

# UC Davis

## Dermatology Online Journal

### Title

Hormonal therapies for hidradenitis suppurativa: Review

### Permalink

<https://escholarship.org/uc/item/6383k0n4>

### Journal

Dermatology Online Journal, 23(10)

### Authors

Clark, Ashley K  
Quinonez, Rebecca L  
Saric, Suzana  
et al.

### Publication Date

2017

### DOI

10.5070/D32310036990

### Copyright Information

Copyright 2017 by the author(s). This work is made available under the terms of a Creative Commons Attribution-NonCommercial-NoDerivatives License, available at <https://creativecommons.org/licenses/by-nc-nd/4.0/>

Peer reviewed

# Hormonal therapies for hidradenitis suppurativa: Review

Ashley K Clark<sup>1</sup> BS, Rebecca L Quinonez<sup>2</sup> BS, Suzana Saric<sup>1</sup> BA, Raja K Sivamani<sup>3,4</sup> MD MS CAT

Affiliations: <sup>1</sup>School of Medicine, University of California, Davis, Sacramento, California, <sup>2</sup>School of Medicine, Universidad Autonoma de Guadalajara - San Antonio, Texas, <sup>3</sup>Department of Dermatology, University of California, Davis, Sacramento, California, <sup>4</sup>Department of Biological Sciences, California State University-Sacramento, Sacramento, California

Corresponding Author: Raja Sivamani MD, MS, CAT, Department of Dermatology, University of California, Davis, 3301 C Street, Suite 1400, Sacramento, CA 95816, Tel: 916-703-5145, Fax: 916-734-7183, Email: raja.sivamani.md@gmail.com

## Abstract

Hidradenitis suppurativa is a recurrent inflammatory skin condition characterized by abscesses and boils, predominantly in the groin, armpit, and buttocks areas. HS is not a life-threatening condition, but severely impairs quality of life in those affected. Finding a successful treatment approach for HS has been challenging, in part because of the lack of a gold-standard treatment method, limited research-based information, and the nature of clinical variation in the disease. Treatment commonly consists of antibiotics, anti-inflammatory therapy, hormonal therapy, and more invasive clinical procedures. Treatment is chosen by the degree of severity by which the condition presents and is modified accordingly. This review describes the roles of hormones in the pathogenesis of hidradenitis suppurativa and describes the use of hormonal therapy such as, finasteride, dutasteride, spironolactone, and oral contraceptives. The outcomes of the use of these modalities in various clinical studies are summarized.

*Keywords: hormones, androgens, estrogens, therapeutics, hidradenitis suppurativa, acne inversa*

## Introduction

### Background on Hidradenitis Suppurativa

Hidradenitis suppurativa (HS) is a recurring inflammatory condition caused by hyperkeratosis of the epithelial follicle, affecting apocrine-gland dense areas such as the axillae, inframammary areas, groin, and buttocks [1]. Obstruction of the apocrine/sebaceous glands caused by excess production of sebum clogs the follicle and results in inflammation

of the surrounding tissue [2]. Abscess formation is commonly seen and it can extend deep into the subcutaneous tissue, further promoting deep sinus tract formation. Hypertrophic scarring is a common sequela of the condition, primarily affecting those with darker skin tones.

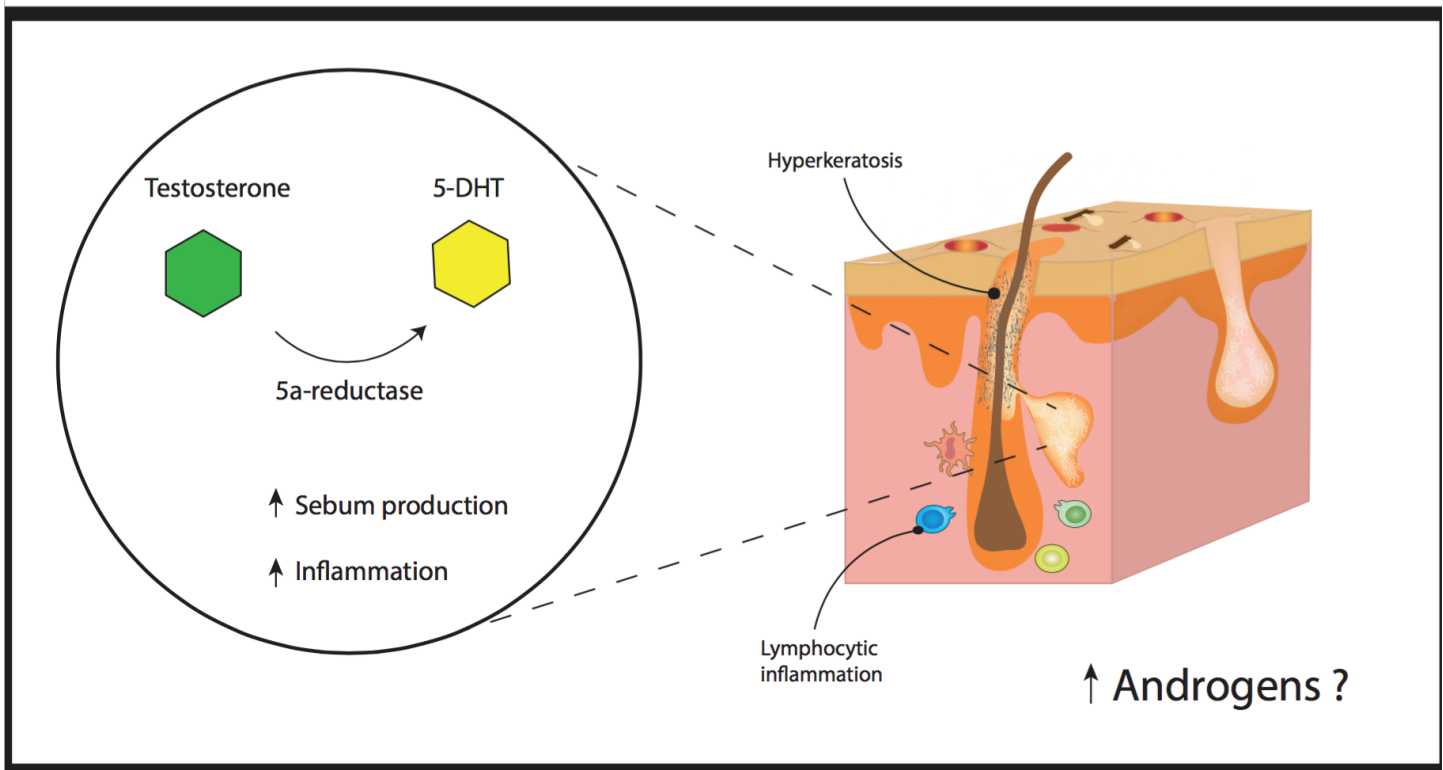
Clinically HS presents as painful papules and nodules, eventually progressing to abscess formation and severe scarring. It may also be characterized by having a malodorous sterile discharge. The severity of the disease is described by the Hurley stages. Stage I exhibits few lesions; Stage II presents with abscesses and invasion with sinus tracts; Stage III designates full involvement of sinus tracts, along with many abscesses throughout the body [3]. Most cases are reported to be Hurley stages II-III [3].

HS is reported to affect 1% of the population and is more common in females than males [4]. It usually presents in the second and third decades of life. HS has a high association with smoking, obesity, Crohn disease and other auto-inflammatory diseases [5]. Among dermatological conditions, HS is known to be one of the most debilitating conditions, having a detrimental psychosocial impact on the individual's life [5].

### Background on hormonal therapy pathways

The pilosebaceous unit (consisting of hair, hair follicle, arrector pili muscles, and the sebaceous gland) is densely populated with sebaceous and apocrine glands in the axillae, groin, and buttocks area [1]. These glands have two types of androgen-converting enzymes, 5-alpha-reductase type I and 5-alpha-reductase type II [6]. Type I is found in both

# Hidradenitis Suppurativa



5-DHT= 5-dihydrotestosterone

Image created by: Ashley Katherine Clark

**Figure 1.** *Hidradenitis Suppurativa*-The pilosebaceous unit is filled with sebaceous and apocrine glands that have two types of androgen-converting enzymes responsible for converting testosterone into 5-dihydroxytestosterone (5-DHT). Activation of androgen receptors in the gland then leads to increased sebum and inflammation. The role of hormones in HS is unclear but evidence supports a connection.

hair follicles and apocrine glands, whereas Type II is found only in hair follicles [6].

5 $\alpha$ -reductase (5-AR) is best known for the conversion of testosterone into its more potent form, 5-dihydroxytestosterone (5-DHT), [6]. Testosterone and 5-DHT bind to androgen receptors on the sebaceous gland, thus causing an increase in activity. This causes increased secretion of sebum and increased inflammation in the tissue.

Patients with HS were not found to have higher than normal plasma levels of testosterone or 5-DHT than normal individuals [7]. However, studies have demonstrated that the use of anti-androgenic medications has a favorable response in comparison to antibiotic based therapy alone [8,9].

## Body of Article

### Role of hormones

The role of sex hormones in the pathogenesis of HS remains unclear. The prevalence of HS is most often reported to be higher in women and changes in HS activity have been reported during times of fluctuating hormones such as during premenstrual periods, pregnancy, and menopause [10].

The age of onset of a disease can provide important clues into the association with hormonal changes. HS in children is rare [10]. Reported cases have occurred in normally developed children with no signs of hormonal aberrations such as premature menarche or adrenarche, although obesity was a commonly reported finding [11]. The condition seldom occurs before puberty and less than 2% of patients have onset of the disease before the age of 11 years. Studies analyzing the age of onset for HS found the most common time was between 11 and 30 years old [10]. One hypothesis is that adrenal androgen synthesis may be related to the peak time of onset and noted that cutaneous androgen enzyme activity

is at its highest between 11 and 30 years old [10].

Premenstrual flares of HS reportedly occur in between 44-63% of patients [10]. Both estradiol and progesterone levels decline with the premenstrual period, suggesting HS is affected by the hormonal fluctuations of the menstrual cycle [12]. Further evidence favoring a hormonal influence in HS are the reported cases of exacerbation or resolution of HS during pregnancy when progesterone and estrogen levels rise. Regardless of whether authors describe improvement or worsening, most authors agree that disease activity is affected by pregnancy. This finding suggests hormonal surges are catalysts for clinical changes in the disease state. Although studies vary, the overall consensus indicates amelioration of HS during pregnancy and a deterioration post-partum [13-16]. The decline of estrogen and progesterone during menopause is associated with a decline in HS symptoms [17] and HS cases [18]. One study by Kromann et al. reported 48% of women experienced a decrease or complete resolution of HS and its symptoms with the onset of menopause [15]. Additionally, a second study found a substantial decrease of HS prevalence among people aged 55 and older [19].

Progesterone and estrogens may influence HS through their effects on the immune system. Macrophages are present in HS lesions and overexpress Il-12 and Il-23, which induce a Th-17 response. High levels of progesterone suppress the development and function of Th-17 cells [20]. Additionally, progesterone reduces TNF production of macrophages [21]. The role of estrogen on inflammation is not as well understood. Mouse studies suggest high levels of estrogen increase Il-12 and induce a Th1 response leading to interferon gamma production, which is increased in HS [22].

Testosterone is the major circulating androgen. The role of androgens in HS remains unclear. One hypothesized role is that androgens may act through altering the immune response since activation of the androgen receptor increases macrophage production and TNF, leading to suppression of wound healing [23, 24]. Additionally, a second study found that a synthetic androgen, R1881, stimulated keratinocytes to produce TGF-Beta, a cytokine

suspected to play a role in the pathogenesis of HS [25]. A study by Mortimer et al. compared blood levels of various hormones in patients with HS and age matched controls. Testosterone levels and androgen index in HS patients was increased compared to controls [16]. However, subsequent studies have reported conflicting results showing no difference in plasma testosterone or dehydroepiandrosterone levels between female patients with hidradenitis and controls [13,26]. Interestingly, patients with HS flares and controls showed no difference in hormone levels, whereas patients from the no-flare group had reduced progesterone and increased levels of testosterone, androstenedione, and androgen index [13].

The role of androgens remains unclear. Factors that continue to confound an understanding of the role of hormones include reports of the continuation and primary development of HS in postmenopausal women [27]. Furthermore, pregnancy and menstruation do not have consistent effects on the disease and hidradenitis is predominantly a disease of women. The relationship between androgen levels and the condition remains under discussion. Although there is no increase in serum androgens in most patients with HS, the mechanism may relate to altered end-organ sensitivity instead. The strongest supportive evidence for the role of androgens is the effectiveness of anti-androgen therapy.

## Hormone therapy - Anti-androgens:

### Finasteride

Finasteride is an antiandrogen that blocks 5 $\alpha$ -reductase type II and type III, thus blocking the conversion of testosterone to the more potent DHT. This drug, which is usually used in prostate cancer, has been used successfully for HS. Farrel et al. reported two cases of improvement in HS symptoms after 1 and 3 months of treatment with 5 mg/day of finasteride [28]. One of the reported case subjects was a 55-year-old postmenopausal woman who previously failed to respond to cyproterone acetate. Joseph et al. reported on 7 patients who experienced resolution or improvement in symptoms with 6-16 weeks of treatment on 5 mg/day of finasteride [29]. Subsequently, Kraft and Searles demonstrated the superiority of finasteride over oral antibiotics.

Specifically, they reported on 41 women with HS refractory to antibiotics, retinoids, and surgery who showed 75% improvement, with 59% experiencing complete resolution. Side effects reported in the study were minimal with some swelling and menstrual irregularities. Lastly, Domenech et al. reported a case of a 28-year-old man with severe HS treated for one year who developed complete resolution of his symptoms on 5mg/day [30]. The precise means by which finasteride can improve symptoms in HS is unclear; many propose it acts by decreasing local concentrations of dihydrotestosterone at the level of the hair follicle by altering end-organ sensitivity rather than a more systemic effect on circulating androgen. An alternative hypothesis is an enhanced target tissue response to relatively normal androgen levels [8]. Although generally well tolerated by both sexes, finasteride is not without its own drawbacks. Multiple side effects including teratogenicity, decreased libido, erectile dysfunction, gynecomastia, and breast enlargement in women make it a less favorable option for many patients [31].

### **Dutasteride**

Similarly, dutasteride (0.5 mg), has helped clear HS in both men and women in anecdotal cases. Dutasteride acts by blocking blocks 5 $\alpha$ -reductase type I (which is most active in the skin) and type II. Dutasteride therapy reduces serum DHT significantly more than does finasteride. According to an experienced dermatologist's anecdote, dutasteride and finasteride appear most useful in obese patients, whose disease is potentially more influenced by hormonal effects [32]. However, formal studies are lacking. The adverse event profiles of dutasteride and finasteride are similar and both can affect sexual function and lead to breast enlargement and tenderness [28]. Weak evidence suggests a difference in the onset of clinical benefit, although the available data does not confirm this finding. Similarly to finasteride, dutasteride must be used with caution given its teratogenicity.

### **Spironolactone**

Spironolactone is a potassium-sparing diuretic with anti-androgen properties. The effectiveness of spironolactone has been mixed in various studies. In a study from Kraft and Searles, only 1 out of 5 patients taking spironolactone experienced improvement in symptoms [9]. More recently, in 2015, a case series

of 20 women with HS treated with 100-150 mg spironolactone demonstrated notable results. Of the 20 patients, 17 reported improvements in their HS symptoms, 11 of which experienced complete resolution of disease as determined by a patient global assessment score designed for the study. Furthermore, they concluded spironolactone is an effective and safe long-term option for women with HS and found no advantage in concurrent treatment with tetracycline or OCP. Side effects of spironolactone included irregular periods (1 of 6) and heart palpitations (1 of 6) but the women continued adhering to the treatment regimen. Gynecomastia may develop with spironolactone treatment. The development of gynecomastia appears to be related to the dosage level and duration of therapy and is reversible with discontinuation. In rare instances, breast enlargement may persist when spironolactone is discontinued. Although the results are impressive the cases have confounding factors. For example, 7 of the patients initiated contraceptive therapy at the same time.

As documented in the early literature, a similar hormone blocker, cyproterone acetate, has been used frequently for the treatment of HS. Multiple studies have demonstrated that spironolactone and cyproterone acetate may be equivalent in efficacy, although large-scale studies are lacking [33]. Cyproterone acetate is unavailable in the United States.

### **Oral Contraceptive Pills**

Although the relationship with endocrine abnormalities is not clear, some patients suffer from hormonal irregularities that contribute to their HS. Establishing whether a patient with HS has irregular hormone levels, irregular periods, or polycystic ovarian syndrome is important in understanding the patient's HS pathophysiology and treatment options. Female patients have anecdotally reported that combination progesterone/estrogen oral contraceptive pills (OCPs) with a high estrogen to progesterone ratio and low androgenicity of progesterone have ameliorated their disease symptoms [16]. On the other hand, isolated case reports have suggested a link between oral contraceptive pill use and HS [34]. In the absence of more thorough studies, there is little evidence supporting or refuting the effects of

oral contraceptives on HS. Regardless, the current use of oral contraceptives is mainly based on anecdotal evidence and the supportive evidence for OCP use in acne. If oral contraceptives are considered, those containing ethinyl estradiol and drospirenone are preferred, combined with the antiandrogen spironolactone, 50 to 100 mg, when possible [16]. Overall, supportive data is lacking regarding the use oral contraceptives in HS and more research is needed.

### Differences in Men versus Women

HS affects men and women differently. In the United States HS is more common among women [35]. However, in some countries, such as Tunisia, HS is more common in men [36]. The disease presentation itself varies between men and women as well. Women are more likely to have axillary involvement, whereas men have perineal and perianal lesions. However, HS can occur in any area of the body in men and women. The differences may be attributed to a variety of factors such as follicular trauma, shaving, hormone levels, skin microbiome, adipose tissue, and lifestyle (such as choice of soap and clothing). In addition, the fact that women seek medical care more often than men in the United States may be a confounding factor [37]. Regarding treatment, both men and women have reported improvements with all three of the anti-androgen medications: finasteride, dutasteride, and spironolactone [8,9,32]. Studies have yet to report differences in response rates between the sexes to the three hormonal therapies.

### Conclusion

HS is a chronic, debilitating inflammatory skin disease that may progress from painful papules and nodules to abscess formation and permanent scarring. Although the pathogenesis is unclear, endocrine involvement has been suggested owing to symptom variation during menstrual cycle and pregnancy. Additionally, HS in women may be promoted by hyperandrogenism, but the data are conflicting. The lack of understanding of HS pathogenesis makes it challenging to treat. There is not a recommended "gold standard" treatment; typically, individuals have to try various treatment modalities. Data on the precise effects of hormonal therapies (anti-androgens and OCPs) in individuals with HS are limited. It is theorized that anti-androgens decrease

the local concentration of DHT and may also alter end-organ sensitivity to circulating androgens. Some individuals have achieved relief with anti-androgen therapies, but the data on OCP use in HS treatment is conflicting. If OCPs are considered as a treatment modality, combination therapy with the anti-androgen spironolactone is advised. Our manuscript highlights the need for large scale randomized controlled trials to improve the evidence base for the use of hormonal therapies in HS. Additionally, further understanding of HS pathogenesis may lead to greater treatment options.

### References

1. Ball SL, Tidman MJ. Managing patients with hidradenitis suppurativa. *Practitioner*. 2016;260(1793):25-9. 3. [PMID: 27382916].
2. Menderes A, Sunay O, Vayvada H, Yilmaz M. Surgical management of hidradenitis suppurativa. *Int J Med Sci*. 2010;7(4):240-7. [PMID: 20714346].
3. Hurley HJ. Axillary hyperhidrosis, apocrine bromhidrosis, hidradenitis suppurativa and familial benign pemphigus: surgical approach. In: Roenigk RK, Roenigk HH Jr, editors. *Dermatologic surgery: principles and practice*. 2nd ed. New York: Marcel Dekker; 1996. p. 623-45.
4. Schmitt JV, Bombonato G, Martin M, Miot HA. Risk factors for hidradenitis suppurativa: a pilot study. *An Bras Dermatol*. 2012;87(6):936-8. [PMID: 23197222].
5. Gill L, Williams M, Hamzavi I. Update on hidradenitis suppurativa: connecting the tracts. *F1000Prime Rep*. 2014;6:112. [PMID: 25580266].
6. Makrantonaki E, Ganceviciene R, Zouboulis C. An update on the role of the sebaceous gland in the pathogenesis of acne. *Dermatoendocrinol*. 2011;3(1):41-9. [PMID: 21519409].
7. Matusiak L, Bieniek A, Szepletowski JC. Hidradenitis suppurativa and associated factors: still unsolved problems. *J Am Acad Dermatol*. 2009;61(2):362-5. [PMID: 19615551].
8. Khandalavala BN, Do MV. Finasteride in hidradenitis suppurativa: a "male" therapy for a predominantly "female" disease. *J Clin Aesthet Dermatol*. 2016;9(6):44-50. [PMID: 27386051].
9. Kraft JN, Searles GE. Hidradenitis suppurativa in 64 female patients: retrospective study comparing oral antibiotics and antiandrogen therapy. *J Cutan Med Surg*. 2007;11(4):125-31. [PMID: 17601419].
10. Riis PT, Ring HC, Themstrup L, Jemec GB. The role of androgens and estrogens in hidradenitis suppurativa - a systematic review. *Acta dermatovenerol Croat*. 2016;24(4):239-49. [PMID: 28128074].
11. Mirmirani P, Carpenter DM. Skin disorders associated with obesity in children and adolescents: a population based study. *Pediatr Dermatol*. 2014;31(2):183-90. [PMID: 24329996].
12. Jayasena C, Comminos A, Nijher G, Abbara A, De Silva A, Veldhuis JD, Ratnasabapathy R, Izzi-Engbeaya C, Lim A, PaTel:DA. Twice-daily subcutaneous injection of kisspeptin-54 does not abolish menstrual cyclicity in healthy female volunteers. *J Clin Endocrinol Metab*. 2013;98(11):4464-74. [PMID: 24030945].
13. Harrison B, Read G, Hughes L. Endocrine basis for the clinical presentation of hidradenitis suppurativa. *Br J Surg*. 1988;75(10):972-5. [PMID: 3219545].
14. Jemec G. The symptomatology of hidradenitis suppurativa in women. *Br J Dermatol*. 1988;119(3):345-50. [PMID: 3179207].
15. Kromann C, Deckers IE, Esmann S, Boer J, Prens EP, Jemec GB. Risk factors, clinical course and long-term prognosis in hidradenitis

- suppurativa: a cross-sectional study. *Br J Dermatol*. 2014;171(4):819-24. [PMID: 24804604].
16. Mortimer PS, Dawber RP, Gales MA, Moore RA. A double-blind controlled cross-over trial of cyproterone acetate in females with hidradenitis suppurativa. *Br J Dermatol*. 1986;115(3):263-8. [PMID: 2944534].
  17. Burger HG, Hale GE, Robertson DM, Dennerstein L. A review of hormonal changes during the menopausal transition: focus on findings from the Melbourne women's midlife health project. *Hum Reprod Update*. 2007;13(6):559-65. [PMID: 17630397].
  18. Barth JH, Layton AM, Cunliffe WJ. Endocrine factors in pre- and postmenopausal women with hidradenitis suppurativa. *Br J Dermatol*. 1996;134(6):1057-9. [PMID: 8763424].
  19. Revuz JE, Canoui-Poitrine F, Wolkenstein P, Viallette C, Gabison G, Pouget F, Poli F, Faye O, Roujeau JC, Bonnelye G. Prevalence and factors associated with hidradenitis suppurativa: results from two case-control studies. *J Am Acad Dermatol*. 2008;59(4):596-601. [PMID: 18674845].
  20. Schlapbach C, Hänni T, Yawalkar N, Hunger RE. Expression of the IL-23/Th17 pathway in lesions of hidradenitis suppurativa. *J Am Acad Dermatol*. 2011;65(4):790-8. [PMID: 21641076].
  21. Zambrano-Zaragoza JF, Romo-Martínez EJ, Durán-Avelar MdJ, García-Magallanes N, Vibanco-Pérez N. Th17 cells in autoimmune and infectious diseases. *Int J Inflamm*. 2014. [PMID: 25152827].
  22. Hughes GC. Progesterone and autoimmune disease. *Autoimmun Rev*. 2012;11(6-7):A502-14. [PMID: 22193289].
  23. Chuang KH, Altuwaijri S, Li G, Lai JJ, Chu CY, Lai KP, Lin HY, Hsu JW, Keng P, Wu MC. Neutropenia with impaired host defense against microbial infection in mice lacking androgen receptor. *J Exp Med*. 2009;206(5):1181-99. [PMID: 19414555].
  24. Lai JJ, Lai KP, Chuang KH, Chang P, Yu IC, Lin WJ, Chang C. Monocyte/macrophage androgen receptor suppresses cutaneous wound healing in mice by enhancing local TNF- $\alpha$  expression. *J Clin Invest*. 2009;119(12):3739-51. [PMID: 19907077].
  25. Inui S, Itami S. Molecular basis of androgenetic alopecia: from androgen to paracrine mediators through dermal papilla. *J Dermatol Sci*. 2011;61(1):1-6. [PMID: 21167691].
  26. Franks S, Kiddy DS, Hamilton-Fairley D, Bush A, Sharp P, Reed MJ. The role of nutrition and insulin in the regulation of sex hormone binding globulin. *J Steroid Biochem Mol Biol*. 1991;39(5B):835-8. [PMID: 1954173].
  27. Buimer MG, Wobbles T, Klinkenbijn JH. Hidradenitis suppurativa. *Br J Surg*. 2009;96(4):350-60. [PMID: 19283748].
  28. Farrell AM, Randall VA, Vafaei T, Dawber RP. Finasteride as a therapy for hidradenitis suppurativa. *Br J Dermatol*. 1999;141(6):1136-52. [PMID: 10722269].
  29. Joseph MA, Jayaseelan E, Ganapathi B, Stephen J. Hidradenitis suppurativa treated with finasteride. *J Dermatolog Treat*. 2005;16(2):75-8. [PMID: 16019620].
  30. Doménech C, Matarredona J, Escribano-Stablé JC, Devesa JP, Vicente J, Jaén A. Facial hidradenitis suppurativa in a 28-year-old male responding to finasteride. *Dermatology*. 2012;224(4):307-8. [PMID: 22759836].
  31. Roberts JL, Fiedler V, Imperato-McGinley J, Whiting D, Olsen E, Shupack J, Stough D, DeVilz R, Rietschel R, Savin R. Clinical dose ranging studies with finasteride, a type 2 5 $\alpha$ -reductase inhibitor, in men with male pattern hair loss. *J Am Acad Dermatol*. 1999;41(4):555-63. [PMID: 10495375].
  32. Scheinfeld N. Hidradenitis suppurativa: a practical review of possible medical treatments based on over 350 hidradenitis patients. *Dermatol Online J*. 2013;19(4):1. [PMID: 24021361].
  33. Kelekci KH, Kelekci S, Yengel I, Gul S, Yilmaz B. Cyproterone acetate or drospirenone containing combined oral contraceptives plus spironolactone or cyproterone acetate for hirsutism: randomized comparison of three regimens. *J Dermatolog Treat*. 2012;23(3):177-83. Epub 2011/01/25. [PMID: 21254871].
  34. Stellon AJ, Wakeling M. Hidradenitis suppurativa associated with use of oral contraceptives. *BMJ*. 1989;298(6665):28-9. [PMID: 2492847].
  35. Vazquez BG, Alikhan A, Weaver AL, Wetter DA, Davis MD. Incidence of hidradenitis suppurativa and associated factors: a population-based study of Olmsted County, Minnesota. *J Invest Dermatol*. 2013;133(1):97-103. [PMID: 22931916].
  36. Mebazaa A, Ben HR, Cheikh RR, Trojjet S, El Euch D, Mokni M, Zitouna M, Ben OA. Hidradenitis suppurativa: a disease with male predominance in Tunisia. *Acta Dermatovenerologica Alp Pannonica Adriat*. 2009;18(4):165-72. [PMID: 20043054].
  37. Bertakis KD, Azari R, Helms LJ, Callahan EJ, Robbins JA. Gender differences in the utilization of health care services. *J Fam Pract*. 2000;49(2):147-52. [PMID: 10718692].

*Funding sources, grants and sponsors: AKC was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through grant number UL1 TR001860 and linked award TL1 TR001861. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.*