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The Role of Androgens and Estrogens in Hidradenitis Suppurativa – A Systematic Review

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ABSTRACT Hidradenitis suppurativa (HS) is an inflammatory skin disease. Several observations imply that sex hormones may play a role in its pathogenesis. HS is more common in women, and the disease severity appears to vary in intensity according to the menstrual cycle. In addition, parallels have been drawn between HS and acne vulgaris, suggesting that sex hormones may play a role in the condition. The role of androgens and estrogens in HS has therefore been explored in numerous observational and some interventional studies; however, the studies have often reported conflicting results. This systematic review includes 59 unique articles and aims to give an overview of the available research. Articles containing information on natural variation, severity changes during menstruation and pregnancy, as well as articles on serum levels of hormones in patients with HS and the therapeutic options of hormonal manipulation therapy have all been included and are presented in this systematic review. Our results show that patients with HS do not seem to have increased levels of sex hormones and that their hormone levels lie within the normal range. While decreasing levels of progesterone and estrogen seem to coincide with disease flares in premenopausal women, the association is speculative and requires experimental confirmation. Antiandrogen treatment could be a valuable approach in treating HS, however randomized control trials are lacking.

KEY WORDS: androgens, estrogens, hidradenitis suppurativa, acne inversa

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, inflammatory, and often painful skin disease presenting as recurrent nodules and tunnels (sinus tracts), with subsequent scarring predominantly involving the intertriginous regions (1). The HS nodules gradually progress from non-inflamed to inflamed nodules to abscesses, which may rupture and cause suppuration and severe malodorous discharge (1). The estimated prevalence ranges from 0.05% to 4% (2).

Several clinical observations imply that sex hormones may play a role in the pathogenesis of the disease. The prevalence of HS is most often reported to be higher in women. Many women have reported flares of HS activity in premenstrual periods and decreased activity during pregnancy. Furthermore, the similarities between acne vulgaris and HS have strongly influenced the research on the association between sex hormones and HS. Acne vulgaris is a well-known androgen-dependent disorder, which has led researchers to hypothesize that a similar pattern could occur in HS. The important similarities between acne and HS are: pre-menstrual flares are a common manifestation of acne (3); the most severe cases in both diseases appear to occur predominantly in male patients (4,5); androgens increase skin keratinization (6), implying that both these diseases are

androgen-dependent; lastly, follicular plugging has been demonstrated in both acne and HS lesions, suggesting that parallel pathogenic steps occur, at least in part (7).

Our objective in this study was to systematically review the previous body of literature concerning the role of androgens and estrogens in HS in order to provide an overview of the field. This may aid researchers and physicians in understanding the potential role of sex hormones in HS.

MATERIALS AND METHODS

We searched Pubmed, Ovid, and Web of science using the search "((Hidradenitis OR Acne invers*)) AND (Hormon* OR Endocrin* OR androgen OR Finasteride OR contraceptive OR Estrogen OR Progest*)" on 12-03-2016. Cochrane Library was searched using the search "hidradenitis OR Acne Invers*", also on 12-03-2016. Inclusion criteria were cases, case-series, case control studies, or randomized controlled trials and reviews on treatment or the endocrine aspect of HS. Titles were screened for inclusion. For each title included, the abstract was read and either included in the study or dismissed. All included articles had their reference lists screened for further articles of interest. Articles in English or Danish were included.

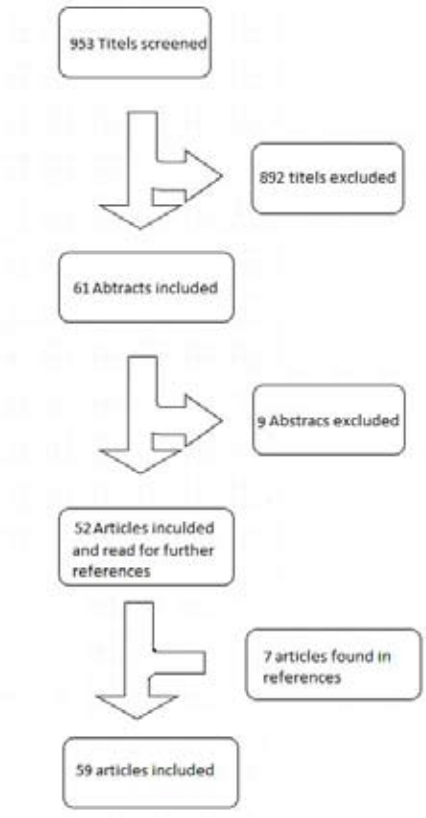

Figure 1. Flowchart of the systematic search.

We found 135 unique titles and included 61. After reading the abstracts, we excluded 9 additional studies. The remaining 52 studies were read and scanned for references. Seven new studies were found in this way, thereby including a total of 59 studies in the review (see Figure 1). Upon reading the articles, patterns emerged, forming the categories that this review is based on.

RESULTS

Natural variation

Onset and remission

Because of the natural lifetime fluctuation of androgens and estrogens, the age of onset of a given disease may provide important endocrinological clues. Reports of HS in children are rare (8), however in most of the cases reported (9) HS occurred in normally developed children with no signs of premature adrenarche or menarche, although obesity seems to be a common finding. Pediatric populations have only been examined in one study, estimating the prevalence of HS in children and adolescents to be 0.06% and the highest among obese patients (10).

Based on recall data, Jemec *et al.* (11) reported no difference in menarche in patients with HS and controls. However, early onset seems to be related to familial forms of HS and more wide-spread lesions (12).

Several authors (12-16) have examined the age of onset, and these data were compiled by Palmer and Keefe (17). All authors found that the most common time of onset was between the ages of 11-30. Harrison (13) speculates that the rise in adrenal androgen synthesis may be related to the peak at time of onset (18) and notes that cutaneous androgen enzyme activity is at its maximum between 11-30 years of age (19,20).

Occurrences after menopause seem to be exceedingly rare, but some cases have been reported (21).

Table 1. Distribution of premenstrual flares

Menstrual flares			
Study	n	Flares (Percentage)	No flares (Percentage)
Mortimer, 1986 (14)	36	22 (61%)	14 (39%)
Harrison, 1988 (13)	87	49 (57%)	38 (43%)
Jemec, 1988 (15)	65	33 (51%)	32 (49%)
Von der werth, 2000 (84)	93	41 (44%)	52 (46%)
Barth, 1996 (21)	51	32 (63%)	19 (37%)

n: number

A study by Kromann *et al*. (22) reported the effect of menopause and the declining levels of estrogen and progesterone (23). The study showed that 48% of women experience a decrease in symptoms, 38% felt no change, and 15% reported a worsening, indicating a slight but not convincing effect of the hormonal changes.

A retrospective study found that when asked after a median time interval of 22 years, 39.4% of patients reported remission of HS(22), with remission being associated with increased age. Prevalence studies indicate that older patients have a lower prevalence of HS (24), and quality of life studies have reported that the psychological impact of HS decreases as patients age, although this may either be an effect of disease amelioration or improved coping (25).

Menstrual flares and pregnancy

Overall, premenstrual flares in women with HS are experienced frequently. As presented in Table 1, studies have found occurrence rates of premenstrual flares between 44%-63%, a rate comparable with that of acne patients (26). Notably, Barth's (21) and Harrison's (13) findings are contradictory. Barth finds that oral contraceptives (OC) seem to facilitate premenstrual flares, while Harrison reports no flares in any OC users. Harrison also noted that women with regular menses (>15 and <45 days) have a much higher risk of premenstrual flares (13). In these articles, the implicit assumption is that premenstrual flares occur with every menstruation. This, however, remains to be established.

The premenstrual hormone levels are characterized by a sudden drop in both estradiol and progesterone levels (27), and these observations suggest that HS is affected by the hormonal changes during the menstrual cycle or that at least a large subgroup of female patients with HS is susceptible to such changes.

HS was originally thought to be a disease of the apocrine glands (28). The recent S1 European guidelines state that the co-occurrence of HS lesions and apocrine glands cannot be ignored (29), which opens the possibility of an apocrine involvement without specifying a mechanism. In 1952, Conway *et al*. pointed out that apocrine glands have a cyclic activity which is greatest in the premenstrual phase, which in many cases overlap with premenstrual flares in HS (30). However, the role of the apocrine glands in HS was questioned by Morgan and Hughes (31) in the late 70s. These authors found no difference in size, density, and distribution of the apocrine glands when they compared 20 patients with HS to 10 controls, leaving the precise role of the apocrine gland yet to be determined.

One of the arguments in favor of HS activity being influenced by the endocrine system is the many published cases of either deterioration or amelioration of HS during pregnancy. Regardless of whether authors describe improvement or deterioration, most authors agree that disease activity is affected by pregnancy. It is suggested that the hormonal surges during pregnancy are the catalysts of clinical changes. Several studies have elaborated on the subject of HS during pregnancy (13,15,22,32,33) (Table 2).

While numbers vary, the overall published consensus seems to indicate an amelioration of HS during pregnancy and a deterioration post-partum. However, most women do not experience any change during pregnancy.

Sex hormones in hidradenitis suppurativa

Androgens

Androgens are the steroid hormones responsible for the development of male characteristics, mainly produced in the testicular Leydig cells; testosterone is the major circulating androgen (34). Testosterone can be converted to 5α-dihydrotestosterone (DHT) which displays 10-times more potent binding to the androgen receptor (AR) (35). The receptor exerts its effect in the nucleus by affecting transcriptions (34).

Table 2. Changes during pregnancy

Pregnancy					
Study	n	Improvement	No change	Deterioation	Post-partum exacerbation
Cornbleet, 1952 (33)	2	2 (100%)	0 (0%)	0 (%)	1 (50%)
Mortimor, 1986 (14)	6	5 (83%)	1 (17%*)	*	5 (83%)
Harrison, 1988 (13)	44	14 (32%)	24 (54%)	6 (14%)	**
Jemec, 1988 (15)	37	9 (24%)	22 (60%)	6 (16%)	11 (39%***)
Kromann, 2014 (22)	85	17 (20%)	61 (72%)	7 (8%)	**

* = not reported if no change or deterioration, **= not reported, *** = only 28 completed pregnancy. n: number

How androgens affect HS remains unclear; however, it could be by altering immune responses. In mice models, androgen receptor deficient mice develop neutropenia (36), while activation of the androgen receptor increased local macrophage TNF-α production enough to suppress wound healing (37). In keratinocytes, R1881, a synthetic androgen, induces production of TGF-β (38), a cytokine suspected to influence HS pathogenesis.

The androgen receptor and the theory of end-organ conversion

Acne studies have shown that androgen receptors (39) are present in the outer root sheath keratinocytes of the hair follicle (40), exerting their influence by regulating transcription (41). The androgen receptor can be affected by dietary habits, and evidence suggests that insulin and insulin-like growth factor-1 (IGF-1) sensitize the receptor by inhibiting its co-regulatory transcription factor, forkhead box 01 (Fox01), leaving it open to be affected by androgens (42). Researchers have hypothesized that an insulinotropic diet, especially one with high dairy intake, could drive or aggravate HS (43) mainly due to a number of androgen precursors in dairy products. However, no diet intervention studies focusing on reducing dairy consumption or glycose load have yet been performed to confirm this hypothesis.

The hitherto popular theory of increased end-organ enzyme conversion of androgens in apocrine glands received a major blow in a study by Barth and Kealy in 1991 (45). In this study, the authors isolated apocrine glands from non-lesional axillary skin from five patients with HS and compared it to axillary skin from five controls undergoing staging for breast cancer matched for age. The conversion of dehydroepiandrosterone, androstenedione, and testosterone were measured, thus measuring the enzyme activity of 3 β-hydroxysteroid dehydrogenase, 17 β-hydroxystroid dehydrogenase, and 5 α-reductase. Interestingly, the trial showed a reduced activity of both 3 β-hydroxysteroid dehydrogenase and 17 β-hydroxystroid in patients with HS and no difference in enzyme activity of 5 α-reductase. The authors note that while whole skin preparations from acne and hirsute patients appear capable of increased enzyme conversion (45,46), isolated appendages do not possess increased enzyme activity when standardized by size or DNA content, suggesting hypertrophy of the sebaceous gland and hair follicle as the source of increased enzyme conversion in acne and hirsute patients.

Buimer *et al.* (47) took a closer look at the apocrine glands in HS using immunohistochemistry. They examined the expression of estrogen and androgen receptors (ER and AR) in apocrine glands from axillary, inguinal, and perianal skin from 22 patients with HS compared with 10 controls. They found apocrine glands in 11 of the HS biopsies and four of the control biopsies. They found no difference in ER or AR expression in patients with HS compared with controls.

It is also important to note that the theory of increased susceptibility of androgens in HS need not be on a receptor-level basis; it could be constituted by an increased post-receptor response to androgens. More than 300 androgen receptor-interacting proteins have been identified (48). AR action is cell-type specific and is in part dependent on cell-type specific cofactors that initiate pre- and/or posttranscriptional modification (48). The susceptibility to HS in subgroups of the general population might be explained by a genetic, or even epigenetic, increased response to androgens on a post-receptor basis. This remains to be examined.

Table 3. Levels of androgens in patients with hidradenitis suppurativa; levels of androgens in controls in parenthesis

Author	Testosterone nmol/L	DHEAS µg/L	Androstenedione nmol/L	SHBG nmol DHT/L
Harrison 1985 (49)	1.66 (1.73)	15.6 (14.4)		
Sawers 1986 (51)	0.825		10.12	31.7
Mortimer 1986 (32)	2.12			50
Mortimer 1986 (14)	1.7 (1.1)*	5.5 (5.1)		54 (51.1)
Harrison 1988, non-flare group (13)	1.9 (1.5)*		6.2 (3.7)*	
Harrision 1988, flare group (13)	1.5 (1.5)		4.4 83.7)	
Barth 1995 (52)	1.6 (1.5)	5.4 (4.3)		44.5 (45)
Palmer 2001 (17)	0.9	2.6	3.9	53.3
Kraft 2007 (50)	1.48	4.56		

* = significant difference. DHEAS: dehydroepiandrosteronsulfate, SHBG: sex hormone binding globulin

Observational studies and circulating hormones

Inspired by similar studies on acne, Harrison *et al*. (49) set out to measure response in patients with HS to 100 µg gonadotropin releasing hormone (GRH) and 200 µg thyrotropin releasing hormone (TRH). Levels of estradiol 17β, progesterone, free T3, free T4, prolactin, testosterone, dehydroepiandosterone sulphate, thyrotrophin, luteinizing hormone, and follicle stimulating hormone were measured at baseline and after 10, 20, and 60 minutes in thirteen women, all with premenstrual flares, compared with nine age-matched healthy volunteers. All women were tested in the luteal phase. Approximate levels for this and similar studies (13,14,17,32,49-52) are given in Table 3. No significant differences were found at baseline or after GRH or TRH, except that patients with HS had a greater rise in Thyroid-stimulating Hormone (TSH) and Prolactine (PRL) levels after 20 and 60 minutes. This study suggests that if HS is androgen-dependent, it is not because of total levels of testosterone. However, the biological free active part was not measured, and end-organ conversion of testosterone to DHT may be a way for the disease to be androgen-dependent without high levels of total testosterone.

Mortimer *et al*. (14) analyzed the blood levels of several hormones in 42 patients with HS, and compared them to 25 controls and 37 women with hirsutism, all matched for age. They found increased levels of testosterone and androgen index in patients with HS compared with controls (Table 3). In 78% of the cases, the levels of individual patients were, however, within the normal range.

Harrison *et al.* (13) performed an assessment of 134 patients with HS to determine if HS was indeed androgen-dependent, but unlike their predecessors, Harrison *et al*. excluded patients with known endocrine disorders including hirsutes and patients with severe acne. Patients were tested again in their premenstrual phase. Interestingly, patients with HS flares and controls showed no difference in hormone levels, while patients from the no-flare group had reduced progesterone and increased levels of testosterone, androstenedione, and androgen index. This suggests that menstrual flares could be related to the effect of progesterone.

When Franks *et al*. (53) reported sex hormone-binding globulin (SHBG) to be negatively correlated with body mass index (BMI) in 1991, Barth *et al*. (21) reevaluated the endocrine levels of 34 women suffering from HS. Their levels of testosterone, sex hormone-binding globulin (SHBG), and Dehydroepiandrosterone sulfate (DHEAS) was measured and compared with control groups matched for age, BMI, and hirsutism. Unlike previous reports, Barth failed to find any difference, indicating that previous results were due to differences in BMI and an increased amount of hirsute in the HS groups.

Using the definition of the Rotterdam criteria for polycystic ovarian syndrome (PCOS) (54), Kraft and Searles (50) retrospectively examined biochemical tests, looking for an androgen state in their patients with HS and determined that 8 out of 21 patients (38.1%) with available tests suffered from PCOS. It is unclear whether these patients were examined for polycystic ovaries or had irregular menses, at least one of which is required to diagnose PCOS according to the Rotterdam criteria. It does, however, show that patients had increased androgen levels in these cases. In an American study, Shlyankevich *et al*. (55) report an odds ratio of 13.7 (4.00-47.30) for suffering from PCOS for patients with HS in a case-control study of 1730 patients with HS and an equal number of controls.

Treatment with drugs that interact with androgens

Testosterone

Hormone manipulation of patients with HS began not, as one could expect, with anti-androgen treatment, but with a successful case series describing treatment with testosterone propionate (56). The argument for using testosterone was its effect on mammary tumor metastases and that the mammary glands are related to the apocrine glands (56). At the time, HS was considered an apocrine disease, which made it a reasonable assumption. Dr. Cornbleet (56) presented eight cases of HS treated with 25 mg testosterone thrice a week or 50 mg twice a week for up to 9 months, in 4 of the 8 cases augmented by penicillin for the first few weeks. Improvement was in all cases "considerable". The studies provide no further description of the outcome.

The use of anabolic steroids in bodybuilding has not, to the best of the authors' knowledge, been linked to cases of development or remission of HS.

Finasteride

In 1999, Farrel *et al*. (57) reported that "Many fail to respond to cyproterone acetate + oestrogen treatment," (See the following section on "Treatment affecting both estrogens and androgens") this claim, while unsupported by data, led the authors to try another antiandrogen, namely 5 mg/day finasteride, a 5α-reductase type II and type III inhibitor, blocking the conversion from testosterone to the more potent DHT. The authors reported two cases of HS "improvement" after 1 and 3 months of therapy, one of the cases being a 55-year-old postmenopausal woman who had previously failed to respond to cyproterone acetate.

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The use of finasteride treatment was adopted by Joseph *et al*. in 2005 (58), who reported a case series of 7 patients treated with 5 mg/day finasteride. To ensure that the finasteride effect was exerted only on HS, the authors excluded patients with clinical or biochemical signs of hyperandrogenism. The treatment lasted for 6-16 weeks, during which 3 patients healed completely, 3 others responded well, and the last case of severe HS did not respond. Doménech *et al*. reported (59) a case of severe HS and acne conglobate responding superbly to a year of finasteride treatment in 2012.

A case report of HS as a presenting feature of premature adrenarche (60) combined with failures of previous treatment might have led Randhawa *et al*. to treat pediatric cases with finasteride (61). In 2013, the authors published a cases series of 3 pediatric cases of HS. All of the cases had failed to properly respond to antibiotics and other forms of treatment. They used 5-10 mg/day of finasteride in combination with OC and antibiotics, resulting in marked improvement in the 3 cases. The combination of OC and antibiotics had been tried previously in all cases; however, improvement only happened after the addition of finasteride. As a sidenote, the use of antiandrogens is contraindicated in pregnant women because it may cause feminization of male fetuses.

Metformin

A case report in 2009 by Arun and Loffeld (62) described an increase of HS activity after discontinuation of metformin treatment in a PCOS patient, suggesting that the drug had a beneficial effect on HS management. Kraft and Searles (50) reported no effect of metformin in a single case where the drug was used for 6 months. The effect of metformin was examined in a case series in 2012 by Verdolini *et al*. (63). In this series, 25 patients with HS were treated with metformin 500 mg once, twice, or thrice daily. After 24 months of treatment, patient Sartorius score had improved by 12.7 and DLQI by 7.6, suggesting that metformin could be a very effective treatment. The proposed mechanism of action for metformin is a reduction in ovarian androgen production (64) and/or by decreasing sensitization of the androgen receptor (65).

Spironolactone

Spironolactone, a diuretic with anti-antiandrogen properties (66), was found useful in only 1 out of 5 patients reviewed by Kraft and Searles (50). Additional observations were added by a case series by Lee and Fisher in 2015 (66). This retrospective case series reviewed the effect of 3-month treatment with 100-150 mg spironolactone in female patients with HS: 17 of 20 patients saw improvement on a patient global assessment (PGA) score specific for this trial, and 11 obtained complete disease control (80% of mild cases, 58% of moderate cases, and 0% of the severe cases). The impressive results from this series are somewhat diminished by the fact that 7 patients initiated contraceptive therapy at the same time (66).

Progesterone and estrogen effects of HS

Progesterone is the most prevalent progestogen in the human body. It is mainly produced in the gonads and affects cell expression by binding in intracellular progesten receptor-A and -B or the membrane-bound progesterone receptor membrane component-1 and -2. Progesterone mainly affects pregnancy, but has a range of other target tissues (47).

Estrogens are mainly produced in the ovaries, but also in the adrenal cortex, adipose tissue, chondrocytes, and even in parts of the brain (68). Estrogen activates three different receptors: the intracellular mainly genomic estrogen-α and -β receptor and the mainly non-genomic G protein-coupled estrogen receptor-1. Like the androgens, estrogen's effects are affected by both co-regulators and epigenetic regulation (68).

Estrogens receptors are present in the outer root sheaths (40), and Buimer *et al*. found no difference in estrogen receptor expression in the apocrine glands in HS vs non-HS cases(47).

Observational studies

The levels of progesterone and estrogen both rise through pregnancy (69) and decrease premenstrually (27), implying a pattern in which increasing levels of estrogen and/or progesterone appears to relieve symptoms.

The mode of action could be through the intracellular progesterone receptor (70) of the macrophages (71). Macrophages are present in lesional HS skin and overexpress Il-12 and Il-23 (72), which induces a Th17 response (73). High levels of progesterone suppress the development and function of Th1 and Th17 cells (74). Additionally, progesterone reduces TNF-α production of macrophages and myeloid dentritic cells (74). The effect could also be caused by another part of the inflammatory response, namely through the immune mechanisms involved in the primary disease process or through a yet unknown mechanism.

The influence of estrogens on inflammation is less well described. However, studies in mice suggest that estrogen receptors play a role in the Th1 response differentiation. In mouse models, high levels of estrogen can increase levels of IL-12 and induce a Th1 response leading to interferon γ (INF-γ) production (75,76). INF-

γ has been shown to be increased in HS on an mRNA level (77), but the significance of estrogens is unclear. Studies on systemic lupus mouse models showed that estrogen induced INF-γ production leads to B-cell class switch mutation in a pathogenic direction (78). If the same applies for HS, this would support the theory that HS is an autoimmune disease. This theory is further supported by patterns in other autoimmune diseases like rheumatoid arthritis (79) and multiple sclerosis (80), in which premenstrual flares and amelioration during pregnancy also occurs (78).

Interventions

The most popular use of hormone modulating therapy is oral contraceptives. In 1989, Stellon and Wakeling (81) published an interesting case series of 7 women who developed HS lesions closely after the initiation of progestogen containing oral contraceptives. Out of 7 patients, 2 recovered completely with discontinuation of the contraceptive, while another 3 benefited from changing to pills with a higher estrogen/progesterone ratio. The close temporal proximity of 1-2 months in 5 of the cases suggests a causal relationship. The role of oral contraceptives has not been examined since, except indirectly by Jemec *et al*. (11) who, in 1996, reported no differences in disease impact, which included number of work days lost, self-reported health, appearance, malodor, soreness, and discharge in either estrogen-based or progesterone-based contraceptive therapy. However, it is know that female patients with HS use oral contraceptives less frequently than controls (82).

Cyproterone acetate

In 1986, Sawers *et al*. (51) presented 4 cases of HS treated with antiandrogen cyproterone acetate (CPA) combined with estrogen. This treatment had already proven to be of some efficacy in patients with acne and works by reducing several hormones (i.e. estrogen and testosterone) (51). Using a reversed sequential regimen, patients were treated in cycles of 28 days with 100 µg of CPA for 10 days and 50 µg ethinyl estradiol every day. After 3-7 months, they reduced estradiol to 30 µg a day in order to reduce side effects. All 4 patients experienced rapid objective and subjective improvement of their condition.

Mortimer *et al*. (32) reported the findings of a randomized controlled trial (RTC). In this cross-over study, 24 moderate to severe HS cases were treated with 50 µg ethinyloestradiol and either 50 mg CPA or 500 µg Norgestrel for 6 months and then crossed over to the other treatment. Only 18 patients completed the trial, in 4 cases due to intolerance and in 2 cases due to deterioration. However, the lack of a uniform scoring system makes it difficult to assess the efficacy of this study's treatments with other drugs; both groups displayed subjective improvements, most noticeably in the CPA group with 7 patients clearing totally during the course of the trial. Unlike in Sawers' trial (51), Mortimer *et al*. found a reduction in free testosterone and an increase in SHBG during the treatment period for both groups. It is of note that all 24 patients suffered from premenstrual flares. Mortimer concludes that antiandrogen therapy is efficient, but the circulating levels of testosterone do not seem to be an indicator of severity nor does a reduction seem to correlate to clinical response.

In 2007, Kraft and Searles (50) reviewed their cases of HS treated with hormonal therapy. Hormonal manipulation had been used in cases where antibiotics failed to alleviate symptoms or when the patients' biochemical profile suggested a hyperandrogen state. In total, 29 of their patients were treated with a mixture of CPA 2 mg and ethinyl estradiol 0.035 mg (Diane – 35®) alone, Diane – 35® and CPA 25 mg in a reverse sequential regiment, and 12.5 mg CPA and 100 mg spironolactone. Subjective and clinical improvements were seen in 16 patients, but only few cases had levels of androgens measured. The authors found no difference in levels of testosterone, the DHEA-S LH/FSH ratio, or insulin levels between responders, non-responders, and all patients. This might be because of the low number of cases. The small number of patients in each treatment group and the limited information about why hormonal therapy was initiated makes conclusions based on this paper tenuous at best. It serves more as a reminder that hormonal manipulation is a valid treatment option for patients with HS.

Gonadotropin-releasing hormone agonists

In 1989, Camisa *et al*. reported a case with a 33-year-old severely afflicted patient with HS with androgenic alopecia and increased hair growth, who experienced "marked improvement" following treatment with the gonadotropin-releasing hormone agonist (GnRH), leuprolide acetate. The drug has never been examined since with regards to efficacy in HS.

Another GnRH agonist was reported as a successful treatment option in a case report from 1992 by Bogers *et al*. (83). Buserelin acetate 0.21 mg 3 times daily successfully cleared a 30-year-old woman suffering from premenstrual flares, with a 14 years duration of HS. After 10 months of treatment, 2 mg of estradiol daily was introduced to test if the disease was estrogen-dependent. As no new lesions occurred after 3 months, the patient was hysterectomied with a bilateral salpino-oophorectomy and put on estradiol replacement therapy. While this is an extreme form of

treatment, it does suggest that HS might be a steroid but not estrogen dependent disease.

CONCLUSION

The many cases describing premenstrual flares and changes in severity during pregnancy combined with the effect of antiandrogen therapy suggests an endocrine role in HS. Estrogen and progesterone seem to alleviate HS, as the premenstrual and postpartum decline lead to flares, but this conclusion is tenuous at best when considering that menopause seems to alleviate symptoms. The female sex hormones have never been the focus of treatment or manipulation in large-scale studies; the case series on HS onset after the initiation of progestin containing oral contraceptives makes this an ethical gray area unlikely to be explored. RTCs of antiandrogens vs either placebo, rifampicine/clindamycin, or adalimumab are notably absent. Further research on the post-receptor response to androgens, progestens, and estrogens in patients with HS are needed and recommend.

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