

Infertility rates among the pemphigus population

Keywords: Infertility, pemphigus

Introduction

The impact of pemphigus on male and female infertility is unknown. Infertility affects up to 15% of couples and counseling patients on impact on fertility when given a new medical diagnosis is an important part of medical care.¹ In women, the diagnosis of pemphigus tends to occur at a time when fertility is rapidly declining, making this information even more important. One prior case series described 9 patients with pemphigus vulgaris, 8 of whom were unable to become pregnant.² Our goal was to further determine rates of infertility in patients with pemphigus.

Materials and methods

A retrospective chart review was performed for patients of reproductive age (ages 15–49) with a diagnosis of pemphigus vulgaris or foliaceus, as confirmed by laboratory testing or clinician assessment, at the University of Minnesota MHealth Dermatology Clinic from 2005 to 2019. Each chart was assessed for diagnosis or mention of infertility via chart review and included review of obstetric/gynecology, primary care, and endocrinology notes as well as utilization of the keyword search function for “infertility.” Mutually exclusive groups were defined as “definite infertility” (DI; meeting criteria as per obstetrician/gynecologist clinician assessment and/or formal infertility definition), “reproductive issues” (RI; infertility or recurrent pregnancy loss discussed in any clinician notes, though the diagnosis was not confirmed by clinician and/or infertility definition), and having a “diagnosis associated with infertility” (DAI) as is listed in Table 1. We assessed all the above groups so as not to miss an association with pemphigus and infertility. Patients with pemphigus were compared to age- and sex- matched control patients who had been evaluated in our general dermatology clinic without a diagnosis of pemphigus. We then compared controls to those with DI as well as to those with those RI and DAI using Fisher’s exact tests. Measures assessed included demographics, rates of infertility, and for patients who met criteria for infertility, the severity of their pemphigus, associated comorbidities, and medications taken.

Results

Of 46 patients of reproductive age with pemphigus, 3 (6.5%) had DI, 3 (6.5%) had RI, and 6 (13.0%) had DAI (Table 1).

Two patients with either RI or a DAI had vaginal involvement of their pemphigus; no patients with DI had genitourinary involvement (Table 2). Demographic information collected for pemphigus patients with and without fertility were similar. Compared to patients with pemphigus and no fertility issues, patients with DI and RI did not have more severe disease as assessed by rates of hospitalizations and desmoglein titers. Rates of rituximab usage were similar. No patients with pemphigus had received cyclophosphamide. Compared to controls, there was no statistically significant difference in rates of infertility in patients with DI ($P = 1.0$; 4.3% controls vs 6.5% pemphigus), in patients with DI and RI ($P = .739$; 8.7% vs 13.0%), or in patients with DI, RI, and DAI ($P = .052$; 8.7% vs 26.1%).

Discussion

Infertility rates in patients with pemphigus do not appear increased relative to the general dermatology population, even when considering patients with possible RI and DAI. This information can aid in counseling patients of reproductive age diagnosed with this condition. Larger prospective studies are needed to confirm these findings.

This was a single-center, retrospective chart review at an institution without a dedicated Reproductive Endocrinology and Infertility clinic, which may underestimate rates of infertility. Although the rates of infertility approached significance when including RI, and DAI in addition to DI, including these categories likely overestimates rates of infertility.

Conflicts of interest

The authors made the following disclosures: D.R.P. is a consultant for Biogen, Inc. and Pfizer, Inc., and a clinical trials investigator for Pfizer, Inc., EMD Serono, Priovant, Emerald Health, Kadmon, and Argenx. B.S. is a consultant for Argenx and has served as a clinical trials investigator for Argenx, AstraZeneca, and Elorac. The other authors have no conflicts of interest to disclose.

What is known about this subject in regard to women and their families?

- The impact of pemphigus on both female and male fertility is unknown.

What is new from this article as messages for women and their families?

- Infertility rates in patients with pemphigus do not appear increased relative to age- and sex- matched controls in the general dermatology population, even when considering patients with a diagnosis associated with infertility.

Copyright © 2024 The Authors. Published by Wolters Kluwer Health, Inc.

on behalf of Women’s Dermatologic Society. This is an open-access article

distributed under the terms of the Creative Commons Attribution-Non

Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible

to download and share the work provided it is properly cited. The work cannot be

changed in any way or used commercially without permission from the journal.

International Journal of Women’s Dermatology (2024) 10:e153

Received: 29 November 2023; Accepted 18 April 2024

Published online 16 May 2024

DOI: 10.1097/JW9.000000000000153

Table 1
Demographic characteristics of pemphigus versus control patients

	Control (%)	Pemphigus (%)
No. (%)	46 (50.0)	46 (50.0)
Mean age (SD)	48.5 (9.0)	47.5 (8.8)
Sex		
Female	31 (67.4)	32 (69.6)
Male	14 (30.4)	14 (30.4)
Other (F at Birth)	1 (2.2)	0 (0.0)
Chemotherapy ^a (throughout the lifespan)	4 (8.7)	5 (10.9)
Cyclophosphamide	1 (2.2)	0 (0.0)
Diabetes	5 (10.9)	4 (8.7)
Infertility		
No infertility	42 (91.3)	34 (73.9)
Definite infertility ^b	2 (4.3)	3 (6.5)
Reproductive issues ^c	2 (4.3)	3 (6.5)
Disease associated with infertility ^d	0 (0.0)	6 (13.0)

^aChemotherapy associated with infertility searched and/or extracted from notes (not including cyclophosphamide) were ifosfamide, chlorambucil, cisplatin, procarbazine, busulfan, methotrexate, trastuzumab, doxorubicin, paclitaxel, pembrolizumab, ipilimumab, systemic 5-fluorouracil.

^bMeeting criteria as per obstetrician/gynecologist clinician assessment and/or formal infertility definition.

^cInfertility or recurrent pregnancy loss discussed in any clinician notes, though the diagnosis was not confirmed by obstetrician/gynecologist clinician and/or meeting criteria of formal infertility definition.

^dObstetric, gynecologic, and endocrine conditions associated with infertility which were extracted from notes included polycystic ovarian syndrome, endometriosis, uterine polyps/fibroids, pelvic inflammatory disease, recurrent bacterial vaginosis, abnormal uterine bleeding, ovarian torsion, mumps, and undescended testes.

Funding

Supported by the National Institutes of Health's National Center for Advancing Translational Sciences, grant UL1TR002494. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes

of Health's National Center for Advancing Translational Sciences.

Study approval

The authors confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies.

Author contributions

SAK and BS developed the study and wrote the manuscript. AH was a subspecialty contributor to manuscript development. DRP assisted with methodology and design. RF provided statistical analysis.

References

1. Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile female: a committee opinion. *Fertil Steril* 2015;103:e44–50.
2. Ouahes N, Qureshi TA, Ahmed AR. Infertility in women with pemphigus vulgaris and other autoimmune diseases. *J Am Acad Dermatol* 1997;36(3 Pt 1):383–7.

Sara A. Kullberg, MD^{a,*}

Rebecca Freese, MS^b

Amanda Huepfel, MD, FACOG^c

David R. Pearson, MD, FAAD^a

Brittney Schultz, MD, FAAD^a

^a Department of Dermatology, University of Minnesota, Minneapolis, Minnesota

^b Biostatistical Design and Analysis Center, Clinical and Translational Science Institute, University of Minnesota, Minneapolis, Minnesota

^c OBGYN, Southdale ObGyn, Premier Women's Health of Minnesota, Edina, Minnesota

* Corresponding author.

E-mail address: kull0057@umn.edu (S. A. Kullberg).

Table 2
Demographic characteristics of pemphigus patients with and without infertility

	Overall	No infertility	Infertility (DI + RI + DAI)
No. (%)	46 (100.0)	34 (73.9)	12 (26.1)
Mean age (SD)	47.5 (8.76)	48.9 (8.0)	43.6 (10.0)
Mean age in years at pemphigus diagnosis (SD)	39.6 (10.53)	41.2 (10.4)	35.5 (10.3)
Sex			
Female	32 (69.6)	20 (58.8)	12 (100.0)
Male	14 (30.4)	14 (41.2)	0 (0.0)
Race			
African	3 (8.6)	1 (4.3)	2 (16.7)
African American	2 (5.7)	1 (4.3)	1 (8.3)
Asian	4 (11.4)	3 (13.0)	1 (8.3)
Chose not to answer	1 (2.9)	0 (0.0)	1 (8.3)
Native Hawaiian/Pacific Islander	1 (2.9)	1 (4.3)	0 (0.0)
White	24 (68.6)	17 (73.9)	7 (58.3)
Missing	11	11	0
Ethnicity			
American	26 (61.9)	18 (58.1)	8 (72.7)
American (Ashkenazi Jewish)	1 (2.4)	1 (3.2)	0 (0.0)
Caucasian	4 (9.5)	4 (12.9)	0 (0.0)
Hispanic/Latino	2 (4.8)	2 (6.5)	0 (0.0)
Indian	1 (2.4)	1 (3.2)	0 (0.0)
Latino	1 (2.4)	1 (3.2)	0 (0.0)
Native Hawaiian/Pacific Islander	1 (2.4)	1 (3.2)	0 (0.0)
Not Hispanic or Latino	2 (4.8)	1 (3.2)	1 (9.1)
Pakistani	1 (2.4)	1 (3.2)	0 (0.0)
Somali	3 (7.1)	1 (3.2)	2 (18.2)
Missing	4	3	1
Pemphigus hospitalization	6 (13.0)	4 (11.8)	2 (16.7)
Pemphigus primary sites			
Mucous membranes only	6 (13.0)	4 (11.8)	2 (16.7)
Skin only	11 (23.9)	8 (23.5)	3 (25.0)
Skin + mucous membranes	29 (63.0)	22 (64.7)	7 (58.3)
Diabetes	4 (8.7)	4 (11.8)	0 (0.0)
Mean number of pregnancies (SD)	2.3 (1.99)	2.3 (1.4)	2.4 (2.5)
Mean number of living children (SD)	1.9 (1.26)	2.1 (1.1)	1.6 (1.4)
Mucous membrane sites of involvement			
Oral	34 (73.9)	26 (76.5)	8 (66.7)
Eyes	6 (13.0)	3 (8.8)	3 (25.0)
Nose	10 (21.7)	10 (29.4)	0 (0.0)
Esophagus	9 (19.6)	6 (17.6)	3 (25.0)
Vagina	6 (13.0)	4 (11.8)	2 (16.7)
Penis/Scrotum	0 (0.0)	0 (0.0)	0 (0.0)
Urethra	2 (4.3)	1 (2.9)	1 (8.3)
Anus	2 (4.3)	1 (2.9)	1 (8.3)
Dsg 1 ELISA titer (units)			
Mean (SD)	174.7 (688.60)	211.4 (798.4)	68.6 (78.8)
Median [range]	9.0 [0.0, 4100.0]	5.5 [0.0, 4100.0]	64.0 [1.0, 240.0]
Dsg 3 ELISA titer (units)			
Mean (SD)	256.4 (374.52)	301.5 (383.5)	136.2 (340.5)
Median [range]	98.0 [0.0, 1400.0]	144.0 [0.0, 1400.0]	12.0 [0.0, 1040.0]
Cyclophosphamide	0 (0.0)	0 (0.0)	0 (0.0)
Current or previous chemotherapy	5 (10.9)	4 (11.8)	1 (8.3)
Comorbidities	9 (19.6)	6 (17.6)	3 (25.0)
Henoch Schonlein purpura	1 (2.2)	1 (2.9)	0 (0.0)
Inflammatory arthritis	1 (2.2)	0 (0.0)	1 (8.3)
Possible T1DM (unmasked with prednisone)	1 (2.2)	1 (2.9)	0 (0.0)
Raynaud's phenomenon	1 (2.2)	1 (2.9)	0 (0.0)
Spondylo-arthropathy (HLA-B27+, 1:320 ANA)	1 (2.2)	1 (2.9)	0 (0.0)
Thyroid disease	4 (8.7)	2 (5.9)	2 (16.7)
Methotrexate	4 (8.7)	3 (8.8)	1 (8.3)
Rituximab	21 (45.7)	16 (47.1)	5 (41.7)