed women worked full time, whereas the remaining 26% worked part time [3]; 3.7 million women held multiple jobs [4].

According to the US Bureau of Labor Statistics job classifications, from the totals of all persons employed in specific occupational sectors in 2004, the highest percentage of women were seen in the following occupations: 89.3% held health care support positions (mainly as dental assistants); 77.6% worked in personal care and service occupations (hairdressers, hairstylists, and cosmetologists); 75.9% worked in office and administrative support occupations (secretaries); and 73.2% held health care practitioner and technical positions (nurses and dental hygienists) [2].

With 64.8 million women in the workforce, their representation in various occupational sectors is crucial, as is their health and safety. They may be at risk for musculoskeletal disorders; workplace violence; reproductive hazards; and job stressors, such as sexual harassment, gender-based discrimination, and family balance issues [5]. Recently, the National Institute for Occupational Safety and Health (NIOSH) issued a fact sheet [5] highlighting working women and associated occupational hazards. Sprains and strains, carpal tunnel syndrome, tendonitis, and other musculoskeletal disorders accounted for more than half of the injuries and illnesses suffered by female workers. Stress has been cited by women as the number one problem at work, and levels of stress-related illness are nearly twice as high for women as for men. Homicide is the leading cause of injury death for women in the workplace accounting for 40% of all workplace deaths among female workers. Also according to NIOSH, 70% of injuries resulting from nonfatal workplace assaults were directed at women employed in service occupations, such as health care [5]. Women in nontraditional employment also may face health and safety risks. The US Department of Labor defines a nontraditional occupation for women as one in which less than 25% of those employed in the field are women. Examples include detectives, architects, chefs, clergy, computer and office machine repairers, construction and building inspectors, railroad conductors, machinists, truck drivers, fire fighters, aircraft pilots, construction occupations, and small engine mechanics [6]. Personal protective equipment and clothing (eg, respirators, work gloves, and work boots) are also issues for women in the workplace. They are often designed for average-sized men, and their protective function may

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be reduced when they do not properly fit female workers [5].

Although not specifically discussed in the NIOSH fact sheet, occupational skin diseases are also a major hazard for working women. Data from the US Bureau of Labor Statistics show that of the 269,500 cases of nonfatal occupational illnesses reported in 2003 for both genders, 16% (43,400 cases) were skin diseases (Fig. 1) [7], the second most frequent cause of all occupational diseases reported. An occupational skin disease is one in which workplace exposure to some physical, chemical, or biologic hazard has been a causal or a major and necessary contributing factor in the development of the disease [8]. This article reviews the diagnosis and prevention of work-related skin diseases among female-dominated occupations in health care and cosmetology. Quality of life issues and the role of female gender in developing contact dermatitis are discussed.

Health care workers

Seventy-eight percent of the 9.6 million people employed in health care occupations in the United States are female, with dental hygiene (98.8%), dental assisting (96.5%), and nursing (92%) accounting for the highest percentages of women [2].

Nurses

The reported prevalence of occupational skin diseases in nurses is about 47.3% [9]. Among health care workers, nurses represent 58.5% of the occupational contact dermatitis cases [10]. Occupational contact dermatitis is a common problem in nurses, who are exposed to a wide variety of irritants and allergens. In a study conducted in 44 nurses with hand dermatitis (40 female), irritant contact dermatitis (ICD) was found to be occupationally relevant in 23% of the cases, and allergic contact dermatitis (ACD) was relevant in 18% [11].

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and coworkers [14] and by Allmers and coworkers [15], concluding that conversion to powder-free NRL gloves has resulted in a decreased frequency of occupational contact urticaria associated with NRL exposure. An increased awareness of latex allergy in health care settings, changes in NRL product manufacturing, improved diagnostic testing, and efficacy of preventive measures are other factors that have played a critical role in the reduction of the frequency of latex allergy [16].

ACD, a type IV hypersensitivity reaction, from rubber gloves is usually caused by rubber additives (accelerators and stabilizers), with thiuram mix and carba mix being the most frequent allergens found in some studies. In a 16-year period study, Gibbon and coworkers [17] demonstrated that there was a statistically significant increase in thiuram allergy among health care workers with hand dermatitis (OR, 2.55; 95% CI, 1.25–5.20; \( P = 0.01 \)), which peaked in the early 1990s. Nettis and coworkers [18] in 2002 evaluated 295 health care workers with glove-induced skin symptoms; thiuram mix (4%) and carba mix (3%) were the most frequent rubber-related allergens found in this study. Three years later, Clayton and Wilkinson [13] conducted a retrospective study of 224 health care workers with a diagnosis of hand dermatitis, and once again thiuram mix (8%) and carba mix (4%) were the most prevalent. Depree and coworkers [19], however, detected no thiuram in any of the recently manufactured latex and nitrile gloves.

Contact allergy can also be induced by disinfectants, such as glutaraldehyde and benzalkonium chloride [10]. Drugs handled by health care workers can play an important role as sensitizers. The most common sensitizers reported in a recent study were antibiotics (penicillins, cephalosporins, and amino-glycosides), followed by propacetamol hydrochloride and ranitidine hydrochloride [20]; of interest, the greatest numbers of sensitized patients in this series were nurses.

Needlestick injuries are a well recognized occupational hazard to health care workers, putting them at risk of acquiring an infectious disease from bloodborne pathogens. The reported risks of seroconversion following a contaminated needlestick injury have been evaluated in different studies [21–23] and are 0.31% for HIV infection [21]. For hepatitis B, the rates of seroconversion in nonimmunized health care workers range from 0.76% to 7.35% versus 0.23% to 2.28% in immunized workers [22]. There is a 6% risk of transmission of hepatitis C virus following a percutaneous injury with a contaminated needle [23]. The most accurate figures in needlestick and sharp injuries are derived from prospective studies that yield an estimated annual incidence ranging from 562 to 839 injuries per 1000 health care workers per year [24]. Nurses have the most patient contact, and it is not surprising that this occupational group comprises most reported cases [5,24]. Seven epidemiologic studies reported the breakdown of needlestick injuries by personnel category, and all indicated that most (42%–74%) of such injuries were suffered by nurses [25–31].

### Dental assistants

Dental personnel are exposed to a wide range of chemical compounds in the course of their clinical duties or technical procedures. In 2004, more than 96% of all dental hygienists and dental assistants were women [2]. Because of the nature of their job duties, dental assistants have more chemical exposures than dental hygienists. In addition to instructing patients on general oral health care and obtaining their records, dental assistants primarily handle instruments. They sterilize and disinfect instruments and equipment, and prepare instrument trays for various procedures and hand them to the dentist [32]. Moreover, according to their subspecialty, some dental assistants also prepare materials for impressions and restorations, remove excess cement used in the filling process, and place rubber dams on the teeth for isolation [32]. A recent Finnish study [33] conducted in 799 dental nurses (mostly dental assistants) revealed a 6.5% prevalence rate of occupational skin diseases in this population. Irritation constitutes a big problem accounting for up to 67% of work-related hand dermatitis in dental personnel [34]. Frequent hand washing and exposure to detergents and disinfectants and glove use comprise the most common causes of irritant dermatitis among dental personnel [33,35]. In addition, their skin may be exposed to grinding dust and frictional forces from holding small objects with sharp edges [36].

ACD and contact urticaria to components of protective rubber gloves are also frequently seen in dental workers. Rubber-related chemicals are among the most common causes of ACD in this occupational group [33]. NRL allergy with prevalence rates ranging from 1.8% to 10% [33,34,37] accounts for a greater frequency of reporting than ACD, however, because of the severity of its reactions. ACD caused by (meth)acrylates is a common finding among dental personnel [33,34,37]. (Meth)acrylates are esters of (meth)acrylic acid. Acrylic resins, also known as acrylics, are made by the polymerization of (meth)-acrylates [38] and are widely used as dental-
restorative materials. In several studies, acrylics and rubber-related chemicals remain as the most frequent contact allergens reported in dental personnel [33, 34, 37]. 2-Hydroxyethylmethacrylate, methylmethacrylate, ethyleneglycol dimethacrylate, and triethylene glycol dimethacrylate are the most frequent "occupationally related" acrylic allergens [34, 39].

Glutaraldehyde is a sporidical chemical used for cold sterilization and high-level disinfection of dental instruments. It is associated with a wide spectrum of adverse effects, such as skin and respiratory sensitization, and irritation [40]. Ravis and coworkers [41] reported that 79% of dental workers had been exposed to glutaraldehyde, and that glutaraldehyde-induced ACD was found to be eightfold more likely to occur among dental workers than healthy control subjects (10.9% versus 2%). Because of glutaraldehyde’s extensive adverse effect profile, two substitutes have recently been introduced: orthopthalaldehyde, and a mixture of hydrogen peroxide and peracetic acid. Orthopthalaldehyde, however, has been found to be a potential dermal and respiratory sensitizer. Sokol [42] has recently reported nine episodes of anaphylaxis in four patients following a urologic procedure using orthopthalaldehyde-disinfected cystoscopes. Although these substitutes seem to be safer alternatives, glutaraldehyde is still commonly used in dentistry. The most frequently reported reasons for not introducing glutaraldehyde substitutes are increased cost, damage to existing equipment, staining, and lack of apparent benefit from use of these new products [40].

Cosmetologists

Cosmetologists include hair stylists, beauticians, and manicurists [43]. They may also specialize in providing facials, scalp treatments, and applying cosmetics [44]. Aromatherapy is usually practiced by cosmetologists as part of their work [45]. Of interest, according to US Bureau of Labor Statistics job classification in 2004, 91.5% of those employed in the hairdressing, hairstylist, and cosmetology sector were women [2].

Hairdressers

The principal occupational hazard for hairdressers is contact dermatitis of the hands. The actual prevalence is difficult to determine, however, with estimates ranging from 10% to 20% [46] to nearly 79% [47]. Frequent and repeated exposure to water, detergents, hair dyes and bleaches, alkaline and acid permanent waves, metal equipment, and frictional forces leads to the development of hand dermatitis, a problem that frequently ends in work-related disability. ICD is a major problem during apprenticeship and early in the career of hairdressers, when repetitive wet work, such as shampooing and rinsing, results in damaged skin barrier function [48]. Hand dermatitis of the web spaces has been noted as a “sentinel event” for developing occupational skin disease in hairdressers [49]. ACD is more likely to develop later in their careers.

A significant increase in the frequency of occupational ACD in Spanish hairdressers has been reported over a 10-year study period [50]. Furthermore, a significant increase in sensitization to most allergens was also observed. Paraphenylenediamine in hair dyes is the most common allergen reported in hairdressing, causing up to 60% of the cases of ACD in this occupation [47, 48, 50, 51]. Glyceryl thioglycolate, a reducing agent in acid permanent wave solutions, is also a frequent sensitizer [52]. Glyceryl thioglycolate has the tendency to cause a strong ACD reaction, and sensitized hairdressers may present with a widespread dermatitis, involving the hands, arms, neck, and face [53]. Glyceryl thioglycolate accounts for up to 31% of ACD cases among hairdressers [46–48, 54], and in Germany a decline in its sensitization frequency has been observed since it was banned for use [54, 55]. Ammonium persulfate is a strong oxidizer used in hair bleaching agents. It is both an irritant and a sensitizer, and it less frequently causes immediate urticarial-type reactions. Borelli and Wuthrich [56] described a hairdresser with both immediate and delayed-type hypersensitivity to ammonium persulfate acquired during work. Another uncommon allergen is henna, a vegetable dye derived from the dried leaves and stem of Lawsonia inermis; its active component is lawson (2-hydroxy-1,4-naphthoquinone). Henna has been reported to cause immediate-type hypersensitivity reactions in hairdressers [57–59]. This vegetable dye rarely causes ACD, with most cases incorrectly attributed to henna when they were most likely caused by other coloring sensitizers, such as paraphenylenediamine, with which henna is sometimes mixed. Perez and coworkers [60], however, reported a patient with palpebral eczema and a strong positive patch test reaction to henna, which was used to dye her hair.

Atopy and nickel sensitivity are two important risk factors for the development of hand dermatitis in hairdressers. An atopic skin diathesis has been found significantly to increase the likelihood of developing ICD in the initial period of this profession [48, 51, 54, 61]. In 1986, van der Burg and coworkers [62]...
examined hairdressing apprentices and novice nurses; of those who had hand eczema, 45% were atopic, whereas only 17% of the remaining trainees without dermatitis were atopic. A decade later, Uter and coworkers [54] in their study found that a previous history of atopic eczema was twice as common among hairdressers in contrast to their clients (27.5% versus 14.5%).

Some reports have shown an association between dermatitis in hairdressers and nickel sensitivity [62]. The apparent increase in nickel allergy among hairdressers probably results from the preponderance of women in this profession and the much higher prevalence of nickel allergy among women. Holness and Nethercott [48] patch tested 53 hairdressers (87% women), 17% of whom exhibited a positive response to nickel sulfate. Likewise, from a total of 103 hairdressers studied by van der Walle and Brunsveld [46], 95 of them were also women, and nickel sulfate presented similarly a high frequency of positive reactions.

**Manicurists**

Also called “nail technicians,” manicurists work exclusively on nails providing manicures, pedicures, coloring, and nail extensions to clients. This profession is increasingly popular, and in 2002, personal appearance workers (US Bureau of Labor Statistics job classification) held about 754,000 jobs. Of these, manicurists and pedicurists accounted for about 51,000 jobs [63]. Currently, there are no recent data on adverse reactions related to the use of nail care products among consumers. In the 5-year study conducted 20 years ago by the North American Contact Dermatitis Group, however, nail cosmetics were found as the fourth leading cause of ACD from cosmetics [64]. In the consumer market, there is a wide variety of nail cosmetics, such as polishes, hardeners, extenders, wraps, and preformed nails. Liden and coworkers [65] described 18 cases of toluene sulfonamide formaldehyde resin nail polish allergy, which were referred to an occupational dermatology clinic with suspected work-related skin disease. Dermatitis was scattered involving the face, eyelids, neck, and hands; periungual lesions were noted in 11 cases. Patch testing was positive to toluene sulfonamide formaldehyde resin in all cases and the dermatitis resolved or improved significantly within a few weeks of stopping nail polish use in all but one case. Before diagnosis there were serious sociomedical consequences; nine were on sick leave, four were hospitalized, and two lost jobs. The presence of other contact allergies made the diagnosis easy to miss. Brun [66] reported a manicurist with contact allergy of hands to an orangewood stick used as a cuticle remover; and Lazarov [67] reported a case of perianal dermatitis caused by contact allergy to nail lacquer.

With the recent increase in the use of artificial or acrylic nails, the frequency of skin disorders related to acrylic nails and glues has also increased. In 1984, Shelley and Shelley [68] described a woman with small-plaque parapsoriasis caused by cyanoacrylate adhesive used on her fingernails. Despite the recommendations of a 1999 NIOSH bulletin [69], the reported prevalence of occupationally related acrylic nail allergy among manicurists is high, ranging from 10% to 15% [70]. Acrylics are thermoplastic resins that polymerize either at room temperature or by heating. Initiators, accelerators, and catalysts may be added to speed the process [71]. Acrylic monomers are powerful sensitizers. Nail technicians use different techniques to elongate and enhance nails (sculptured nails, light-curing gels, preformed artificial nails, and nail wrapping). In the 1950s, Canizares [72] was the first to report contact allergy to methylmethacrylate used in artificial nails in a manicurist. The following year, Fisher and coworkers [73] reported a similar occupational case. In the United States, the use of methyl methacrylate was prohibited in nail preparations by the Food and Drug Administration in 1974 [74]. Since then, ethylacrylate, butylacrylate, and other acrylics have been used, and adverse reactions to them have also been reported [39,75,76]. In a recent case Torres and coworkers [75] described the case of a manicurist who developed occupational rhinitis and ACD induced by the application of acrylic sculptured nails.

Recently, Sood and Taylor [39] reviewed 56 cases of acrylic contact allergy over a period of 15 years (1988–2002); 43 of the 56 patients were women. Exposure to acrylic nails was the most common source of contact dermatis in 25 cases, 7 of whom were nail technicians. The most common sensitizers found in this group were 2-hydroxypropyl methacrylate, 2-hydroxyethyl methacrylate, and ethylene glycol dimethacrylate.

In addition to contact dermatitis, manicurists may also sustain minor skin injuries working with sharp instruments, and are also at risk for skin infections [71].

**Aromatherapists**

Aromatherapy, a treatment using essential oils, has become increasingly popular. Its principal aim is to promote physical and psychologic well-being. It was developed in France, where topical application,
inhalation, or compresses were the most common uses for essential oils. In Britain, aromatherapy was introduced by the Beauty Therapy profession, and since then has generally consisted of the use of essential oils diluted in carrier oil and applied through massage [77]. Currently, aromatherapy is primarily performed by beauticians or cosmetologists [45].

Essential oils are aromatic substances extracted from flowers, plants, and wood resins by a variety of methods. Each essential oil is composed of many different chemical constituents, primarily terpenes and terpenoid molecules. Contact allergy from essential oils has been observed, most often to ylang-ylang; tea-tree (Melaleuca alternifolia); lavender; jasmine; citronella; narcissus; rose; sandalwood; cas- sia; lemon; orange; and clove oils [45,78]. The frequency of contact dermatitis from essential oils is unknown and nearly impossible to determine because they are components of most of the commonly used chemical fragrances [79].

Occupationally related ACD to essential oils has been reported in hairdressers [80], bar workers [81], citrus fruit pickers [82], and in a chemist with a particular interest in aromatherapy and massages [83]. There are only a few reports of occupational ACD from aromatherapy [78,84–88]. Selvaag and coworkers [87] reported a case of extensive dermatitis in an aromatherapist, who displayed positive patch test results to 17 out of 20 essential oils that she had used in therapy. It is important to emphasize that almost all of the patients presented in these reports were women, and hand dermatitis was their major complaint. Recently, Crawford and coworkers [78] evaluated the risk factors of hand dermatitis in a group of massage therapists, of whom 84% were women. This questionnaire study demonstrated that the prevalence of hand dermatitis in massage therapists is high and use of aromatherapy products in oils, lotions, or creams was found to be a significant independent risk factor (OR, 3.27; 95% CI, 1.53–7.02; \( P = .002 \)). Although some evidence suggested an increased risk of dermatitis for women therapists compared with men (OR, 2.91; 95% CI, 0.65–12.94; \( P = .16 \)), statistical significance was not reached because of the low number of men in this group.

**Discussion**

In epidemiologic studies, case reports, and reviews of various occupations, women are often reported to be at higher risk than men of developing hand dermatitis and ACD [89–92]. Multiple other risk factors have been implicated: previous or widespread atopic dermatitis (atopic skin diathesis); previous hand eczema; low irritant threshold; history of sensitive skin; metal allergy and job-specific allergy; age; race; specific occupational, avocational, and home exposures; and the number of women employed in a specific job [92–95]. Of these, endogenous (atopic skin diathesis) and exogenous (chemicals, water, salt, and friction) factors are the most important. A history of atopic eczema has been shown to double the risk of hand eczema in many occupational groups [93], but exceptions have been reported [96]. Modjtahedi and coworkers [91] reviewed the role of the gender of the individual as a factor in ACD. They concluded that female gender was a predisposing factor to increased risk for ACD mainly because of different exposure patterns rather than biologic difference between the sexes. In the same way, the higher prevalence of ICD among females is most likely caused by their increased exposure to irritants [97]. In the 2000 Danish work environment cohort study [98], 13% of the workforce reported skin problems on hands or forearms within the past 3 months (women 15%; men 10%). A significant increase was observed among women, especially in the age group between 30 and 39 years.

Recently, Templet and coworkers [99] reported that 56% of all hand dermatitis was occupationally related. Among women, ICD of the hands peaked in the third decade and then diminished, whereas ACD of the hands remained constant between 21 and 60 years of age. In this large patch test clinic study ACD was diagnosed almost twice as often as ICD but some allergens were not contained in standard patch test trays.

As reported, many female-dominated occupations involve extensive wet work (eg, cleaning, hairdressing, health care work). When women are asked about their occupations, they usually list “homemaker” as their second job. The development of hand dermatitis in this population, formerly called “housewives’ eczema” [100] or “housewives’ hands” [101], has been described for many years. Even though gender roles have changed over the past decades, women still perform most household activities, which mainly involve wet work and detergents. In a 10-year period epidemiologic survey in Italy, Sertoli and coworkers [102] found that “housewife’s activity,” which was considered an occupation in this study, was responsible for 43% of the cases of occupational ICD. Moreover, it has been demonstrated that the development of hand dermatitis during domestic work may vary among women in high-risk jobs. Women with-
out dishwashers and those who have children under the age of 4 may have a fourfold probability of acquiring hand eczema over women without these risk factors [95].

Lastly, a number of skin conditions are of particular concern to women, and have a negative influence on social contacts. ACD has been demonstrated to impact an individual’s quality of life, with females reporting a higher degree of emotional distress than males [103]. The impact of occupational contact dermatitis on quality of life was also evaluated in another study based on the Dermatology Life Quality Index and Short Form-36 [104]. There was no statistically significant difference between male and female median scores ($P = .98$); although females scored highest in problems associated with symptoms and feelings, daily activities, and leisure.

### Prevention

In addition to their impact on quality of life, occupational skin diseases also have a considerable economic impact. Skin diseases account for 16% of reported nonfatal occupational illnesses in private industry [7]. About 25% of affected workers lose time from work [105], and prognosis for some occupational skin disease is poor. Because most occupational skin diseases are preventable, an integrated approach to their control and prevention is required. Strategies in the prevention of occupational contact dermatitis include administrative, environmental, and personal measures [106]. Administrative measures encompass worker education and training regarding specific job hazards and protective measures. Environmental measures are most important and include (1) hazardous material elimination or substitution, which may be achieved by using less noxious substances that are still suitable for the task, including allergen alternatives; (2) isolation and enclosure of the work process; (3) exhaust ventilation (eg, the installation of ventilated work tables in nail salons to reduce the chance of ethyl methacrylate exposure among manicurists) [69]; and (4) good housekeeping. Personal measures include (1) application of emollients, which can be helpful in preventing hand irritation and ICD in various occupations including healthcare workers and hairdressers [107]; (2) personal cleansing and hygiene; and (3) personal protective equipment.

Personal protective equipment usually consists of gloves, garments, and boots. Since approximately 85% of all occupational skin diseases involve the hands, gloves are of great potential usefulness. Selection of a well-fitting and appropriate protective glove for the specific working situation is of utmost importance, and can be performed by taking into consideration user acceptance, glove performance, and cost [108]. Selected sources of information on protective equipment are listed in Box 1.

### Box 1. Sources of information on gloves

<table>
<thead>
<tr>
<th>Manufacturers</th>
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<tbody>
<tr>
<td>Ansell Edmont, 1-800-800-0444 (<a href="http://www.ansell-edmont.com">www.ansell-edmont.com</a>)</td>
</tr>
<tr>
<td>Best Gloves, 1-800-241-0323 (<a href="http://www.bestglove.com">www.bestglove.com</a>)</td>
</tr>
<tr>
<td>MAPA Gloves, 1-800-537-2897 (<a href="http://www.mapaglove.com">www.mapaglove.com</a>)</td>
</tr>
<tr>
<td>North Safety, 1-843-745-5900 (<a href="http://www.northsafety.com">www.northsafety.com</a>)</td>
</tr>
<tr>
<td>Allerderm, 1-800-365-6868 (<a href="http://www.allerderm.com">www.allerderm.com</a>)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Internet</th>
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<tbody>
<tr>
<td>The Michigan State University, Office of Radiation, Chemical and Biological Safety website: <a href="http://www.hazmat.msu.edu:591/glove_guide/">http://www.hazmat.msu.edu:591/glove_guide/</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Books</th>
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### Table 1

<table>
<thead>
<tr>
<th>Glove material</th>
<th>Glove type</th>
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<tbody>
<tr>
<td>Household vinyl</td>
<td>Allerderm Heavy Duty</td>
</tr>
<tr>
<td></td>
<td>Nyplex by Magla</td>
</tr>
<tr>
<td></td>
<td>Mr Clean Heavy Duty Vinyl Glove</td>
</tr>
<tr>
<td></td>
<td>by Magla</td>
</tr>
<tr>
<td>Industrial vinyl</td>
<td>Monkey Grip by Ansell</td>
</tr>
</tbody>
</table>


Table 2
Selected synthetic gloves for healthcare workers with latex allergy or rubber contact allergya

<table>
<thead>
<tr>
<th>Glove material</th>
<th>Accelerators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic isoprene latex</td>
<td>Carba mix or thiuram mix / MBT</td>
</tr>
<tr>
<td>Vinyl</td>
<td>No accelerators</td>
</tr>
<tr>
<td>Nitrile</td>
<td>Carba mix / MBT</td>
</tr>
<tr>
<td>N-Dex Free by Best Glove</td>
<td>No accelerators</td>
</tr>
<tr>
<td>Neoprene</td>
<td></td>
</tr>
<tr>
<td>Micro-Touch DermaPrene E by Ansell</td>
<td>Thiourea</td>
</tr>
<tr>
<td>DermaPrene Ultra S by Ansell</td>
<td>No accelerators</td>
</tr>
<tr>
<td>Biogel S by Regent</td>
<td>DPG</td>
</tr>
<tr>
<td>Duraprene Synthetic S by Allegiance</td>
<td>Carba mix</td>
</tr>
<tr>
<td>Neolon PF S by Maxxim Medical</td>
<td>Carba mix</td>
</tr>
<tr>
<td>Polyurethane</td>
<td>No accelerators</td>
</tr>
<tr>
<td>Sensicare Advantix by Maxxim Medical</td>
<td>No accelerators</td>
</tr>
<tr>
<td>Block polymers</td>
<td>No accelerators</td>
</tr>
<tr>
<td>Elastylite S by ECI Medical Tech</td>
<td>No accelerators</td>
</tr>
<tr>
<td>ElastylPlus/Elastyren S by ECI Medical Tech</td>
<td>No accelerators</td>
</tr>
</tbody>
</table>

Abbreviations: DPG, diphenylguanidine; E, exam; MBT, mercaptobenzothiazole; S, surgical.

a Information current as of October 2005.

gloves are listed in Box 1. Of special note are laminated, multilayered polyethylene-ethylvinylalcohol gloves, which offer better protection than rubber gloves for dental assistants and hairdressers. Selected alternative gloves for patients with rubber contact allergy and latex allergy are listed in Tables 1 and 2.

Summary

Women comprise 50% of the working population in the United States. They are predisposed to contact dermatitis because of job selection to high-risk occupations and their avocational and homemaking activities. Because occupational skin diseases continue to be a major cause of morbidity and lost earnings often with a poor prognosis, early diagnosis and prevention is a major health care priority.

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Dermatologic Problems of Older Women

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Women aged 65 and older constitute 7% of the United States population [1]. The total senior population stands at 35 million, which represents 12.4% of all Americans. Older women make up the majority of senior Americans. The percentage of elderly men and women has increased 100% between 1960 and 1994. These increases will continue as the baby boomer group (born between 1946–1964) begins to enter the sixth decade. By 2025, 20% of the United States population is expected to be 65 and older [2]. In both developed and developing nations the number of older people is increasing. Issues in geriatric dermatology therefore cross cultural and ethnic lines. The term geriatric traditionally has been used to describe the senior group aged 65 and older. As we live longer and have more active and healthy lifestyles, 50 is the new 40 and 70 becomes the new 60. Increasing longevity gives rise to issues in skin health that were not addressed when the average lifespan was 55 years.

This article focuses on women aged 65 and older. Some of the more common cutaneous disorders and treatment options in this population are reviewed and evolving issues for elderly women in the 7th through 10th decades are addressed. The top dermatologic diagnoses for the elderly are listed in Box 1. A review of the general dermatologic literature shows the difference in incidence of these disorders in elderly women versus men is generally insignificant. The lifelong environment of the skin is an important factor when evaluating the elderly patient. Photodamage, radiation exposure, and occupational environment often affect skin health. Climate has a significant impact on the skin of the elderly. Xerosis and pruritus are more of a problem in arid climates than in humid areas. Hot, humid areas may result in more cases of intertrigo. Cold climates in which individuals are exposed to indoor heating may eventuate in xerosis.

Skin changes in elderly women

The normal cell cycle of the epidermis is 26 to 42 days and results in desquamation of skin cells. In aging, the length of the cell cycle increases. The epidermal turnover rate slows 30% to 50% between the third and eighth decades of life. The cells in the superficial stratum corneum are older and may have impaired function and desquamation [3]. Intrinsic aging of the skin is associated with the following abnormalities: abnormal barrier homeostasis, reduction in stratum corneum lipid biosynthesis, altered drug permeability, increased susceptibility to contact irritants and allergens, and xerosis [4,5]. Clinically, this manifests as flaking of corneocytes that make the skin surface appear dull and feel rough. There is increased epidermal filaggrin in aging skin epidermis. The epidermal–dermal junction histologically shows flattening of the rete ridges, and in women there is a sharp decline in the number of dermal papilla–epidermal rete ridge interdigitations occurs between ages 40 and 60. There is a greater than 50% reduction in the number of interdigitations between the third and ninth decade. Biochemical abnormalities seen with intrinsic aging of the skin include changes in the biophysical properties of collagen and elastin fibers. There are increased collagen fibrils with an increase...
in collagen III:I ratio, cytokine dysregulation, and decreased response to growth factors, particularly in the interleukin-1 family [6]. A listing of skin changes and their causes in geriatric women is listed in Table 1.

Thick skin

The skin of postmenopausal women histologically shows a thinned epidermis with flattening of the rete ridges. Women 65 and older demonstrate a loss of approximately 20% of dermal thickness [7]. It is currently believed that decreases in skin thickness seen with aging are caused by hormonal effects on collagen, elastic fibers, and dermal hyaluronic acid content [8]. These changes predominate in women compared with men and it has been postulated that estrogen has an important role in determining skin thickness. The decline in skin collagen decreases 30% after the first 5 years of menopause. In studies that measured skin thickness in a population of postmenopausal women with and without hormone replacement therapy (HRT), the HRT group had a skin collagen content up to 48% higher than the non-HRT group. In addition, HRT restored the rete pattern at the epidermal–dermal junction [9]. Glycosaminoglycans, important contributors to dermal thickness, may also be affected by estrogen and have been shown to increase from low to high levels in postmenopausal women on HRT [10–15]. In addition to HRT, studies show that topical estrogens may preserve skin thickness by increasing the collagen and glycosaminoglycans. One study demonstrated improved elasticity, firmness, and moisture content, and decreased wrinkle depth [11,12,15]. Although studies indicate that oral and topical estrogen may be useful to prevent the skin thinning that occurs with menopause, there may be negative side effects to both. Estrogen supplementation may be contraindicated in some women and should be used under physician supervision.

Xerosis

Dryness is a frequent finding in both women and men over 65 years of age. It is a normal finding in aging skin. Xerosis, or dryness of the skin, affects at least 75% of this age group, thus making it the most common skin disorder in the elderly [16]. Dry skin results from abnormalities in the stratum corneum that occur intrinsically with aging. Decreased moisture in the stratum corneum is secondary to an increase in stratum corneum transepidermal water loss (TEWL). The increased TEWL is secondary to a defect in the permeability barrier allowing excessive water to be lost to the atmosphere versus staying in the stratum corneum. The permeability barrier is affected by the reduction in stratum corneum lipid biosynthesis [17]. The stratum corneum lipids are ceramides, triglycerides, and fatty acids [18]. These lipids are integral to the epidermis and function to prevent TEWL. Deficiency in any one of these may result in dry skin [19,20].

The stratum corneum abnormality of decreased epidermal filaggrin leads to decreased natural moisturizing factor (NMF). The NMF has strong humectant properties and maintains the hydration of the outermost layers of the stratum corneum [18,21]. For the skin to appear and feel normal the water content of the stratum corneum must be greater than 10% [22].

Table 1

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>Etiology</th>
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<tbody>
<tr>
<td>Dull gray-white color</td>
<td>Heaps of corneocytes that yield a rough surface unable to refract light</td>
</tr>
<tr>
<td>Rough, dry feeling</td>
<td>Dehydrated corneocytes curled up</td>
</tr>
<tr>
<td>Stellate scars</td>
<td>Torsional stresses on photo-damaged skin with a weak epidermal–dermal junction</td>
</tr>
<tr>
<td>Purpura</td>
<td>Decreased interdigitation of dermal papilla and epidermal rete ridges</td>
</tr>
<tr>
<td></td>
<td>Decreased arteriole elastic content leading to vascular fragility</td>
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</table>
It has been shown that environmental humidity is a major determinant for the rate of evaporative water loss from stratum corneum [23]. Excessive bathing, especially with harsh soaps, detergents, and alcohol or acetone-based products may contribute to stratum corneum barrier disturbances. Some elderly women continue to shower and bathe as frequently as they did when they were younger. Excessive bathing in combination with low humidity and coolness of fall and winter months may result in exacerbation of xerosis. It has been shown that hypocholesterolemic drugs may result in dry skin [18]. Clinically, with xerosis the outer layers of the skin become irritated, inflamed, and itchy. The dull gray-white color of the skin is secondary to the lost cohesiveness of the stratum corneum and to roughness, which lead to the inability to refract light. The uncomfortable feeling of dry, rough, scaly skin and the aesthetic concerns that women in particular have regarding this condition fuel the moisturizer market in the United States to over $1 billion.

Treatment of xerosis is based on hydration of the skin. This is accomplished in two ways. (1) Prevent TEWL by coating the stratum corneum with an occlusive moisturizer such as petrolatum or lanolin-based product. (2) Increase epidermal water absorption with humectants, which are water soluble compounds present in moisturizers with high water absorption capabilities.

Patients should be educated as to the importance of overall hydration and moisturization for their general skin health and function. Moisturized skin is more flexible than dry skin and responds more favorably to environmental insult. In arid climates with low humidity women should be encouraged to moisturize the entire body twice per day with a product that has both occlusive and humectant properties. Humidifiers that increase ambient air water content may be beneficial.

Pruritus

Pruritus, or itch, may be the most common symptom of skin disease, particularly for the seventh and eighth decades [24]. Itch is defined as a sensation that makes the person scratch the affected area. In classic pruritus, itching occurs in the absence of skin findings. In elderly women, pruritus often results initially from xerosis, in which the skin is dry and rough. It may frequently occur in the evening or at other quiet times. This itch–scratch cycle eventuates in lichenification, excoriations, infection, and traumatic purpura (Fig. 1). Dermatologists should review the history of medications and perform a full-body skin examination to look for any cutaneous findings.

The patient should also be aware of any environmental situations that promote itching. These may include home stress, anxiety, itching, pollen, grasses, wool intolerance, pets, and bedding. Certain food intolerances may trigger pruritus without necessarily indicating allergy. A complete medical workup is strongly encouraged in pruritus of unknown cause. Pruritus may be associated with systemic disease, including depression and anxiety. In systemic disease, it may be the presenting symptom of internal malignancies such as lymphoma and leukemia. It may also be associated with endocrine abnormalities. A psychologic evaluation should be considered in some elderly patients who have chronic pruritus.

Emollients are the cornerstone of therapy and should be reviewed and prescribed in every patient with pruritus. There are emollients that have additional agents to provide topical anesthetic action by depressing the cutaneous sensory receptors. This family includes menthol, camphor, phenol, and doxepin [24,25]. Local anesthetics that interfere with the transmission of impulses along sensory nerve fibers may also be used to treat pruritus. Benzocaine, tetracaine, lidocaine, prilocaine, and other relatives are best used in small amounts to discrete areas for short treatment periods and are not recommended for daily use over large body surface areas. Ice or freezing is an inexpensive and effective way to decrease pruritus. Calamine, oatmeal baths, milk baths, and chamomile preparations have all been reported to give relief in various types of pruritus. Pruritus associated with anxiety or depressive disorders may respond well to appropriate therapeutic agents.
Seborrheic keratosis

Often fondly referred to by seniors as barnacles, the seborrheic keratosis (SK) is the most common skin growth in women 65 and older. The SK is a benign epidermal neoplasm with many variants and clinical presentations. SKs frequently necessitate an office visit because they can be dark brown, irregular in shape, and raised, thus resembling a malignant melanoma. The patient or family members may insist that the lesion be checked. This actually provides a wonderful opportunity for the physician to perform a full-body skin examination, inspecting all exposed and covered surfaces. Although benign, the SK can be annoying from functional and cosmetic standpoints. SK often is accompanied by acrochordons in the submammary and axillary locations. The most common cause of SK is genetic.

Treatment options for seborrheic keratosis include (1) Liquid nitrogen cryotherapy. (Benefits: affordable, effective. Risks: postinflammatory pigmentation abnormalities especially in type III to VI skin, slow healing process in all skin types.) (2) Electrocautery. (Benefits: affordable, effective, quick healing. Risks: longer procedure, hyperpigmentation in type III to VI skin if done too vigorously.) (3) Laser. (Benefits: effective, quick healing, less risk for pigmentary abnormalities. Risks: cost.)

Variants of SK include:

- Stucco keratoses: Gray, white chalky plaques on lower legs usually seen in Fitzpatrick type I, II skin that respond well to liquid nitrogen. Follow-up and prevention should include a plan of sun protection factor, keratolytics, and rejuvenation procedures, such as intense pulsed light or chemical peeling.

- Dermatosis Papulosa Nigra: Soft brown papules of the face and neck in skin types III to VI that respond well to electrocautery and laser. Patients should be forewarned that postprocedural hypo- or hyperpigmentation may occur and is transient.

- Acrochordons: Skin tags. Often accompanying SK in the same area of the body. Best removed by scissor excision or electrocautery; laser can be used.

Most of these procedures are best performed with topical anesthetic alone or as an adjuvant to the local injection.

Patients and physicians should be aware that Medicare and many third party payers may refuse reimbursement for treatment of seborrheic keratoses unless medical necessity can be documented. Appropriate indications for treatment, which require chart documentation, include intense itching, pain, inflammation, bleeding, infection, if the lesion is subject to recurrent trauma, or if it obliterates vision or an orifice [25].

Rash of unknown origin

The rash can be a vexing problem in elderly skin as it may not have a classic presentation. A strong knowledge of differential diagnosis is key to helping diagnose a rash. Eczematous dermatitis is the most common cause of a rash in the older female. The most common diagnoses include contact dermatitis, nummular dermatitis, asthetotic eczema, gravitational dermatitis (stasis dermatitis), and lichen simplex chronicus.

Asteatotic dermatitis (eczema craquele), also known as winter itch

This common pruritic dermatitis occurs primarily in older persons. It may be related to high temperatures and low humidity associated with heated houses or desert climate. The primary sites of involvement are the legs, arms, hands, and trunk. Clinically this presents as dry, cracked, and fissured skin with scaling, pruritus and, in advanced stages, features of lichen simplex chronicus. Prevention and treatment options include increasing the environmental ambient humidity with room humidifiers, decreasing the frequency of bathing and showering in hot soapy water that dries the skin, and liberal application of emollients. In addition, topical corticosteroids for severe eczematous component may be used for a limited duration.

Drug eruptions

There is always a reason and a dermatologist is trained to find it. Using the tools of history, morphology, and location, the culprit usually is identified. Historically a drug rash may start any time from minutes (fixed drug eruption) to months (gingival hyperplasia from phenytoin) after exposure to the offender. Morphologically the reactions are mostly exanthems and urticaria [26]. Infrequently a patient may present with pruritus and no skin findings. A clinical clue may be a positive wheal and flare reaction. Location is especially helpful in diagnosing contact dermatitis and photosensitivity reactions. The most common causes of drug eruptions in the elderly
Female are vitamins and supplements (chondroitin sulfate/glucosamine formulations); herbal mixes; hormonal wellness formulations; antibiotics including penicillin, ampicillin, amoxicillin, trimethoprim-sulfamethoxazole; some statins; cardiovascular medications (captopril, levamisole); and nonsteroidal antiinflammatory agents.

Approaches to evaluating a possible drug eruption are:

- Review the complete medication list with particular attention to the timeline of current drugs.
- Ask the patient when each medication was started. Encourage the patient to bring medications to the office.
- Review over-the-counter products. Start sequentially in the morning and continue throughout the day, ending with sleep aids.
- Review dietary habits, including new foods. It is often helpful to ask the spouse/partner.
- Interview the patient, spouse/family/caretakers at least three times on different occasions to allow for memory lapses.

**Intertrigo**

Intertrigo is seen frequently in older women. Clinically it presents as erythematous macerated areas in skin folds. It may burn or itch, and as it progresses fissures, erosions, and even infection may result. The submammary area is the most frequent site, but other areas affected may be subaxillary, genitocrural, gluteal, and interdigital skin. The primary cause of intertrigo is friction that results from two surfaces in apposition [27,28]. In addition to redundant skin, risk factors for development of intertrigo include obesity, heat, humid weather, occlusive clothing, prolonged and frequent sweating, and diabetes. Macerated areas may be colonized with yeast and dermatophytes. Secondary infection may occur with candida and bacteria including streptococci, staphylococci, pseudomonas, or corynebacteria. Although intertrigo has a distinctive clinical picture, other diagnoses in the differential may be overlooked, including erythrasma, seborrheic dermatitis, inverse psoriasis, tinea cruris, and lichen simplex chronicus. Treatment for intertrigo involves a complete review of systems with particular concern about underlying diabetes. Treatment is focused on relieving maceration and treating any underlying infection. Maceration may be reduced by drying agents, non-occlusive clothing, air conditioning, and weight loss. A review of proper cleansing and drying should be covered.

Warm (not hot) air blow-dryers may help dry the submammary area in women with pendulous breasts or prominent skin folds. Mild antibacterial soaps are excellent for prevention and maintenance, but can be harsh and irritating to acutely inflamed skin. An appropriate topical antibiotic or antifungal agent may be used to treat intertrigo. Systemic medications may be needed for severe or refractory cases.

**Seborrheic dermatitis**

Seborrheic dermatitis frequently is seen and misdiagnosed or overlooked entirely in the elderly. Older women who complain of a facial rash or redness are often given the diagnosis of dry skin or rosacea, when in fact they have seborrheic dermatitis. Although seborrheic dermatitis affects infants and younger people, it becomes more common with advanced age. Seborrheic dermatitis in the elderly may be associated more frequently with genitocrural involvement that mimics tinea cruris or intertrigo. Scalp involvement is frequent. The clinical picture varies greatly from faint erythematous plaques with fine scaling of the eyebrow, glabella, and malar area of the face to thick, yellow, greasy scales or erythematous patches. Seborrheic dermatitis may be more common in people with neurologic disorders such as Parkinson disease, ischemic infarcts, and Alzheimer disease. It may also be associated with diabetes mellitus. Its abrupt appearance in an older person may herald an underlying medical problem [27]. Treatment options include cleansing with selenium sulfide, zinc pyrithione, or ketoconazole-containing preparations, and application of topical ketoconazole cream. Topical corticosteroid preparations are effective, but particularly when used in high concentrations or for a prolonged period of time may cause steroid rosacea, telangiectasia, or atrophy, especially when used on the female face. Topical pimecrolimus cream and tacrolimus ointment, alone or in combination with ketoconazole shampoo or cream, have been effectively used off-label for the treatment of facial seborrheic dermatitis.

**Herpes zoster**

The incidence of herpes zoster is increased in older women and men. A major complication of herpes zoster in the elderly is development of postherpetic neuralgia, the incidence of which is as high as 20% in persons 60 years and older. The unilateral dermatomal eruption usually presents as erythematous
papules or vesicles associated with pain, burning, or itching. Rarely the patient may complain only of burning pain or itching in a dermatomal distribution (zoster sine herpete). Because some presentations are atypical or physical findings minimal, correct diagnosis requires a high index of suspicion. Early diagnosis and treatment of herpes zoster may minimize the intensity and duration of postherpetic neuralgia. Whether or not skin lesions are present, systemic antiviral therapy should be initiated promptly, and is most efficacious when begun within 72 hours of the onset of symptoms. Acyclovir, valacyclovir, and famciclovir are all appropriate drugs, and the patient’s renal function should be considered when dosing. The use of systemic corticosteroids in the prevention of postherpetic neuralgia remains controversial, and particularly in patients with other comorbid conditions the risks and benefits must be carefully weighed before use. The varicella vaccination that is now routinely offered to children may help decrease the incidence of herpes zoster in future generations.

**Actinic keratosis**

The actinic keratosis (AK) is the most common precancerous skin lesion. It occurs primarily in light skin types [29]. It affects over 50% of the elderly fair-skinned persons in hot, sunny climates [29,30]. The diagnosis of AK has increased throughout the United States. This may be attributed to the increased aging of the population and a heightened awareness of AK as a precursor to squamous cell carcinoma. AKs present on sun-exposed body surfaces and photo-damage accompanies them. Clinically, they are rough white scales overlying a skin-colored or reddish-brown macule or papule. They may be diagnosed best by running the hand over the skin surface. Actinic keratoses are perhaps most significant because of their risk for progression to skin cancer. There is histologic evidence supported by clinical pathologic correlation showing the progression of AK to in situ and invasive squamous cell carcinoma (SCC) [31–33]. Actinic keratoses may also serve as a marker for people at increased risk for development of malignant melanoma [34]. The cosmetic appearance and rough feel of AKs may be the reason an older patient seeks medical attention; in some cases, the patient perceives the AKs as being dry skin. This provides an excellent opportunity to discuss general skin care, principles of sun avoidance, ultraviolet (UV) sun protection, and the need for regular skin examinations to prevent the development and growth of precancers.

Treatment for AKs must be tailored to the age and abilities of the patient and should address three crucial areas: prophylaxis, destruction, and preventive maintenance. The dermatologist is well trained to select agents and design a treatment protocol that involves all three (Table 2).

**Prophylaxis**

Prophylaxis involves sun avoidance and UV protection, including the regular use of sunscreen. Topical retinoids have been shown to prevent formation of AKs [35].

**Lesion destruction**

Treatment options for AKs in older women include:

**Cryosurgery.** Liquid nitrogen is probably the most frequently used treatment. Application by Q-tip or by spray can result in scaling scabs which take weeks to heal. It is best used on discrete lesions. Hypopigmentation may be an undesirable result when used in tanned or dark skin types.

**Topical chemotherapy.** Locally applied 5-fluorouracil, imiquimod, and diclofenac sodium are increas-

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ingly becoming the treatment of choice for AKs. These products are well suited for multiple AKs, which are frequently present on the sun-damaged skin of the forehead, chest, and forearms.

Each agent has its own mechanism of action and a review of the potential risks and complications of these agents is highly recommended before their use [36]. The most frequent problem is the development of an exaggerated reaction to the product. This may be secondary to a brisk reaction from many precancerous lesions in a small area, or it may result from contact dermatitis to the agent itself or one of the vehicle agents. Exaggerated reactions other than contact dermatitis can be treated by discontinuing the agent for several days and resuming with a decreased dosing schedule. Posttreatment topical corticosteroid preparations may reduce the inflammation from an exaggerated response. To reduce anxiety, patients should be informed before treatment about the dramatic-appearing responses that can be expected. These agents may be used alone or in combination with liquid nitrogen cryosurgery.

Photodynamic therapy. Photodynamic therapy involves application of a sensitizing dye such as 5-aminolevulinic acid, which accumulates in precancerous lesions. After an appropriate incubation period, the area is exposed to light and both clinical and subclinical lesions are destroyed by oxygen free radicals that develop in the light reaction. Side effects may include discomfort during the treatment and postprocedure erythema.

Maintenance and prevention

Diligent use of sunscreens is fundamental. Chemical peels, topical treatments and light-based therapies have shown effectiveness and promise.

Nonmelanoma skin cancer and malignant melanoma

Basal cell carcinoma (BCC) and SCC are the first and second most common malignant neoplasms of the skin in the white population, at an estimated 900,000 and 200,000 cases per year, respectively. The incidence of these malignancies increases with age and is directly related to exposure to UV radiation and degree of inherited skin pigmentation. The incidence is higher in men than women; however, the incidence in women has been on a steady increase in recent years [37]. Both BCC and SCC occur in ethnic skin types including African Americans, but at a much lower prevalence. The incidence of malignant melanoma has increased in women. Lentigo malignant melanoma (LMM) is the least common variant of cutaneous melanoma, representing 4% to 15% of all melanoma patients [38]. It is diagnosed most frequently in older patients, with a median age at diagnosis of 65 years. LMM is a slow-growing insidious lesion that may resemble an enlarging freckle. LMM has most of the atypical features (ABCDs) that are associated with melanoma [38]. Topical chemotherapeutic agents increasingly are being studied for the treatment of nonmelanoma skin cancer (NMSC) and LMM. The initial research has been promising and provides an alternative to the elderly patient who does not want or cannot tolerate a potentially lengthy surgical procedure. In this population, debulking a large NMSC by using a topical chemotherapeutic agent before surgery may be an option [39]. Although they may be resistant to getting undressed, a complete skin examination is important in elderly patients, especially those at high risk for skin cancer development. A full-body skin examination should include inspection of the scalp, submammary area (Fig. 2), and digital web spaces where skin cancers may easily go undetected.

Solar purpura

A frequent finding in elderly women, solar purpura is caused by trauma and torsional stresses in photo-damaged skin. The use of blood-thinning agents such as aspirin, NSAIDs, and Coumadin may contribute to the purpura (see section on Thin Skin elsewhere in this article).
Alopecia in elderly women

Alopecia is not an infrequent finding in elderly women. Although medications, chronic disease, and telogen effluvium may cause alopecia, most alopecia in this age group is caused by female pattern hair loss (FPHL). The frequency and severity of FPHL increases with age [40]. FPHL begins anytime past menarche and tends to be in one of two patterns: diffuse central thinning or frontal thinning. Most women with FPHL have no biochemical evidence of androgen excess [41]. There is a subset of women who have androgen excess associated with hirsutism, acne, and irregular menses. This usually is seen in younger age groups. Screening tests include free or total testosterone and dehydroepiandrosterone (DHEA). Abnormal values of testosterone are greater than two and a half times normal, or greater than 200 mg/dL. Abnormal DHEAS is greater than two times normal or 400 µg/dL. Abnormal values in a postmenopausal woman warrant evaluation for an underlying tumor.

There are few available medical treatments for FPHL. Currently 2% topical minoxidil solution is the only FDA-approved treatment for androgenetic alopecia in women. The 5% solution is also effective, though not FDA approved, and may result in facial hypertrichosis. Women over 65 who have hyperandrogenism may respond to spironolactone, 100 to 200 mg/d. Because of the diuretic effect of spironolactone, patients must be instructed to keep well hydrated. Serum potassium should be monitored. Finasteride 1 mg/d did not prove to be effective in postmenopausal women with FPHL [42], although there have been anecdotal reports of increased hair growth with its use. Surgical treatments for hair loss include hair transplants and less commonly scalp reduction. These are used primarily in men. The commercial hair restoration industry is thriving. Wigs, hairpieces, hair systems (adhesive bases with attached hair pieces), and hair extensions (such as hair weaves) can cover an exposed scalp. Powders, sprays, and sticks tinted to camouflage hairless areas are available. The Internet is an excellent resource for these cosmetic aids.

Rosacea

Rosacea is a common skin disorder that peaks in the third and fourth decades. Women are affected more often than men in the earlier stages at a 3:1 ratio and have a milder course. They are less likely than men to develop late stage rhinophyma. Rosacea is associated with solar elastosis. A new classification system developed by the National Rosacea Society can assist a clinician in formulation of a treatment plan [43]:

- Subtype 1: Facial redness; may respond to topical metronidazole, azelaic acid, vascular laser, intense pulse light as needed.
- Subtype 2: Papules and pustules; treatment with combination therapy that might include topicals and systemic antibiotics. Topical immunomodulators may be effective.
- Subtype 3: Facial skin growth, thickening (rhinophyma); treatment with systemic antibiotics combined with ablative lasers.
- Subtype 4: Ocular rosacea; ophthalmology referral, systemic antibiotics, artificial tears.

Topical medications that may be beneficial in rosacea are azelaic acid, clindamycin/benzoyl peroxide-based products, retinaldehyde products, sodium sulfacetamide/sulfur, vitamin C products and derivatives [44]. Light/laser treatments alone or in combination with topical and systemic medications have shown efficacy.

Legal issues in elderly women

With an increasing elderly population, the dermatologist will be faced with making health care decisions that will impact the patient and the patient’s family and caretakers. The legal authority for advance health decisions law that became effective July 1, 2000 defines a health care decision as any decision made by a patient or patient’s agent, conservator, or surrogate regarding the patient’s health care [44]. These decisions include:

- Selection and discharge of health care providers
- Approval or disapproval of diagnostic tests, surgical procedures, and programs of medications
- Directions to provide, withhold, or withdraw artificial nutrition, hydration, and care, including cardiopulmonary resuscitation

Elderly patients who are unable to speak or communicate for themselves should have an advance health care directive (AHCD). This directive includes both an individual health care instruction and a power of attorney for health care. The AHCD is not just for critical situations; it may be necessary for temporary incapacitation, which can occur for anyone at any age.
The Power of Attorney for Health Care (PAHC) is a written document designating an agent for making health care decisions. This document was formerly known as a durable power of attorney for health. Elderly patients who outlive family or friends or who are geographically separated from family should have an individual health care instruction. It describes a patient’s ability to make written or oral directions for his or her own health without necessarily naming an agent or PAHC.

In the absence of a PAHC the physician usually turns to the next of kin to make health care decisions for incapacitated persons, unless there is a family disagreement. PAHC is also important for non-married couples and domestic partners. California recognizes and enforces a written health director or PAHC. Not all states recognize California’s PAHC. For patients who winter or summer outside of their state, an approved out-of-state form should be used. Conservatorship is the gold standard rendered by the court for incapacitated individuals. It is a court-ordered mandate that gives one person complete authority for medical decision making.

Summary

Women are living longer today, composing the majority of persons aged 65 and older. Their dermatologic needs are unique and cross ethnic and cultural lines. With this increased life expectancy comes an increased occurrence of skin disorders. The identification and treatment of these conditions is important for the practicing clinician.

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