ORIGINAL REPORT

Association between Hidradenitis Suppurativa and Abnormalities in Semen Parameters and Sexual Function: A Pilot Study

Paz Lotan[1,2*], Yossef Haim TAIEB[2,3*], Shira BARMATZ[2,3], Shira FISCH-GILAD[2,3], Adam DALAL[2–4], Jen BARAK-LEVITT[5], Anat STEIN[2,6,7], Eran ALTMAN[2,6,7], Jack BANIEL[1,2], Shay GOLAN[1,2], Emmilia HODAK[2,3], Alexander DIMENT[2,8], Eli ATAR[2,8], Ohad SHOSHANY[1,2#], Yoel SHUFARO[2,6,7#] and Shany SHERMAN[2,3#]

[1]Department of Urology, Rabin Medical Center, Petach Tikva, [2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, [3]Division of Dermatology, Rabin Medical Center – Beilinson Hospital, Petach Tikva, [4]Department of Dermatology, Sheba Medical Center, Tel HaShomer, Ramat Gan, [5]Department of Dermatology, Emek Medical Center, Afula, [6]Andrology and Sperm Bank Service, Rabin Medical Center, [7]Infertility and IVF Unit, Helen Schneider Hospital for Women, Rabin Medical Center and [8]Department of Radiology, Rabin Medical Center, Petach Tikva, Israel
*These authors contributed equally to this work and *share first authorship #share last authorship.*

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease affecting patients of reproductive age. Although HS shares risk factors with male infertility, only 1 epidemiological study has evaluated this association. To further evaluate this potential association, findings on semen and hormonal analysis, testicular ultrasound, and the International Index of Erectile Function (IIEF-15) were compared between 28 men attending a tertiary HS clinic during the period April 2019 to April 2021, and 44 healthy controls, spouses of infertile women undergoing semen evaluation before in vitro fertilization. Patients with HS were divided based on the absence or presence of gluteal and genital lesions. Patients with HS were younger than controls (median 27 vs 34 years, $p < 0.0004$) and had a higher proportion of smokers (86% vs 33%, $p < 0.0001$). Semen parameters in patients with gluteal-genital lesions, specifically those with severe scrotal involvement necessitating surgery, were lower than the WHO reference values and significantly lower than in patients without gluteal-genital lesions and controls. Erectile dysfunction was reported by 93% of patients with HS. These findings suggest that spermatogenesis and sexual function may be impaired in young men with HS. Therefore, multidisciplinary management of HS should include their evaluation to identify patients who might benefit from semen cryopreservation and sexual treatment.

Key words: hidradenitis suppurativa; semen analysis; fertility; sexual function.

Accepted Oct 10, 2023; Published Nov 17, 2023

Acta Derm Venereol 2023; 103: adv11603.

DOI: 10.2340/actadv.v103.11603

Corr: Shany Sherman, Division of Dermatology, Rabin Medical Center – Beilinson Hospital, 39 Derech Ze'ev Jabotinsky, Petach Tikva 4941492, Israel. E-mail: shanyshnush@gmail.com

SIGNIFICANCE

Hidradenitis suppurativa is a chronic inflammatory skin disease affecting patients during their reproductive years. The association of hidradenitis suppurativa with male infertility has hardly been investigated. This study found significant sexual dysfunction and decreased semen parameters in young men with hidradenitis suppurativa, specifically when the gluteal-genital area was involved. Therefore, fertility and sexual function should be evaluated as part of the management of these patients, and when relevant, semen cryopreservation should be discussed. These findings should prompt further research toward implementing a standard of care.

Hidradenitis suppurativa (HS) is a chronic recurrent inflammatory disease affecting apocrine-gland-rich locations. The classic manifestation is the presence of at least 5 painful, deep-seated, inflamed lesions, including nodules, abscesses, sinus tracts, and scarring (1, 2).

The global prevalence of HS is estimated to be 0.4% (3), with a mean of 7–10 years delay in diagnosis from disease onset (4). The chronic nature of HS leads to frequent healthcare service utilization (5) and sometimes warrants multidisciplinary management by dermatologists, general and plastic surgeons, gynaecologists, and other disciplines.

Infertility is the failure to establish pregnancy during 12 months of regular, unprotected sexual intercourse in women younger than 35 years. This definition includes primary and secondary (with a prior pregnancy history) infertility. Infertility affects an estimated 16% of reproductive-age couples worldwide, with wide variations (6). Its aetiologies are diverse; up to 50% of cases involve male factors, such as pre-testicular, testicular, or post-testicular deficiencies (6, 7).

Both HS and male infertility are associated with impaired quality of life, sexual dysfunction, and poor general health, including higher-than-normal rates of cardiovascular diseases, diabetes, and mental health disorders (1, 8–11). They also share several risk factors, such as obesity, hypothyroidism, zinc deficiency, smoking, and substance abuse (2, 6, 11–16). A chronic inflammatory state has been suggested as the underlying mechanism of impaired fertility associated with obesity, inflammatory bowel disease (IBD), psoriasis, atopic dermatitis, and coeliac disease (12, 17–19). Moreover, impaired

fertility has been linked to local testicular hyperthermia attributable to friction, varicocele, environmental heat, and local inflammation (12). Thus, the systemic and local inflammation involving the perineal area in HS could contribute to male infertility (1, 2).

Data on the potential association between HS and infertility are sparse. As a result of the higher HS occurrence in females (1, 2), the few available studies concentrated on comorbid female endocrine abnormalities, such as polycystic ovary syndrome, obstetric and neonatal sequelae (1, 2, 20), and female reproductive potential (21, 22). In the sole epidemiological population-based study that evaluated infertility in both sexes, an association of HS was found only in females (21). However, relevant parameters, such as lesion location and possible hormonal or urological factors, were not considered.

A positive association of HS with male infertility could have psychosocial, medical, and surgical management implications. The current study aimed to investigate the association of HS with male fertility parameters and sexual function. Because of their young age, most patients had not yet tried to conceive with a partner; therefore, this study investigated semen parameters as a surrogate for male fertility. Separate analyses were performed on patient subgroups according to the location of their lesions.

MATERIALS AND METHODS

The study was conducted at the HS clinic of Rabin Medical Center, Beilinson Hospital, a tertiary medical center in Israel. Consecutive male patients aged 18 or older who visited the clinic between April 2019 and April 2021 were enrolled. HS was diagnosed clinically by 2 board-certified dermatologists (YHT and SS). Exclusion criteria were a history of cryptorchidism, orchitis, epididymitis, sexually transmitted infection, hypogonadism, karyotype abnormalities, testicular torsion, trauma, and perineal or inguinoscrotal surgeries other than for HS treatment.

Findings were compared with a control group of healthy men aged 18 years or older undergoing semen analysis before in vitro fertilization in the same medical centre because of female-factor infertility. Exclusion criteria were identical to those for the HS group. Clinical and semen analysis data were collected retrospectively, anonymized, and coded.

The study was approved by the local Institutional Review Board (IRB), the Rabin Medical Center Review Board; Approval No. RMC-20-0058 for the patients with Hidradenitis Suppurativa, and approval No. RMC-19-0697 for the anonymously collected data of the healthy men control group. All patients gave written informed consent at enrollment to participate in the study. The IRB waived the need for informed consent for the control group.

All patients with HS underwent a complete medical history and physical examination by a dermatologist and urologist. Anamnestic and demographic data were recorded, including disease duration, disease severity, by Hurley and the International HS Severity Score System (IHS4) stages (mild-to-severe), comorbidities, and treatments. Fertility history, and physical signs of hormonal imbalances, such as gynaecomastia and abnormal body hair distribution, were evaluated.

Patients with HS completed the International Index of Erectile Function (IIEF-15) questionnaire for sexual function evaluation. The IIEF-15 is a widely used, multidimensional, self-report assessment tool for erectile dysfunction (ED) severity and a primary endpoint for its treatment in clinical trials. It comprises 15 items, each scored on a scale of 0–5, divided into 5 domains. The domain sub-scores are combined to yield a total score (range 5–75). Higher scores indicate better sexual function; 53 is considered the optimal cutoff (24). Erectile function (range 6–30) is the only domain that has been validated to determine cutoffs for 5 categories of severity: no ED (score 26–30), mild (22–25), mild-to-moderate (17–21), moderate (11–16), and severe (6–10) (25). For the rest of the domains, the cutoffs were based on the control group scores in the study of Rosen et al. (23): orgasmic dysfunction, 8; sexual desire, 7; intercourse satisfaction, 10; and overall satisfaction, 8.

Semen samples were obtained at the institute's sperm bank laboratory by masturbation after 3 days of abstinence. Semen analysis was performed within 1 h of liquefaction at room temperature. Parameters were evaluated according to the guidelines of the World Health Organization (WHO) laboratory manual, 5th edition: Semen volume, semen concentration, total semen count, normal semen motility, and morphology percentage (using the strict criteria of Kruger et al. (26)), and total motile semen count (TMSC). TMSC is among the best male fertility outcome predictors (27–29).

Concentration and motility were evaluated by visualizing a 10-µL aliquot of semen on a Makler chamber (Sefi-Medical Instruments, Haifa, Israel) using a phase-contrast microscope (Olympus CX21; Olympus, Tokyo, Japan). The number of cells in a strip of 10 squares indicated semen concentration (millions/mL). TMSC and total count were calculated using the following formulas: co ncentration*volume*motility/100 and volume*concentration, respectively. Morphology was assessed using automated computer-assisted sperm analysis (CASA) (SQA-VISION, Medical Electronic Systems, Los Angeles, CA, USA).

C-reactive protein (CRP) levels, measured during the months before and after study enrollment, were reviewed. Blood levels of testosterone were measured by radioimmunoassay with commercial kits (Radim, Pomezia, Italy). Levels of prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH(, and thyroid-stimulating hormone (TSH) were taken as well.

Scrotal Doppler ultrasound assessment was conducted by a single experienced operator using a 10–4 MHz linear array transducer (WS80 Elite, Samsung, Seoul, South Korea). Testis parameters were recorded, including calculated volume and varicocele (30, 31).

Initial analyses identified the subgroup of patients with gluteal and genital lesions with significantly reduced semen parameters. Therefore, the HS cohort was divided according to the absence or presence of gluteal and genital lesions.

Statistical analysis

Baseline characteristics were summarized as median and range for continuous variables without a normal distribution and absolute number and percent for ordinal and nominal variables. Student's *t*-test, Mann–Whitney *U*, Kruskal–Wallis, and analysis of variance (ANOVA) tests were used to assess differences between groups based on normality tests. Analyses were adjusted for age and smoking (pack-years) using the general linear model (GLM). When necessary, logarithmic and arcsine transformations were performed for symmetry. Post hoc Tukey-Kramer correction was used to adjust for multiple comparisons. Spearman correlation was used to evaluate a possible association between semen parameters and CRP levels.

Table I. Demographic and clinical characteristics of patients with hidradenitis suppurativa (HS) ($n=28$)

Variable	N
Age (years), median (range)	27 (18–42)
Body mass index (kg/m^2), median (range)	26.6 (17–38.6)
Smoking	24 (86)
Cannabis use, *n* (%)	14 (50.0)
Alcohol consumption, *n* (%)[a]	11 (39.3)
Lesion location, *n* (%)[b]	
Genitalia (scrotum)	7 (25.0)
Gluteus	16 (57.1)
Groin	22 (78.6)
Axillae	17 (60.7)
Breast	3 (10.7)
Extra-intertriginous	16 (57.1)
Lesion counts, median (range)	
Total number of abscesses and inflammatory nodules (AN count)	2 (0–8)
Number of abscesses	0 (0–2)
Number of inflammatory nodules	1 (0–8)
Number of draining fistulas	0.5 (0–5)
Disease severity, *n* (%)	
IHS4 score[c]	
Median (range)	5 (1–22)
Mean (SD)	7.46 (6.9)
IHS4 severity[d]	
Mild	10 (35.7)
Moderate	12 (42.9)
Severe	6 (21.4)
Hurley stage	
1	11 (39.3)
2	10 (35.7)
3	7 (25.0)
Comorbidities, *n* (%)	
Psoriasis	1 (3.6)
Inflammatory bowel disease	2 (7.1)
Diabetes	0
HS duration (years), median (range)	5.0 (0.5–28.0)
Time to diagnosis (years), median (range)	5.0 (0.2–18.0)
Family history of HS (first-degree relative), n (%)	11 (39.3)
Treatment, *n* (%)	
Topical antibiotics	16 (57.1)
Systemic antibiotics[e]	26 (92.9)
Isotretinoin	9 (32.1)
Anti-TNFα (adalimumab, infliximab)	4 (14.3)
Analgesics (opiates, gabapentin, NSAIDs)	16 (57.1)
Surgical treatment involving genitalia	4 (14.3)
Surgical treatment not involving genitalia	16 (57.1)

[a]All were light-to-moderate drinkers (no heavy drinkers), according to the drinking status of the Centers for Disease Control and Prevention (https://www.cdc.gov/nchs/nhis/alcohol/alcohol_glossary.htm). [b]The percentage sum is > 100% because some patients had lesions in more than 1 location. [c]The IHS4 was calculated using the formula: (number of nodules)*1+(number of abscesses)*2+(number of draining tunnels [fistulae/sinuses])*4. [d]The IHS4 score was subdivided into levels of severity according to mild (≤ 3), moderate (4–10), and severe (≥ 11). [e]Doxycycline, rifampicin clindamycin, and trimethoprim/sulphamethoxazole.
HS: hidradenitis suppurative; IHS4: International HS Severity Score System; anti-TNFα: anti-tumour necrosis factor alpha; AN: abscess and nodules.

Statistical analyses were performed with SPSS version 25.0 and SAS version 9.4. Two-sided significance was set at $p<0.05$.

RESULTS

Baseline characteristics of patients with hidradenitis suppurativa and controls

A total of 28 patients with HS were enrolled. Their demographic and clinical characteristics are shown in **Table I**. The median duration of HS was 5 years (range 0.5–28). Most patients had moderate-to-severe disease (60.7% Hurley stage ≥2, 64.3% IHS4 moderate-to-severe). Forty-four healthy men comprised the control group. Patients with HS were younger than the controls (median 27.0 vs 34.0 years, $p<0.0004$) and had a higher smoking rate (86% vs 33%, pack-years 10.3 vs 0; $p<0.0001$ for both) (**Table II**). There was no between-group difference in body mass index (BMI).

Semen parameters

Semen analysis parameters of the HS and control groups are shown in Table II. Compared with controls, patients with HS had a significantly lower total semen count (median 58*10^6 vs 172*10^6, $p<0.0001$), semen concentration (median 20*10^6/mL vs 60*10^6/mL, $p<0.0001$), and TMSC (median 27.6*10^6 vs 77.6*10^6, $p=0.0004$). Significance was maintained even after controlling for age and smoking. However, these were just above the WHO reference values (27, 28).

Intake of possible gonadotoxins (11, 12, 32), such as cannabis, was not associated with lower semen parameters in the HS group. Within this group, there was no difference in semen concentration between those who used cannabis ($n=14$, 50%) and those who did not (median 24.5*10^6/mL vs 17.5*10^6/mL, respectively; $p=0.945$). Rates of heavy alcohol and opiate consumption were negligible overall and were, therefore, not analysed separately. Medical treatment for HS was heterogeneous, but none of the drugs used (Table I) were associated with semen parameters.

Sixteen patients (57%) had lesions in the gluteal-genital area. Their semen parameters were significantly

Table II. Demographic characteristics and semen parameters of patients with hidradenitis suppurative (HS) and control group

Demographic and semen characteristics	WHO ref. value [27–29]	HS group ($n=28$)	Control group ($n=44$)	*p*(v) Unadjusted	*p*(v) Adjusted*
Age (years), median (range)	NA	27.0 (18.0–42.0)	34.0 (27.0–41.0)	**0.0004**	
BMI (kg/m^2), median (range)	NA	26.6 (17.0–38.6)	25.5 (24.0–36.6)	0.9001	
Smoking (pack-years), median (range)[a]	NA	10.3 (0–48.0)	0 (0–15.0)	**<0.0001**	
Smoking, *n* (%)[a]	NA	24.0 (86.0)	12.0 (33.0)	**<0.0001**	
Semen count (*10^6), median (range)	≥39.0	58.0 (0.5–320.0)	172.0 (19.6–533.0)	**<0.0001**	**<0.0001**
Motility (%), median (range)	≥40%	50.0 (10.0–80.0)	50.0 (18.0–90.0)	0.4582	0.1310
Normal morphology (%), median (range)	≥4%.	7.0 (0–15.0)	5.0 (0–17.0)	0.1221	0.8590
Semen concentration (*10^6/mL), median (range)	≥15	20.0 (0.2–90.0)	60.0 (20.0–176.0)	**<0.0001**	**<0.0001**
Total motile semen count (*10^6), median (range)[b]	≥20	27.6 (0.1–216.0)	77.6 (5.9–378.0)	**0.0004**	**0.0002**

[a]Only 36 controls had data on smoking status. [b]Calculated by semen concentration/mL* volume (mL)*motility/100% (29).
NA: not applicable. *Adjusted for age and pack-years of smoking. BMI: body mass index; ref: reference; AN: abscess and nodules. Bold denotes statistical significant results.

Table III. Demographic characteristics and semen parameters of subgroups of patients with hidradenitis suppurative (HS) and control group

Demographic and sperm characteristics	WHO ref. value [27–29]	Control group ($n=44$)	Non-gluteal-genital ($n=12$)	Gluteal-genital ($n=16$)	p(v)	
					Unadjusted	Adjusted*
Age (years), median (range)	NA	34.0 (27.0–41.0)	25.5 (18.0–34.0)	28.0 (21.0–42.0)	**0.0003**	
BMI (kg/m^2), median (range)	NA	25.5 (24.0–36.6)	27.7 (17–37.2)	26.2 (19.4–38.6)	0.7	
Smoking (pack-years), median (range)[a]	NA	0 (0–15.0)	10.25 (0–24.0)	10.25 (0–48.0)	**<0.0001**	
Semen count (*10^6), median (range)	≥39.0	172.0 (19.6–533.0)	126.5 (32.0–270.0)	41.1 (0.5–320.0)	**<0.0001**	**<0.0001**
Motility (%), median (range)	≥40%	50.0 (18.0–90.0)	55.5 (25.0–80.0)	45.5 (1.5–80.0)	0.2	0.115
Normal morphology (%), median (range)	≥4%.	5.0 (0–17.0)	9.0 (3–15.0)	6.0 (0–15.0)	0.067	0.13
Semen concentration (*10^6/mL), median (range)	≥15	60.0 (20.0–176.0)	48.0 (10–90.0)	14.5 (0.2–50.0)	**<0.0001**	**<0.0001**
Total motile sperm count (*10^6) median (range)[b]	≥20	77.6 (5.9–378.0)	73.5 (10.5–216.00)	5.4 (0.1–107.2)	**<0.0001**	**<0.0001**

[a]Only 36 controls had data on smoking status. [b]Calculated by semen concentration/mL* volume (mL)*motility/100% (29).
NA: not applicable. *Adjusted for age and pack-years of smoking with post hoc Tukey-Kremer correction for multiple comparisons. Bold denotes statistical significant results.

lower than both the patients without gluteal-genital lesions and controls (**Table III**): total semen count (median 41.1*10^6 vs 126.5*10^6 vs 172*10^6, respectively, $p<0.0001$), semen concentration (median 14.5*10^6/mL vs 48*10^6 /mL vs 60*10^6 /mL, respectively, $p<0.0001$), and TMSC (median 5.4*10^6 vs 73.5*10^6 vs 77.6*10^6, respectively, $p<0.0001$). Semen concentration and TMSC were below the WHO reference values (27, 28). There were no differences in semen parameters between the subgroup without gluteal-genital lesions and controls.

Seven patients (25%) were classified as Hurley 3, and 6 (21.4%) as IHS4-severe (Table I). All patients classified as IHS4-severe also had Hurley 3 disease. Six patients with Hurley 3 disease had gluteal-genital lesions, and only 1 patient, classified as Hurley 3 and IHS4-severe, did not. Among the patients with gluteal-genital lesions, 7 (25%) had scrotal lesions (including 4 Hurley 3 and IHS4-severe disease); 4 of them required scrotal surgery (3 Hurley 3, 1 Hurley 2). Patients with scrotal involvement had even lower semen values than the rest of the gluteal-genital subgroup. Still, the difference was not statistically significant: total semen count (median 12*10^6 vs 50*10^6, respectively, $p<0.9$), semen concentration (median 6*10^6/mL vs 16*10^6 /mL, respectively, $p<0.8$), and TMSC (median 6*10^6 vs 4.8*10^6, respectively, $p<0.53$). Patients in the gluteal-genital subgroup without scrotal lesions had semen count and concentration just above the WHO reference values, but still significantly lower than the values of those without gluteal-genital lesions ($p=0.008$ and $p=0.015$, respectively) and controls ($p<0.0001$ for both). Patients who underwent scrotal surgery had the lowest semen parameters; semen concentration (median 2.7*10^6), total semen count (median 3.66*10^6), and TMSC (median 1.96*10^6).

There were no between-subgroups differences in BMI, smoking rate, age, type of medical treatment, disease duration, and years to diagnosis.

Inflammatory markers

Highly sensitive CRP levels were measured in 21 patients with HS (75%). CRP was significantly higher in patients with more severe disease (Hurley 3, IHS4-severe) than in the rest of the cohort (Hurley 3: median 1.8 mg/L (0.38–11.3) vs 0.34 mg/L (0.04–0.8), $p=0.012$; IHS4-severe: median 2.9 mg/L (0.4–11.3) vs 0.38 mg/L (0.04–0.8), $p=0.0045$). There was a tendency for a negative correlation between consecutive CRP levels and semen parameters, but it did not reach statistical significance ($r_s=(-0.22)$, $p=0.35$). There was no difference in semen parameters between patients with or without an abnormal CRP level (>0.5mg/L, $p=1$). CRP level was not associated with the presence/absence of gluteal-genital lesions or scrotal involvement. There was no difference in semen parameters between patients who had or did not have a CRP test.

Hormonal parameters and Doppler ultrasound of the testes

All patients with HS had normal LH, FSH, prolactin, total testosterone, and TSH levels without in-between-subgroup differences. On Doppler ultrasound, the median volume was within the normal range in both testes (≥15 cm^3) (33). Four patients (14%) had varicocele, 2 bilaterally, a rate similar to the general population (12) (Table SI).

Sexual function questionnaire

Median IIEF-15 scores (Table SII) in patients with HS were decreased in all domains except sexual desire. The median total score was 49 (range 38–57). Only 2 patients (7%) reported a normal penile erection. Among the remainder, ED was rated mild by 8 patients (29%), mild-to-moderate by 10 (36%), moderate by 7 (25%), and severe by 1 (3%). There was no difference in IIEF-15 scores by subgroups, scrotal involvement, surgery, disease severity, disease duration, or type of treatment.

DISCUSSION

This study comprehensively evaluated the association of HS with spermatogenesis and male sexual function using semen analysis, testicular Doppler ultrasound, the IIEF-15 questionnaire, and hormonal and endocrine profiles. Patients with HS involving the gluteal-genital area had significantly reduced semen parameters compared with

the remaining patients with HS and healthy men. The poorest results, below the WHO reference values (27, 28), were found in patients with severe scrotal involvement who had surgery. However, even in patients with gluteal-genital lesions without scrotal involvement, semen parameters were borderline, and their TMSC, an important fertility outcome predictor (29), was even lower than those with scrotal lesions.

These findings align with our previous nationwide epidemiological study wherein a possible association between HS and male infertility was found on univariate analysis but not on multivariate analysis adjusted for demographic and clinical characteristics (21). That study did not consider the location of the lesions or semen parameters. In the current study, although the semen parameter values were lower in the total HS group than in controls, they were just above the WHO reference values (27, 28). It is possible that the heterogeneity of the HS population masked significant pathological findings that can be refined by phenotyping.

Cazzaniga et al. (34) recently described 3 HS phenotypes using latent class (LC) analysis: LC1- axillary-mammary-groin, LC2- axillary-gluteal-groin, and LC3- regular axillary-groin. LC2 was characterized by mainly non-obese males with moderate-to-severe disease and a high probability of gluteal and genital lesions, corresponding to patients with gluteal-genital lesions in the current study. Our subgroup of patients without gluteal-genital lesions had predominantly axillary and groin involvement and milder disease similar to the LC3 phenotype, except for 1 patient who had Hurley 2 disease with primarily anterior and mammary lesions corresponding to the LC1 phenotype. We believe the similarity between these phenotypes and our subgroups strengthens our findings, highlighting that a subset of men with a specific HS phenotype is at risk of fertility impairment.

Inflammation has been suggested as the pathophysiological link between infertility and other chronic inflammatory diseases, such as IBD, psoriasis, and atopic dermatitis (17–19). Both systemic inflammation and local hyperthermia have been associated with increased semen DNA fragmentation and damage, arrest of spermatogenesis, and lower male fertility potential (35). HS is accompanied by systemic and local inflammation with increased serum inflammatory markers, such as CRP and interleukins, local hyperaemia, and oedema (1, 2). In the current study, CRP levels were associated with disease severity but not semen parameters. In previous studies, CRP did not associate with male infertility (36).

Chronic recurrent gluteal-genital inflammation and scrotal surgery can affect male fertility through several local mechanisms, including blood-testis barrier disruption and anti-semen antibodies formation, hyperthermia, and possible obstruction of the seminal canals (35). Our results suggest that a severe local inflammatory process, possibly with the additive effect of systemic inflammation, might compromise the fertility potential of young men with an HS phenotype characterized by genital and gluteal lesions.

Abnormal hormonal levels have been suggested as a possible mechanism underlying female HS-associated infertility (1, 37). However, no abnormalities in prolactin, gonadotropins, or testosterone were observed in the current study. In addition, although others reported an association of hypothyroidism and diabetes mellitus with semen impairments and HS (1, 11, 13, 14), our patients had normal TSH levels, and none had diabetes. These findings suggest that hormonal changes are less significant in HS-related male infertility.

Advanced age is associated with higher rates of infertility and sexual dysfunction (14). Nevertheless, in the current study, although the patients with HS were considerably younger than controls, they had worse semen parameters and abnormal IIEF-15 scores in all domains except sexual desire. Notably, 93% of the HS cohort had some degree of ED, much higher than the suggested 15% rate for men younger than 49 years (38). Previous studies reported a higher incidence of sexual dysfunction in men with HS aged 18–44 years, with rates of ED reaching 50–60% and total IIEF-15 scores between 42 and 50, similar to our cohort. However, they did not report IIEF-15 scores according to domains or specify the erectile function domain in their analysis (10). The younger age of the current HS cohort emphasizes the need to evaluate and monitor fertility and sexual function in affected men to detect early impairments. A finding of abnormal semen parameters may guide toward counselling the patient regarding semen cryopreservation to conserve future fertility.

This study was limited by its design and relatively small patient population, which precluded the establishment of causality rather than association. Furthermore, data on possible confounders were missing in the control group, such as the use of medications, cannabis, and alcohol, as well as IIEF-15 scores. However, a recent study describing the reproductive-age population in Israel found a 66.7% rate of recreational cannabis use among men (39). Thus, the 50% rate in our patients with HS would not be expected to differ significantly from controls. In addition, the 33% smoking rate in the control group was similar to the rate in Israeli men (27.3%), according to the Israel Ministry of Health (40). Thus, we believe the control group is representative of the general population.

The heterogeneity in HS treatments may have limited our ability to account for all possible gonadotoxins that could have affected the semen parameters. However, no significant effect on male fertility was previously identified for these treatments (32).

Finally, our tertiary HS clinic treats patients with the most severe manifestations of HS, whereas milder HS

is treated in community settings, which might affect the generalizability of the current results.

In conclusion, this study of an association between HS in reproductive-age men and impaired semen parameters and sexual function has considerable clinical relevance. These findings suggest that fertility and sexual function should be routinely assessed as part of the multidisciplinary management of HS in young men, specifically those with gluteal and genital lesions. Patients found to have abnormal semen parameters should be counselled regarding possible semen cryopreservation. These findings should prompt further research toward implementing a standard of care.

ACKNOWLEDGEMENTS

The authors would like to thank Maya Ash for her technical assistance organizing the data.

This research received no specific grants from public, commercial, or not-for-profit funding agencies.

The study was reviewed and approved by the local Institutional Review Board (IRB), the Rabin Medical Center Review Board; approval number RMC-20-0058 for the patients with Hidradenitis Suppurativa, and approval number RMC-19-0697 for the anonymously collected data of the healthy men control group. The study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Informed consent was obtained from all participants included in the study.

The patients in this manuscript have given written informed consent to the publication of their non-identifiable, anonymized health information. The submission does not include images or data that may identify the person.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

The authors have no conflicts of interest to declare.

REFERENCES

1. Nguyen TV, Damiani G, Orenstein LAV, Hamzavi I, Jemec GB. Hidradenitis suppurativa: an update on epidemiology, phenotypes, diagnosis, pathogenesis, comorbidities and quality of life. J Eur Acad Dermatol Venereol 2021; 35: 50–61.
2. Goldburg SR, Strober BE, Payette MJ. Hidradenitis suppurativa: epidemiology, clinical presentation, and pathogenesis. J Am Acad Dermatol 2020; 82: 1045–1058.
3. Jfri A, Nassim D, O'Brien E, Gulliver W, Nikolakis G, Zouboulis CC. Prevalence of hidradenitis suppurativa: a systematic review and meta-regression analysis. JAMA Dermatol 2021; 157: 924–931.
4. Saunte DM, Boer J, Stratigos A, Szepietowski JC, Hamzavi I, Kim KH, et al. Diagnostic delay in hidradenitis suppurativa is a global problem. Br J Dermatol 2015; 173: 1546–1549.
5. Shalom G, Babaev M, Freud T, Tiosano S, Pam N, Horev A, et al. Demographic and health care service utilization by 4417 patients with hidradenitis suppurativa. J Am Acad Dermatol 2017; 77: 1047–1052.e2.
6. Skakkebaek NE, Rajpert-De Meyts E, Buck Louis GM, Toppari J, Andersson AM, Eisenberg ML, et al. Male reproductive disorders and fertility trends: influences of environment and genetic susceptibility. Physiol Rev 2016; 96: 55–97.
7. Katz DJ, Teloken P, Shoshany O. Male infertility – the other side of the equation. Aust Fam Physician 2017; 46: 641–646.
8. Lotti F, Corona G, Castellini G, Maseroli E, Fino MG, Cozzolino M, et al. Semen quality impairment is associated with sexual dysfunction according to its severity. Hum Reprod 2016; 31: 2668–2680.
9. Yee D, Collier EK, Atluri S, Jaros J, Shi VY, Hsiao JL. Gender differences in sexual health impairment in hidradenitis suppurativa: a systematic review. Int J Womens Dermatol 2020; 7: 259–264.
10. Varney P, Guo W, Brown M, Usmani H, Marquez J, Ayasse M, et al. A systematic review and meta-analysis of sexual dysfunction in patients with hidradenitis suppurativa.Int J Dermatol 2023; 62: 737–746.
11. Daumler D, Chan P, Lo KC, Takefman J, Zelkowitz P. Men's knowledge of their own fertility: A population-based survey examining the awareness of factors that are associated with male infertility. Hum Reprod 2016; 31: 2781–2790.
12. Durairajanayagam D. Lifestyle causes of male infertility. Arab J Urol 2018; 16: 10–20.
13. Sherman S, Tzur Bitan D, Kridin K, Pavlovsky L, Hodak E, Cohen AD. Hidradenitis suppurativa is associated with hypothyroidism and hyperthyroidism: a large-scale population-based study. Int J Dermatol 2021; 60: 321–326.
14. La Vignera S, Vita R. Thyroid dysfunction and semen quality. Int J Immunopathol Pharmacol 2018; 32: 2058738418775241.
15. Poveda I, Vilarrasa E, Martorell A, García-Martínez FJ, Segura JM, Hispán P, et al. Serum zinc levels in hidradenitis suppurativa: a case-control study. Am J Clin Dermatol 2018; 19: 771–777.
16. Khan MS, Zaman S, Sajjad M, Shoaib M, Gilani G. Assessment of the level of trace element zinc in seminal plasma of males and evaluation of its role in male infertility. Int J Appl Basic Med Res 2011; 1: 93–96.
17. Wdowiak A, Gujski M, Bojar I, Raczkiewicz D, Bartosińska J, Wdowiak-Filip A, et al. Chronic inflammation impairs male fertility – a case-control study in ulcerative colitis patients. J Clin Med 2021; 10: 1460.
18. Finelli R, Leisegang K, Finocchi F, De Masi S, Agarwal A, Damiani G. The impact of autoimmune systemic inflammation and associated medications on male reproductive health in patients with chronic rheumatological, dermatological, and gastroenterological diseases: a systematic review. Am J Reprod Immunol 2021; 85: e13389.
19. Horev A, Shalom G, Weintraub AY, Freud T, Cohen AD. Atopic dermatitis and infertility: a nationwide retrospective cohort study. Dermatology 2022; 238: 313–319.
20. Althagafi H, Spence AR, Czuzoj-Shulman N, Abenhaim HA. Effect of hidradenitis suppurativa on obstetric and neonatal outcomes. J Matern Fetal Neonatal Med 2022; 35: 8388–8393.
21. Tzur Bitan D, Kridin K, Hodak E, Cohen A, Sherman S. The association between hidradenitis suppurativa and male and female infertility: a population-based study. Australas J Dermatol 2021; 62: e223–e227.
22. Montero-Vilchez T, Salvador-Rodriguez L, Rodriguez-Tejero A, Sanchez-Diaz M, Arias-Santiago S, Molina-Leyva A. Reproductive potential and outcomes in patients with hidradenitis suppurativa: clinical profile and therapeutic implications. Life (Basel) 2021; 11: 277.
23. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997; 49: 822–830.
24. Wiltink J, Hauck EW, Phädayanon M, et al. Validation of the German version of the International Index of Erectile Function (IIEF) in patients with erectile dysfunction, Peyronie's disease and controls. Int J Impot Res 2003; 15: 192–197.
25. Cappelleri JC, Rosen RC, Smith MD, Mishra A, Osterloh IH. Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. Urology 1999; 54: 346–351.
26. Kruger TF, Acosta AA, Simmons KF, Swanson RJ, Matta JF, Oehninger S. Predictive value of abnormal sperm morphology in in vitro fertilization. Fertil Steril 1988; 49: 112–117.
27. Cooper TG, Noonan E, von Eckardstein S, Auger J, Baker HW, Behre HM, et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update

2010; 16: 231–245.
28. World Health Organization. WHO Laboratory Manual For The Examination and Processing of Human Semen, 5th ed. [created 2010, available 16.6.2012]. Available from: https://apps.who.int/iris/handle/10665/44261.
29. Hamilton JA, Cissen M, Brandes M, meenk JM, de Bruin JP, Kremer JA, et al. Total motile sperm count: a better indicator for the severity of male factor infertility than the WHO sperm classification system. Hum Reprod 2015; 30: 1110–1121.
30. Lenz S, Giwercman A, Elsborg A, Cohr KH, Jelnes JE, Carlsen E, et al. Ultrasonic testicular texture and size in 444 men from the general population: correlation to semen quality. Eur Urol 1993; 24: 231–238.
31. Pilatz A, Altinkilic B, Köhler E, Marconi M, Weidner W. Color Doppler ultrasound imaging in varicoceles: is the venous diameter sufficient for predicting clinical and subclinical varicocele? World J Urol 2011; 29: 645–650.
32. Semet M, Paci M, Saïas-Magnan J, Metzler-Guillemain C, Boissier R, Lejeune H, et al. The impact of drugs on male fertility: a review. Andrology 2017; 5: 640–663.
33. Condorelli R, Calogero AE, La Vignera S. Relationship between testicular volume and conventional or nonconventional sperm parameters. Int J Endocrinol 2013; 2013: 145792.
34. Cazzaniga S, Pezzolo E, Bettoli V, Abeni D, Marzano AV, Patrizi A, et al. Characterization of hidradenitis suppurativa phenotypes: a multidimensional latent class analysis of the National Italian Registry IRHIS. J Invest Dermatol. 2021; 141: 1236–1242.e1.
35. Wright C, Milne S, Leeson H. Sperm DNA damage caused by oxidative stress: modifiable clinical, lifestyle and nutritional factors in male infertility. Reprod Biomed Online 2014; 28: 684–703.
36. Hærvig KK, Kierkegaard L, Lund R, Bruunsgaard H, Osler M, Schmidt L. Is male factor infertility associated with midlife low-grade inflammation? A population based study. Hum Fertil (Camb) 2018; 21: 146–154.
37. Mortimer PS, Dawber RP, Gales MA, Moore RA. Mediation of hidradenitis suppurativa by androgens. Br Med J (Clin Res Ed) 1986; 292: 245–248.
38. Rosen RC, Fisher WA, Eardley I, Niederberger C, Nadel A, Sand M; Men's Attitudes to Life Events and Sexuality (MALES) Study. The multinational Men's Attitudes to Life Events and Sexuality (MALES) study: I. Prevalence of erectile dysfunction and related health concerns in the general population. Curr Med Res Opin 2004; 20: 607–617.
39. Isralowitz R, Reznik A, Zolotov Y, Grinstein-Cohen O, Wacht O, Pruginin I, et al. Toward medical cannabis education in Israel. Complement Ther Med 2021; 58: 102709.
40. Israel Ministry of Health. Updated data on smoking rates in Israel. [accessed 15/01/2023] Available from: https://www.health.gov.il/Subjects/KHealth/smoking/Pages/SmokingRatesInIsrael.aspx.