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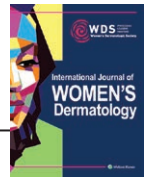

Burden of pemphigus vulgaris with a particular focus on women: A review

Nika Kianfar, MD-MPH[a], Shayan Dasdar, MD-MPH[a], Hamidreza Mahmoudi, MD[a], Maryam Daneshpazhooh, MD[a,*]

ABSTRACT

Pemphigus vulgaris is a chronic autoimmune mucocutaneous blistering disorder. Apart from the disease itself, other aspects of patients' life, including psychological, social, and financial, can be affected. Women are particularly more disposed to the impact of the disease due to their physiological characteristics, the specific periods of pregnancy and lactation as well as their social and familial role. In this review, we summarized the burden of pemphigus vulgaris on various aspects of women's lives. It is essential to understand these problems and provide appropriate support for patients with such a burdensome disease.

Keywords: autoimmune bullous diseases, burden, pemphigus, pemphigus vulgaris, women

Introduction

Pemphigus vulgaris (PV) is a chronic autoimmune blistering disorder of the skin and mucous membranes.[1] The main immunohistopathologic features of PV are acantholysis and suprabasal cleft as well as IgG and/or C3 intercellular deposits in the epidermis. The presence of anti-desmoglein-3 IgG is mainly responsible for the pathogenesis of PV.[2]

In managing patients with PV, it is essential to know that all the problems these people experience are not merely related to the disease activity. In recent years, a great body of literature has been devoted to examining how this condition would interfere with patients' normal lives. Women with pemphigus, due to their physiological characteristics and the periods of pregnancy and breastfeeding, would be more vulnerable to the impact of disease than men.[3] Herein, a brief overview of the studies concerning the effect of PV on various aspects of individual, social, and family life with a particular focus on women is provided.

Prevalence

In most countries, PV is the predominant form of the pemphigus group.[1] The incidence of PV varies widely depending on the geographic area and ethnicity.[4] The annual new cases of PV per million individuals range from 0.5 in Germany,[5] 0.8 in Finland,[6] 16.0 in Iran,[7] 16.1 in Israel,[8] to 32.0 among Jewish individuals in Connecticut, the United States.[9] Certain ethnic groups of Ashkenazi Jews and Mediterranean descent are exceptionally predisposed to PV, suggesting genetic susceptibility.[1,10,11]

A female preponderance of pemphigus has been reported, with an average female/male ratio of 1.4:1, ranging between 1.1 in Finland and 5.0 in the United States.[1,10] However, some exceptions with a male predominance are also available.[12] The majority of patients are aged 40 to 60 years at the onset of the disease. However, PV may arise at any age, and the onset of disease in some regions like the Middle East was reported to be in younger ages.[10]

Treatment

Innumerable management strategies have been employed for the treatment of PV. Owing to the recently conducted randomized controlled trials with long-term follow-up data, experts have developed comprehensive guidelines for disease management.[13,14]

Corticosteroids (CSs), usually in the form of oral predniso(lo)ne, with or without adjuvant therapies, are recommended as first-line therapy.[15] The evidence for the optimal CS dose is yet to be delineated, but oral predniso(lo)ne 1 mg/kg daily is generally used, which should be tapered at the end of the consolidation phase.[16,17] The adjuvant therapies supported by the literature are immunosuppressive agents, like azathioprine, mycophenolate mofetil (MMF), cyclophosphamide, and rituximab (RTX). The use of other conventional immunosuppressives, including

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

- Pemphigus vulgaris is a chronic blistering disease of the skin and mucous membranes that is expected to further affect women's lives due to their physiological and psychosocial characteristics.

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

- Pemphigus vulgaris has more severe effects on women patients in various aspects such as psychological, treatment costs, daily activities, family relationships, and quality of life. They also experience an additional burden due to the possible effect of disease and medications on the fetus in pregnancy and lactation period. Therefore, this point should always be considered by all health care providers to pay special attention to women in the process of decision making.

[a] *Autoimmune Bullous Diseases Research Center, Tehran University of Medical Sciences, Tehran, Iran*

N. K. and S. D. contributed equally to this work.

**Corresponding author.*

E-mail address: maryamdanesh.pj@gmail.com (M. Daneshpazhooh).

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methotrexate and cyclosporine, was not recommended in recent guidelines.[13,16]

Following the study of Joly et al.[18] showing the superiority of RTX plus prednisone versus prednisone alone, RTX has been designated by the European Medicines Agency and the US Food and Drug Administration as the first-line therapy of adults with moderate-to-severe PV.[16] Werth et al.[19] also demonstrated that RTX acted better than MMF in inducing sustained complete remission in PV. More recently, various case series also reported the possible use of RTX in vulnerable patients.[20–23]

Azathioprine (AZT) (2 mg/kg/d) and MMF (2 g/d) were the most commonly used first-line CS-sparing agents in PV before identifying the efficacy of RTX.[16,17] Nowadays, they are prescribed when RTX is contraindicated or lacks insurance coverage.[15,24] Finally, intravenous immunoglobulin (IVIg), plasmapheresis, or immunoadsorption are other options for treating severe or refractory PV.[25–27]

Adverse events

Although CSs have dramatically improved PV prognosis, they come with various well-documented cutaneous, metabolic, and systemic complications.[28] Postmenopausal women are the group most vulnerable to primary osteoporosis, and CSs can expose them to higher risk.[29] The chronic use of CSs in women can also harm reproductive function. CSs affect the ovary by suppressing the hypothalamo-pituitary-gonadal axis or directly connecting to its receptors. Patients may experience menstrual difficulties in the form of amenorrhea and postmenopausal bleeding.[30] Infertility is also reported in women with pemphigus.[31] RTX is generally a safe treatment option, and its most accompanied complications are infusion-related adverse events, which are mild and transient. On the other hand, RTX makes patients susceptible to opportunistic infections.[32,33] Both AZT and MMF decrease the reliance on CSs; however, they carry the risk of hematologic abnormalities, hepatotoxicity, and opportunistic infections.[17,34,35]

Pregnancy

Women with PV may desire to become pregnant, but their underlying disorder would become a major impediment in their way. Like many other autoimmune disorders, PV course may exacerbate during pregnancy and postpartum with reported rates of 54% and 44%, respectively.[36] Several factors might fluctuate pemphigus status during pregnancy. Hormonal changes, including estrogen and progesterone as well as cortisol, norepinephrine, and dehydroepiandrosterone, occur to accommodate the fetus.[37] These hormonal alterations evoke shifting of naive T cells toward more T helper (Th) 2 immune response in order not to reject the fetus.[38] The disturbance of the Th1:Th2 balance may trigger or exacerbate Th2-mediated autoimmune diseases, such as pemphigus, during pregnancy.[39,40] In addition to this immunological pathway, women's concern for the potential harm of medications to their pregnancy may affect their adherence to the treatment.[41] Although no estimate of drug cessation during pregnancy in patients with pemphigus exists, it may be an important factor affecting disease exacerbation in pregnancy. Some women may also develop new lesions induced by the trauma of cesarean section and breastfeeding, as a form of Köbner phenomenon.[42]

Poor control of maternal PV may result in some adverse pregnancy outcomes, including preterm birth, spontaneous abortion, stillbirth, and occasionally neonatal pemphigus.[43] Pregnant women with active PV can passively transfer autoantibodies to their neonate, causing transient blisters of the skin and rarely the mucous membranes of the neonates. Neonatal PV usually spontaneously resolves within 1 to 4 weeks without special treatment. Noteworthy is that if the disease is well-controlled, most women with pemphigus would give birth to a term, healthy baby.[43–45]

A great challenging issue in women with PV is the choice of medication due to safety concerns during pregnancy and lactation. CSs are considered the treatment of choice in PV in this period.[46,47] CSs can be used alone or combined with other immunosuppressive drugs such as AZT, IVIg, or plasmapheresis in refractory disease.[46] Data regarding paternal exposure to immunosuppressive agents are limited. Although there were concerns regarding the use of MMF and methotrexate, recent studies reported no increased risk of infertility and adverse pregnancy outcomes in fathers taking immunosuppressives.[48,49] Table 1 outlines the key points of therapeutic plans during pregnancy and breastfeeding. Given these circumstances, it is recommended to use family planning and contraceptive measures until their disease is well controlled. Medical consultation of PV during pregnancy requires collaboration among dermatologists, obstetricians, and pediatricians to control the disease. They should also reassure the mother that their treatments are safe causing no harm to the fetus's health.

Psychosocial burden

Pemphigus is a debilitating disorder that predisposes patients to a high risk of psychological problems.[50] A recent systematic review has shown that the prevalence of depressive symptoms and clinical depression among patients with autoimmune bullous disorders (AIBDs) ranged from 40 to 80% and 11.4 to 28%, respectively.[51] Wohl et al.[52] evaluated records of 764 individuals in Israel (255 pemphigus patients and 509 controls) and found that depression was higher in pemphigus patients with an odds ratio of 1.19 (95% confidence interval (CI): 1.12-1.27). Similarly, Hsu et al.[53] analyzed 4600 medical records in Taiwan (926 pemphigus patients and 3674 controls) and reported that pemphigus patients were more likely to suffer from depression with an adjusted hazard ratio of 1.99 (95% CI: 1.37-2.86).[53] Smaller cross-sectional studies also reported mental health impairment prevalence of 74% in Iran,[54] 59% in Egypt,[55] 47% in Korea,[56] 40% in Italy,[57] and 40% in India.[58] Other less-documented psychiatric disorders with higher prevalence among pemphigus patients than healthy individuals are schizophrenia,[59] bipolar disorder,[60] obsessive-compulsive disorder,[54] and post-traumatic stress disorder.[61]

Some studies have tried to figure out factors that predispose pemphigus patients to mental health challenges. Accordingly, Hsu et al.[53] reported that the female gender appears to increase the risk of depression in patients with PV. Regarding steroid-induced psychiatric reactions, the female gender was considered as a risk factor as well.[62] Although this gender disparity was not further investigated to detect the role of social, biological, and hormonal factors, it still suggests the vulnerability of this population. The disease activity is another well-supported predisposing factor for psychiatric syndromes.[54,56–58,63] However, even in the quiescent periods of disease, the psychological burden of the disease remains quite high, specifically for women.[64,65] Evaluating psychological morbidity of pemphigus patients who were in clinical remission demonstrated a prevalence of depression and anxiety of 30.8 and 35.5%, respectively.[66] The duration of active illness and hospitalization are among the factors affecting psychological symptoms in the remission phase of the disease.[66] Therefore, it is not surprising that RTX therapy with rapid and prolonged therapeutic effect could improve pemphigus patients' mental well-being.[67]

The association of pemphigus and psychological disorders seems bi-directional as stressful life events can initiate or worsen course of pemphigus.[68,69] A study on AIBDs have revealed a higher odds of disease development among individuals with history of depression and anxiety and importantly with greater probability in women.[70]

To date, no agreement has been reached on why psychological symptoms are so prevalent in pemphigus patients, although

Table 1

Key points of the management of pemphigus vulgaris during pregnancy and lactation[38,44,45]

Agent	FDA pregnancy category	Compatible with pregnancy	Compatible with breastfeeding	Comments
Systemic CSs	C	Safe Unwanted complications like diabetes, hypertension, intrauterine growth restriction, premature rupture of membranes, and orofacial clefts may occur.	Safe	The daily dose should not exceed 20 mg of prednisolone. Breastfeed at least 4 hr after consumption.
Topical CSs	C	Safe	Safe Transmission through breastmilk is negligible.	High-potent topical steroids should be avoided. Breastfeed at least 4 hr after application around the nipple area.
Rituximab	C	Not recommended. The placental passage increases from the first to the last trimester. The neonates of mothers who were receiving RTX showed no increased risk of infection, but prematurity and spontaneous abortion have been reported.	Not recommended. Transmission through breast milk is minimal.	Women are advised to conceive at least 12 mo after the last RTX infusion according to drug leaflet. Due to the lack of safety evidence, women should not breastfeed while treated with this drug and for at least 6 mo after.
Azathioprine	D	Safe. AZT was previously accused of causing congenital anomalies; however, recent studies found no increased risk of the drug to the mother and her fetus.	Safe. Transmission through breastmilk is negligible.	The daily dose should not exceed 2 mg/kg/d. Breastfeed at least 4 hr after consumption.
Mycophenolate compound	D	Contraindicated. Teratogenic	Contraindicated. Transmission through breastmilk is significant.	Must be stopped and replaced 6 wk prior to conception in women.
Intravenous IVIg	C	Safe. The neonates of mothers who were receiving IVIg showed no increased risk of infection or major adverse event.	Safe.	Reserve for severe or recalcitrant PV.
Plasmapheresis or immunoadsorption		Safe. The neonates of mothers who were receiving plasmapheresis or immunoadsorption showed no increased risk of infection or major adverse event.	Safe.	Reserve for severe or recalcitrant PV.
Cyclophosphamide	D	Contraindicated. Teratogenic	Contraindicated. Transmission through breast milk is significant	Must be stopped and replaced 1 mo prior to conception.

CSs, corticosteroids; FDA, US Food and Drug Administration; IVIg, immunoglobulin; RTX, rituximab; AZT, azathioprine.

there are some probable etiologies. First of all, PV and its treatments, specifically systemic CSs, are associated with a disfiguring and cushingoid appearance that might cause social stigma and troublesome changes in patients' lifestyles.[71] Second, current evidence indicated that proinflammatory cytokines are partially involved in developing psychosocial disorders.[72,73] Several observations have recently highlighted the association of mental health challenges with autoimmune conditions.[74,75] Finally, long-term immunosuppressive therapy with CSs may cause disturbance in psychiatric health (depression, mania, and cognitive impairment), known as the most common adverse event of steroids according to the Glucocorticoid Toxicity Index.[28]

The data regarding the relationship between pemphigus and psychiatric disorders is still in its infancy. Further studies are needed to determine the pathophysiology of this association to lessen the psychological burden of the disease. Clinicians should be more careful about the psychological symptoms in patients with pemphigus, especially women, to promptly diagnose and request a necessary therapeutic consult. In addition, ongoing support from family, friends, and society should be provided for these patients to optimize treatment outcomes.

Economic burden

Neglecting the possible economic burden of pemphigus could have detrimental consequences for patients and society.[76] This issue becomes even more prominent in women, as they are often not financially independent, especially in developing countries.

A cohort national-based survey that tracked the inpatient financial burden of pemphigus using the largest available health expenditure database in the United States demonstrated a mean annual cost of $14,520 for patients with a primary diagnosis of pemphigus and $9,948 for patients with any other diagnosis apart from pemphigus.[77] More importantly, they detected a higher rate of hospitalization, length, and cost of stay in the nonwhite race, poor, and underinsured/uninsured patients, which indicated the presence of disparities for minorities in pemphigus care. The female gender was also found to have an odds ratio of 1.10 (95% CI: 1.01-1.20) for admission compared with male patients. The high medical utilization for pemphigus patients compared to other diseases was also highlighted in other societies in Taiwan[78] and Germany.[79] Evaluating the cost of illness from a social perspective illustrated that indirect costs are even higher than direct costs. Brodszky et al.[80] reported that obscure items of health care costs, including productivity loss and informal care, have 75% of the associated costs with pemphigus, which was significantly lower among women.

The introduction of new biological agents such as RTX and IVIg was a shifting paradigm in treating pemphigus patients. Despite the great improvement in the prognosis of patients with pemphigus, there have always been concerns about the high cost of these medications.[81] A pharmacoeconomic study on patients with PV found that IVIg therapy would approximately halve the long-term cost compared to conventional therapy.[82] Similarly, RTX, which is even cheaper than IVIg, results in an effective decrease in health care costs, owing to reducing admissions, length of stay, and treatment-related adverse events.[83–85]

Delay in diagnosis

The prompt diagnosis of pemphigus is of utmost importance to disrupt disease progression and improve prognosis, but unfortunately, many patients experience long delays to diagnosis.[86,87] This frustrating undiagnosed period is often due to a lack of health care providers' knowledge of pemphigus manifestations, long waits for a dermatologist visit, and repeated inconclusive diagnostic tools. This ineffective passage of time makes patients feel they have no control over their bodies and escalates their concerns. Consequently, some of them may decide to change their doctors, which means starting this inconvenient process all over again.[88]

This delay in diagnosis is more or less constant among different reports; accordingly, there is an average 6 months lag from the first presentation to definite diagnosis.[89–92] It is shown that pemphigus in the oral cavity is diagnosed later than on the skin due to more non-specific features of mucosal involvement.[89,91,93] A survey conducted in the United States, employing the International Pemphigus and Pemphigoid Foundation disease registry system to 393 PV patients, revealed a longer period of diagnosis in women as they were more inclined toward mucosal involvement.[93]

Most patients with pemphigus are not satisfied with the level of information shared with them. They believe that if they get proper attention and meet their expectations, this long period would be more tolerable.[88] Therefore, in addition to attempts to reduce this lengthy diagnostic period, physicians should better understand patients' conditions.

Daily activities

Many patients with PV experience extreme restrictions in their daily activities.[94] Due to probable stigmatization in the workplace, productivity loss is not far-fetched.[95] To quantify this phenomenon, Wang et al.[96] utilized the Work Productivity and Activity Impairment Questionnaire-Specific Health Problem, a specific tool to measure productivity loss. They found that pemphigus patients with poor treatment response had significantly greater work and activity impairment than those with a proper response. Besides, approximately 15% of patients were stigmatized at work leading to the resignation of 1 in every 3.[96] Sleep disturbance is another frequent problematic condition for patients with pemphigus, with an odds ratio of 18.02 (95% CI: 2.46-131.88) compared to healthy individuals,[97] which can be worsened by the use of CSs.[98] Patients with lesions in the oral cavity might also experience eating difficulties and alterations in dietary habits.[99]

Pemphigus could also alter patients' engagement with leisure activities. This change largely relies on their social characteristics, not financial and facility status.[100] Encouraging patients to participate in suitable physical activities could be a big move toward a normal life.[101]

Familial relationships

Pemphigus could result in patients' discomfort in domestic and social relationships. Although genital involvement is not rare in women, it may go unnoticed during the examination and cause dyspareunia in many cases.[102] Interviewing 10 patients with PV, Piri et al.[103] documented various familial challenges owing to a lack of knowledge of the disease. A single woman reported the loss of a chance for marriage; another one was divorced after genital involvement and cessation of sexual relationship. Besides, several patients complained about isolation due to fear of affecting others. Therefore, a complete pelvic examination is recommended to provide the appropriate medical treatments and Pap smear when genital involvement exists.[102]

For evaluating the impact of pemphigus on family members, Family Dermatology Life Quality Index is a useful validated tool. Accordingly, pemphigus caused a remarkable impairment in the quality of life (QoL) of patients' families, associated with disease severity, mucocutaneous involvement, shorter disease duration, and male sex of patients that worsened by older age, low education, and the marital status of caregivers.[104,105] Improving knowledge and problem-solving abilities in patients and families can greatly reduce the disease burden.[106]

QoL instruments and measurements

Several assessment tools have been utilized to evaluate the QoL of patients with PV. Some of these instruments were general for any illness, and some were related to skin disorders. Specific tools for AIBDs were also issued in recent years. Herein, a concise review of various studies with different methods of QoL evaluation is provided.

Generic instrument

The Medical Outcome Study 36-item Short-form Survey is the most frequently used questionnaire among the general QoL assessing tools. Terrab et al.,[107] by employing this questionnaire, found great alterations in QoL of pemphigus patients in Morocco, especially women, due to the importance of self-image and various social and marital consequences. From Italy, Tabolli et al.[63] reported mucocutaneous PV involvement as the most burdensome clinical subtype. Moreover, their subsequent investigation emphasized greater health impairment in women and older patients.[57] A meta-analysis of studies that utilized Medical Outcome Study 36-item Short-form Survey from different regions demonstrated that the most prominent health deterioration is caused in physical- and emotional-role domains.[107,108]

Skin-related instrument

For a more specific measure of QoL based on skin symptoms, in several studies, dermatology-specific metrics such as the DLQI were used. One of the first reports on the use of DLQI in blistering disorders was from Germany, recording a mean score of 10 in patients with PV, which was worse than other skin conditions.[109] Subsequent studies also indicated a low QoL in pemphigus patients using this instrument with a mean DLQI score of 10.9 in Iran,[110] 10.2 in Korea,[56] and 5.4 in Hungary.[111] In these studies, several factors were recognized to increase DLQI score, including longer disease duration, mucocutaneous phenotype, itching, positive Nikolsky's sign, and CS dose; but what consistently deteriorated QoL was the severity of the disease. Notably, gender was not found to affect DLQI score in these studies.[56,105,110,111]

AIBD-specific instruments

Autoimmune Bullous Disease Quality of Life (ABQOL) is a more sensitive tool for AIBDs to capture small changes in disease status. In the study conducted by Murrell et al. to assess the validity and reliability of the questionnaire, the authors reported that in patients with PV, the mean ABQOL score was 11.5, and associated poorly with Pemphigus Disease Area Index.[112] The reported mean ABQOL score for PV patients in other studies were as follows: 16.4 in the United States,[113] 17.4 in Poland,[114] 17.3 in China,[115] about 16 in Egypt/Tunisia,[116] and 29.4 in Iran.[117] Regarding the association of ABQOL with Pemphigus Disease Area Index score, those studies have made various comments, from no correlation[116] to poor[114] and moderate correlation.[118,119]

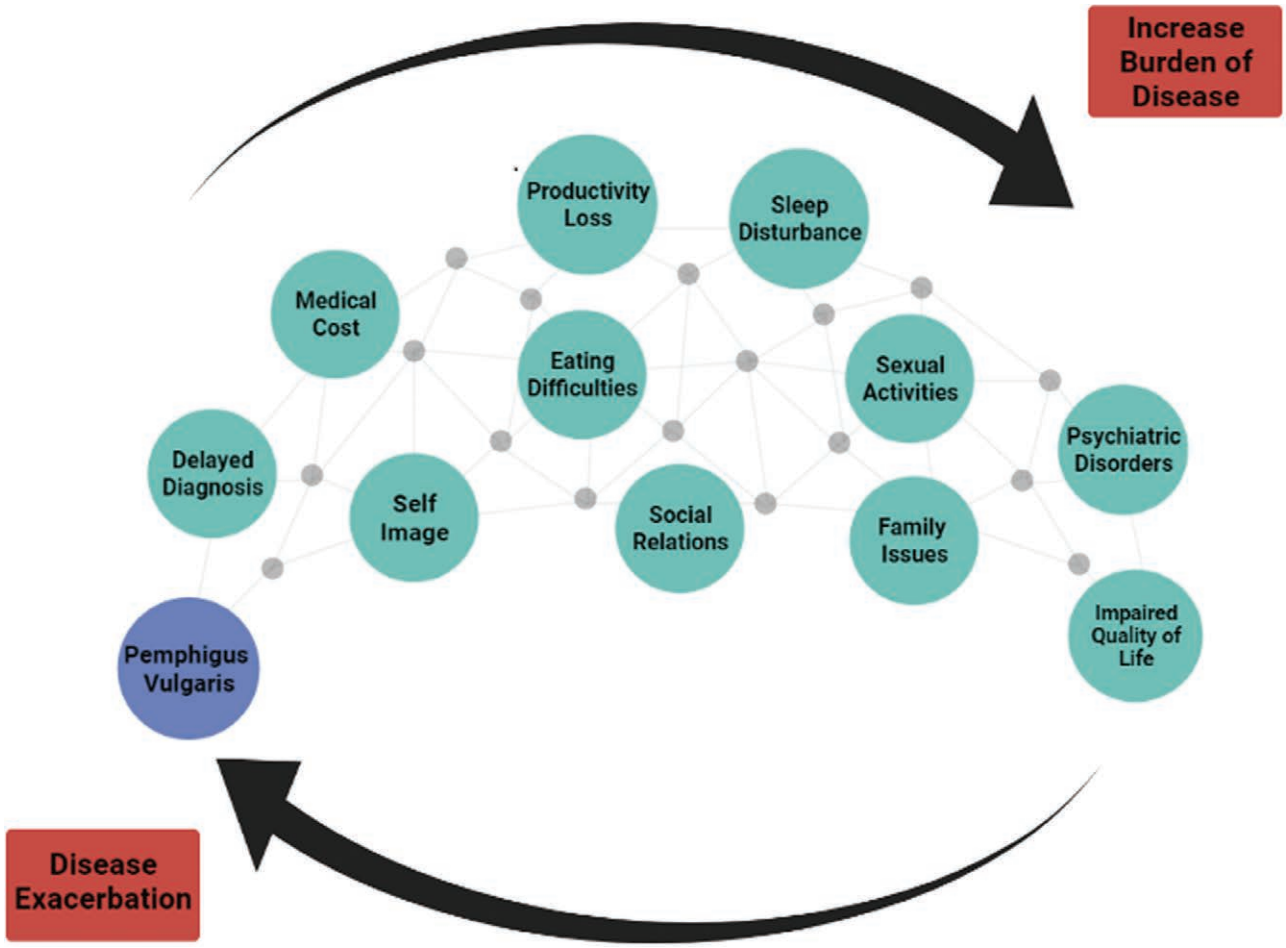

Fig. 1. Problems derived from pemphigus vulgaris are interrelated, leading to an increased burden of disease in one way and disease exacerbation in another way.

Noteworthy, while most patients in those studies were in their remission phase of the disease, only patients with active disease were enrolled in the study from Iran, which explains the higher score in their study. They found significantly lower QoL in women (ABQOL: 31.0) compared to men (ABQOL: 27.7), which was not reported in other studies.[117]

To differentiate treatments effect from the disease itself, Treatment of Autoimmune Bullous Disease Quality of Life (TABQOL) was designed.[120] Based on the available literature, the TABQOL score of pemphigus patients would change according to disease course[114,116] and treatment intensity,[120,121] but unexpectedly, the difference between various treatments[119,122] and time periods[118,119] was not remarkable. Moreover, no study indicated the significant effect of gender on TABQOL score.

Take away points and conclusions

As discussed above, PV would affect different aspects of patient's life. Many of these problems are interconnected and can also worsen the disease either directly or indirectly. Therefore, underestimating these problems, in addition to the augmented burden on patients, could lead to disease exacerbation (Fig. 1). Women have a unique set of difficulties to deal with, such as psychological problems, social and family relationships, and financial issues. Besides, they have specific worries in pregnancy and breastfeeding due to both the alternation in the disease condition and the fear of the medications' effect on the fetus/infant. All indicate that women often endure a more disturbed QoL.

To diminish the disease burden, a multidisciplinary approach is required with the following goals: (a) support patients with healthcare costs by modification at the health legislation, (b) increase general health providers' knowledge of disease for earlier diagnosis, (c) establish support groups to revive patients' social relationships and mental health, and (d) increase patients' and their families' awareness of PV.

Conflicts of interest

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Author contributions

M.D. and H.M. conceived and supervised the study; N.K. and S.D. performed the literature review and wrote the manuscript; all authors approved the final manuscript.

Study approval

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