

# Modern Aesthetics®



## UNDERSTANDING AND TREATING ESTROGEN DEFICIENT SKIN: A PANEL DISCUSSION ABOUT AN ENTIRELY NEW CATEGORY OF SKIN CARE

Biopelle, Inc. has launched Emepelle, the first and only clinically proven skin care line that safely and effectively helps address estrogen deficient skin (EDS) with revolutionary, new MEP Technology™. To coincide with the launch, a panel of leading dermatologists convened recently to discuss the pathogenesis of EDS and how to capture and counsel patients facing this condition. Overall, the dermatologists are extremely enthused about this all-new category of skin care that can address a previously unmet need in perimenopausal and menopausal female patients.



### JOEL L. COHEN, MD, MODERATOR

Director, AboutSkin Dermatology and DermSurgery in Greenwood Village and Lone Tree, CO; Associate Clinical Professor in the Department of Dermatology at the University of California Irvine.



### DIANE BERSON, MD

Private practice, New York City; Associate Professor of Dermatology at Weill Cornell Medical College and an Assistant Attending Dermatologist at the New York-Presbyterian Hospital.



### DORIS DAY, MD

Private practice, New York City; Clinical Associate Professor in the Ronald O. Perelman Department of Dermatology at NYU Langone Health.



### JEANINE DOWNIE, MD

Director of image Dermatology in Montclair, NJ; Assistant Attending at Mountainside and Overlook hospitals in New Jersey.



### SABRINA G. FABI, MD

Dermatologist and dermatologic cosmetic surgeon in San Diego; Assistant Clinical Professor in the Department of Dermatology at the University of California, San Diego.

### ESTROGEN DEFICIENCY AND LACK OF CAUSAL AWARENESS

Many of the causes of intrinsic and extrinsic skin aging are widely recognized and understood, including advancing age, genetics, photo-damage, pollution, stress, smoking, and repetitive facial expressions, but the rapid drop in estrogen that occurs in women around the time of menopause has been underappreciated as a causal factor in skin aging.

**Joel L. Cohen, MD:** Up until now, there has been a lack of awareness of some of the signs of estrogen deficiency in the skin. Estrogen at normal levels in the skin is known to enhance many cutaneous factors including: skin rigidity, elasticity, wound healing, hydration, epidermal and dermal thickness, blood flow, extracellular matrix components, moisture retention, and wrinkle prevention.

**Diane Berson, MD:** Women don't necessarily realize that hormonal changes are causing their signs of aging. They may associate their dryness with menopause because they also have vaginal dryness, but they don't typically realize that estrogen loss is responsible for the other changes in the skin that they are experiencing. They think that these changes are due to aging or chronic photodamage.

**Dr. Cohen:** Many people simply think of estrogen deficiency as causing vaginal dryness without attributing some of the same issues specifically to the skin. In fact, there is a 30 percent drop in collagen during the first five years of menopause, according to a study, and this is likely why women start noticing fine lines and wrinkles as they approach or enter menopause.

### ESTROGEN DEFICIENT SKIN

**Dr. Berson:** The skin's fibroblasts produce less collagen and elastin as a result of estrogen deficiency. There is also less connective tissue and glycosaminoglycans as well as thinner epidermis; this leads to reduced hydration and compromised barrier function. Estrogen deficient skin is therefore thin, atrophic, dry, fragile, dull, and wrinkled.

**Doris Day, MD:** Dryness is definitely a component of estrogen deficient skin. Another component is acceleration of the aging process and wrinkling. Besides dryness and wrinkling, women approaching menopause complain that their skin thickness has changed and their skin feels thinner and different.

**Sabrina G. Fabi, MD:** The word “dullness” resonates with perimenopausal and menopausal patients. They’ll say, “I feel like my skin is dull,” and they are seeking to restore that glow that they feel they have lost.

### DIAGNOSING ESTROGEN DEFICIENT SKIN (EDS)

Ideally, patients with signs or symptoms of EDS could be identified before the onset of menopause when intervention is likely to be maximally effective.

**Jeanine Downie, MD:** On average, a woman’s most rapid aging occurs from 41 to 47 years old. That frightens people. They’re perimenopausal, and their hormones are changing. They’re seeing their facial skin start to sag. Whatever guards they had against aging are just falling rapidly apart, and that’s when they’re coming in looking for help.

**Dr. Cohen:** We don’t want to just capture patients when they notice some of the signs correlating with the 30 percent collagen decline in the first five years of menopause. Instead, we want to capture patients early on, when they will benefit most from the procedures and skin-care recommendations that we can offer.

**Dr. Fabi:** We start to see these changes before a woman goes into menopause, typically in her mid 40s. When patients become perimenopausal, they also notice a dryness and roughness to their skin that imparts a dullness that they can’t quite improve. I think that there’s a place for starting treatment before the drop in estrogen becomes significant, because the subclinical changes in the skin start sooner than we think.

**Dr. Berson:** It’s in that 40 to 50 range that I do see most of the changes, the early wrinkling, pigmentation, irregular tone and texture of the skin, and dryness, starting to develop.

### ADDRESSING EDS WITH MEP TECHNOLOGY

Many of the available topicals and treatments in a dermatologist’s armamentarium, including injectables, lasers and light-based devices (such as intense pulsed light and photodynamic therapy), effectively address some of the signs of skin aging, but none of these modalities target accelerated skin aging due to estrogen loss, the panelists agree.

**Dr. Berson:** A woman could be doing everything right. She could be using her antioxidants every day, using the appropriate skin care, using daily sun protection, eating a healthy diet, drinking enough water, and she’s still not going to look her best because she’s missing that one factor after menopause. She’s missing that estrogen factor.

**Dr. Cohen:** Biopelle’s Emepelle is a new category of skin care. This type of topicals for EDS hasn’t existed until now in our space. The hero ingredient, Methyl Estradiolpropanoate (MEP), is a non-hormonal way to activate the estrogen

## SIGNS OF EDS

- Dry skin
- Dullness
- Atrophy
- Pruritus
- Decreased barrier function
- Decreased moisture
- Decrease in collagen and elastin
- Increase in fine lines and wrinkles
- Increased texture abnormalities

In skin of color, EDS may also include patchy depigmentation and texture abnormalities

receptor. Instead of being a hormone, it is simply an estrogen analog that activates the cutaneous estrogen receptors. It is called a NERA, a Non-hormonal Estrogen Receptor Activator. It is an estrogenic sterol ester. Its effect is totally within the skin, and once absorbed into the bloodstream, it is rapidly deactivated into an inactive metabolite. Since the estrogen receptor activator is specific to the skin, it’s going to thicken the epidermis and stimulate collagen with no off-site activity.

**Dr. Downie:** MEP targets estrogen deficient skin by addressing the significant collagen loss during the first few years of menopause. It is a non-hormonal estrogen receptor activator that is specific to the skin. It has no systemic side effects and helps to improve oxidative stress and improve the appearance of dryness, dullness and fine lines.

### MEP SAFETY AND EFFICACY

**Dr. Day:** For women who have a history of breast cancer, it may be challenging to help some of them get over the emotional aspect and to understand that this is a skin-specific receptor that does not produce any systemic effects.

**Dr. Cohen:** In a 60-patient safety study evaluating topical MEP for facial features of EDS, Zoe Draelos, MD, showed that once MEP enters the bloodstream, it is broken down by esterases to an inactive carboxyl molecule, avoiding systemic estrogen side effects. In addition, Dr. Draelos clinically evaluated 80 patients for efficacy as well. Importantly, this study looked at MEP alone, and the formulation had no other effective ingredients. In addition, the vehicle itself was specifically designed to confer extremely minimal moisturizing qualities—so there wouldn’t be any moisturizer effect from the vehicle. This is important, as historically in some types of formulations, the vehicle and not the hero ingredient could be responsible for the observed benefit seen in those studies. That wasn’t the case in this study. Furthermore, the clinical study also showed a statistically significant improvement from baseline at week 14 in parameters including dryness, laxity, atrophy, and dullness as compared to vehicle.

**Dr. Berson:** There was an increase in the amount of estrogen receptors on the fibroblasts seen in four of nine subjects

## Efficacy study results

Blinded Investigator-assessed % improvement at 14 weeks

VISUAL CRITERIA ASSESSMENT	MEP + VEHICLE (% IMPROVEMENT)	PLACEBO (% IMPROVEMENT)	P VALUE
DRYNESS	54%	16%	$P < 0.001$
DULLNESS	39%	8%	$P < 0.001$
THICKNESS	20%	2%	$P < 0.001$
LAXITY	19%	6%	$P < 0.001$
ERYTHEMA	11%	NO CHANGE	$P = 0.001$
ATROPHY	9%	NO CHANGE	$P < 0.001$
FINE LINES	8%	2%	$P = 0.001$

79/80 subjects completed study (1 subject missed 14-week visit for reasons unrelated to study product). Statistical relevance was not achieved for deep wrinkles or telangiectasias.

in a biopsy sub-study. That's important as it demonstrates MEP's unique mechanism of action; it mimics estrogen and in essence reawakens, or reactivates, the receptors that had disappeared.

### EMEPELLE WITH MEP TECHNOLOGY

Emepelle Serum and Night Cream feature MEP Technology along with additional anti-aging ingredients to help restore the natural function of EDS.

**Dr. Berson:** The serum has a number of potent antioxidants, and both products contain peptides and niacinamide. So we are giving patients very potent antioxidants in the morning, along with peptides and barrier repair ingredients, and the innovative ingredient MEP. And then at night, we are giving them a cream that has MEP again, along with retinol, more peptides and emollient lipids. So we have a product line that includes everything we recommend as part of our whole skin care routine.

An easy-to-administer patient questionnaire to help capture patients experiencing EDS could be developed and implemented in practice, the panelists suggest. Sample questions could include:

- When was your last menstrual period?
- Are you nearing or currently in menopause, or are you postmenopausal?
- Have you noticed an increase in dryness or dullness of your skin?
- Are you noticing more fine lines and wrinkles recently?
- Does it feel like your moisturizer is no longer working?
- Has your skin lost its glow?

**Dr. Day:** And Emepelle Night Cream uses 0.1% retinol, 0.05% hydroxypinacolone retinoate (HPR). I think that is a massive point; it's essentially equivalent to retinoic acid without the irritation. I always tell people that when you look for labels, look for HPR. It's your best high-power retinol.

**Dr. Downie:** Many acne-prone individuals are concerned about using new products. Emepelle Serum is oil free and will not clog pores or break patients out with acne. Emepelle Night Cream is an emollient that hydrates the skin with shea butter and has grape seed oil and apricot oil in it. I recommend both of them to my patients with acne. If oil is a problem, they stick with the serum.

**Dr. Cohen:** In a study on Emepelle conducted at my office, as early as eight weeks into the study, 91 percent of subjects felt they were more comfortable with the appearance of their skin and 50 percent or more of the participants reported improvement in wrinkles, thickness, integrity, dullness, texture, hydration, and color. One of the study parameters was for the investigator to rub their hands over the skin, and during this exam I noticed improvement in roughness and dryness scores compared to baseline. These benefits were similar to what I would expect after a chemical peel or another minimally invasive rejuvenation treatment such as PDT. The study took place during a Colorado winter and study participants' moisture and dryness got so much better, despite the fact that it was a cold, dry winter with lack of humidity and exposure to forced indoor heating. Having just looked at the data, it is interesting to note that some trial participants took longer to respond to the topical MEP regimen—up to 20 weeks. Looking at the subset that took longer for their roughness and dryness to improve, it tended to be the older patient population. Obviously age alone doesn't tell you how long they've been amenorrheic, but it makes sense that it can take more time to rebuild more estrogen deficient skin and turn back on these pathways. It seems that the longer they have been amenorrheic, the more of their estrogen receptors have been lost, more dormant, or at minimum down regulated. And thus it seemingly takes longer, at least a few cycles of skin turnover, before those dormant receptors come back and begin to respond to MEP. Thus, the study that I really want to do next is to break the cohorts out into how long they've been in menopause, and then put this thinking to a test and see how long each group takes to respond to this non-hormonal estrogen receptor activator, MEP.

**Dr. Downie:** The products were tested on Fitzpatrick skin types II-IV, and I would like to see future studies look at its efficacy in darker skin types.

**Dr. Day:** I agree we should see more studies on this. MEP is an exciting new tool; we have really only begun to examine and study all the benefits, both as an individual product, and in combination with other antioxidants and skin rejuvenating enhancers.

**Dr. Cohen:** When the Emepelle products are used in combination with in-office procedures and other topicals that

FEMALE, AGE 60

Photo: Courtesy of Joel L. Cohen, MD



BASELINE



WEEK 8

Unretouched photographs of patient at baseline and after morning use of Emepelle Serum and evening use of Emepelle Night Cream. Individual results may vary.

## ESTROGEN AND AGING: A SHIFTING PARADIGM

For years, supplemental estrogen prescribed at the time of menopause with or without progesterone was considered the "Fountain of Youth." Then a large-scale government-sponsored trial was stopped early in 2002 because it showed that this practice may have more risks than benefits. While many prescribing physicians are comfortable with supplemental hormones in 2019, some women may be reluctant to even discuss estrogen use due to the controversy surrounding hormone replacement therapy (HRT). For those with a family or personal history of breast cancer or a history of deep vein thrombosis, estrogen use is not recommended. Emepelle is non-hormonal, and MEP Technology has been clinically proven to be safe with benefits exclusive to the skin; however, it has not been specifically tested on cancer patients. Patients should consult their specialist(s) with any questions.

For women who are open to taking HRT, non-hormonal Emepelle "offers an added benefit that targets the skin, so you don't have to take a higher dose of that hormone replacement to ensure that you're getting the maximal benefit for the skin," says Dr. Day. "For the person who can't or doesn't want to do HRT, it's something that resonates, because you can do something locally without potentially having systemic implications," adds Dr. Fabi.

we recommend, including sunscreen, the results may even be more pronounced.

This is a maintenance type of formulation that we are going to be advocating our patients use on a regular basis, like a sun-

screen or like a retinoid. Actually in some cases, they may be able to use this as the retinoid, as the Emepelle Night Cream has a mild retinoid as part of its formulation. But it's not necessarily going to get our patients off retinoids completely. There may be people who can't tolerate most retinoids every night and alternate nights between this cream and a dedicated or prescription retinoid, while still using the Emepelle Serum every day. We can still target the individual lasers or procedures to whatever they need in terms of technology to improve discoloration, photodamage, etched lines, or laxity.

## TAKE-HOME POINTS

**Dr. Cohen:** One, we have a new understanding of this concept of perimenopausal and menopausal symptoms of estrogen deficient skin. Two, we understand that there are estrogen receptors in the skin that can be activated by a specific non-hormonal estrogen analog that Biopelle formulated as MEP. Three, we have a 60-patient safety study by Dr. Draelos on this compound. Four, we have an 80-patient efficacy study by Dr. Draelos, as well. Five, it has been exciting for me to see in my own Emepelle study patients a significant improvement in many parameters including dullness and dryness to the skin as well as photographs showing other impressive changes.

**Dr. Berson:** We now have a novel cosmeceutical agent that can address the signs of estrogen deficient skin; it targets one of the elements that no other cosmeceutical has ever targeted before. It's unique, it's novel, and its mechanism of action is different from anything we have had in the past.

**Dr. Fabi:** Estrogen has a powerful effect on stimulating collagen at the level of the skin and improving symptoms that patients complain of, including dullness, dryness, and fine lines. And up until now, we have not had a product to meet that need topically for patients without unwanted systemic effects. Now we do. It's a unique non-hormonal estrogen binding receptor product that can improve these symptoms.

**Dr. Downie:** This is a new innovative product that's not been available before, that's specifically addressing perimenopausal and menopausal skin. The fact that it's a non-hormonal estrogen receptor activator, and that it's very specific to the skin is innovative, different, and new.

**Dr. Day:** It's a new category. It raises the bar and recognizes that aging skin needs to be attended to on many levels, and now we have an angle that looks at those hormone receptors without using hormones and especially without using hormones that have a systemic effect. I think that's very important. It's not a hormone; it has specific effects on specific skin receptors only. ■