SYSTEMATIC REVIEW

Association of dermatological manifestations with infertility: A systematic review of literature

Mubasshir Saleem[1], Samra Azhar[2], Muntaha Durrani[3], Syeda Kashaf Fatima[4], Maha Niazi[5], Maria Atif[6]

Abstract

Objective: To compile and analyse current literature to provide a comprehensive evidence related to the potential links between dermatological manifestations of skin disorders and infertility.

Method: The systematic review comprised literature search up to December 31, 2022, on Pubmed, Medline, Excerpta Medica dataBASE and Global Health databases. All original and published studies in the English language reporting on the dermatological manifestations in humans, associated with or contributing to infertility both in females and males were included. Quality assessment was performed independently by two reviewers using the Joanna Briggs Institute critical appraisal tools.

Results: There were 10 studies comprising 268,570 subjects. Significant positive association between skin manifestations and infertility were found in the studies reporting on the dermatological manifestations of polycystic ovarian syndrome, dermatomyositis, atopic dermatitis and leprosy ($p<0.05$), while the study reporting on the association between skin manifestation of systemic sclerosis did not report a significant result ($p>0.05$).

Conclusion: There was a potential association between cutaneous manifestations of various dermatological disorders and infertility.

Keywords: Infertility, Skin manifestations, Dermatological, Polycystic ovary syndrome. (JPMA 75: 1417; 2025)

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Introduction

According to the World Health Organisation (WHO), infertility or subfertility is defined as a disease of the reproductive system, leading to failure in achieving a clinical pregnancy after regular unprotected sexual intercourse for 12 months or more.[1] The available data suggests that one-sixth of people across the globe face infertility at some point in their lifetime, and currently there are around 48 million couples and 186 million individuals experiencing infertility globally, with the prevalence estimated to be 17.8% of adults in high-income countries and 16.5% in low- and middle-income countries (LMICs).[2]

The causes of infertility are not fully understood, but multiple contributing factors can adversely affect fertility, including problems with female and male reproductive systems, endocrine disorders, lifestyle and environmental factors, including smoking, obesity, diet, etc.[3] It is worth noting that approximately 15% of infertile couples are considered to be affected by "unexplained infertility", a diagnosis based on the absence of any significant abnormalities of the female or male reproductive systems.[4]

Cutaneous manifestations can be highly significant for physicians in making diagnoses, specifically in those who present with an under-diagnosed status. Systemic diseases that are related to infertility may also present with skin manifestations.[5] The association between skin disorders and infertility is an area of ongoing research and understanding, and while there have been studies investigating potential links between certain skin disorders and fertility issues, it is important to note that the relationship between the two can be complex and multifactorial.[5,6] It is, therefore, imperative that the clinical management of the skin disorders should take into account both the direct association between various skin disorders and infertility, as well as the effects of the treatment of skin disorders on fertility.

Polycystic ovarian syndrome (PCOS) is one of the most common gynaecological endocrine disorders that may affect women in their reproductive age, primarily affecting 1 in 10 adolescent women, and potentially presents with multiple complaints, including skin conditions associated with hyperandrogenism and hyperinsulinaemia, such as hirsutism, acne or alopecia.[6] These clinical presentations of hyperandrogenaemia are considered some of the earliest hallmarks of this syndrome, manifesting as early as the pre-pubertal period, even before the establishment of a formal medical diagnosis.[7] Certain autoimmune skin disorders, such as systemic lupus erythematosus (SLE) and

[1]University of Alberta Hospital, Alberta, Canada; [2]Misercordia Community Hospital, Alberta, Canada; [3-5]Department of General Medicine, Alberta Health Services, Alberta, Canada; [6]School of Public Health, Dow University of Health Sciences, Karachi, Pakistan.

Correspondence: Maria Atif. e-mail: drmariatif@yahoo.com

ORCID ID: 0000-0002-9377-1781

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dermatomyositis, may be associated with infertility.[8,9] These disorders can affect various organs and systems in the body, including the reproductive system, and the inflammation and immune dysregulation associated with autoimmune disorders may further contribute to fertility problems.[8,9] A national cross-sectional study in Germany with 339 Caucasian patients of SLE reported a photosensitive skin rash to be one of the most common earliest symptoms of the disease.[10] Literature favours a significant association between atopic dermatitis (AD) and infertility, with AD patients reporting a higher prevalence of infertility, suggesting that infertility may be an additional manifestation of AD, which may be caused by the skin-derived cytokines.[5,11] With the disease onset usually being during infancy, a red infiltrate with oedema, vesicles, oozing, and skin crusting are the earliest and most characteristic signs of AD.[11-14] However, more research is needed to fully understand the relationship between skin diseases and infertility, and identifying and treating skin disorders promptly can help prevent or minimise potential complications that may affect fertility and quality of life.

The current systematic review was planned to compile and analyse relevant studies to enhance understanding of the association between different dermatological manifestations observed in cases of infertility. By summarising the existing evidence, the review aimed at informing healthcare professionals about critical management issues related to dermatological manifestations and infertility so that early identification of fertility issues may be ensured, leading to improvement in disease outcomes, and contributing to a better quality of life for people suffering from dermatological disorders.

Materials and Methods

The systematic review comprised literature search up to December 31, 2022, on PubMed, Medline, Excerpta Medica dataBASE (EMBASE) and Global Health databases. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[15] guidelines, and was registered with the International Prospective Register of Systematic Review (PROSPERO) (CRD 42022380355).[16] The search was conducted with the help of key Medical Subject Headings (MeSH) terms along with Boolean Operators, including skin OR skin diseases OR skin manifestations OR dermatology OR eczema OR atopic OR psoriasis OR suppurativa OR alopecia OR acne OR cutaneous OR scabies OR hirsuitism AND infertility OR male infertility OR female infertility OR fertility OR reproduction OR pregnancy. Relevant abstracts written in English were selected during the screening phase. Full-text articles were critically studied and analysed in detail. Reference lists of the included studies and Google Scholar were also searched for relevant data.

All original and published cross-sectional, cohort and case-control studies in the English language, reporting on the dermatological manifestations in humans, associated with or contributing to infertility both in females and males without time limitations were included. Case reports, case series, conference papers and proceedings, editorials, letters to the editors, reviews and qualitative studies were excluded. Infertility, both in males and females, was the main outcome, and it was defined as a disease of the male or female reproductive system characterised by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse.

Data were extracted by two researchers independently and any missing information was sought by going through the study protocol, and by contacting the corresponding author of that study. Microsoft Excel was used to record the extracted data. Information was gathered regarding the study design, methodology, participants' demographics etc. The extracted data were validated by a third researcher, and any disagreement was resolved through mutual agreement. Quality assessment was performed independently by two reviewers using the Joanna Briggs Institute (JBI) critical appraisal tools.[17] Separate JBI tools are available to critically appraise different study designs. The tool for the appraisal of case-control, cohort and cross-sectional studies comprise 10, 11 and 8 criteria, respectively, for several aspects of studies. These criteria for assessment were based on how the study groups were selected, were they comparable for analytical studies, how the cases and controls matched, was exposure the same for different comparative groups and was it measured in a standardised manner, were confounders identified and addressed, were outcomes measured in a standardised manner, and were appropriate statistical analyses performed to draw valid conclusions. Each item in the list had four options; "Yes", "No", "Unclear" or "Not applicable". Based on the judgement of the reviewers, the options were marked to either include or exclude the study, or to seek further information for clarification before inclusion in the systematic review.

The data of all the included studies and the most important characteristics were recorded, including the place and participants of the individual studies, study design, sample size, inclusion/exclusion criteria, data collection tools used, as well as the significant results.

Results

Of the 3,334 studies identified, 66(2%) were assessed for relevance. Of them, 10(15.2%) studies met the eligibility criteria (Figure)[18-27] and they had data of 268,570

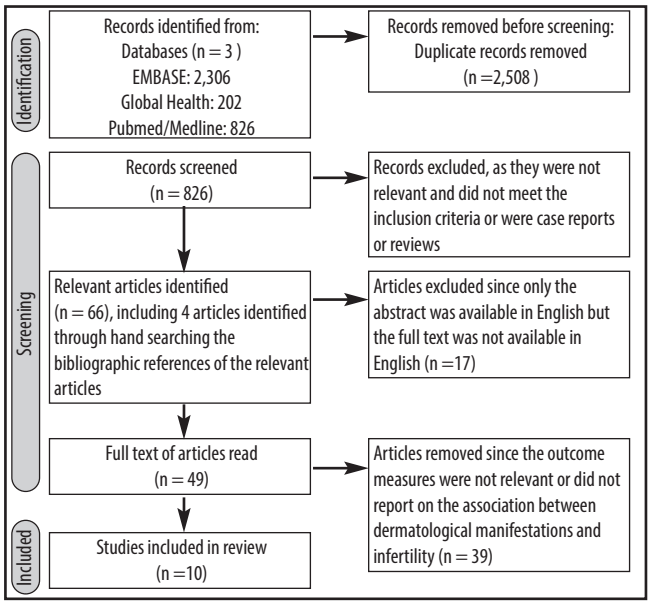

Figure: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart.

participants. The studies were conducted between 1999 and 2022. Overall, 2(20%) studies each were conducted in the United States and Brazil, while 1(10%) each was conducted in Saudi Arabia, Israel, Japan, Indonesia, India and Iran. There were 5(50%) cross-sectional studies, 4(40%) had a case-control design, and 1(10%) was a retrospective cohort study (Table).

Upon critical appraisal using the JBI tools, the 04 of the studies fulfilled all criteria of quality assessment, while 06 studies did not report on confounders or the strategies to deal with confounding factors (supplementary file).

Broadly, the association of infertility was explored with four dermatological manifestations; hormonal disorders, autoimmune disorders, inflammatory disorders, and infectious diseases.

With respect to hormonal disorders, PCOS is one of the most common endocrine disorders in females, with an estimated global prevalence of 4-20%.[28] The disorder is characterised by elevated levels of androgen and insulin resistance along with an array of dermatologic manifestations of hyper-androginism, including hirsutism, acne vulgaris and androgenic alopecia, and the dermatological manifestation of hyperinsulinaemia, including acanthosis nigricans.[29] Being one of the leading causes of female infertility, the dermatological manifestations of PCOS may provide early clinical identification of PCOS and a chance for an early and prompt treatment to avoid infertility.[29] In the current systematic review, 2(20%) cross-sectional studies reported on the cutaneous manifestations in patients with PCOS and associated infertility in the sample.[23,25]

Aljefri et al. had 447 females presenting with PCOS in a tertiary care hospital in Saudi Arabia, with 68% also presenting with cutaneous manifestations, including hirsutism (47.3%), acne vulgaris (40.6%) and androgenic alopecia (20.3%).[23] In addition to these skin disorders, other cutaneous disorders reported by Aljefri et al. included atopic dermatitis, acanthosis nigricans, folliculitis, hair thinning and skin tags. Moreover, the most common hormonal abnormalities reported by Aljefri et al. were raised luteinizing hormone (LH) levels (49.1%) and raised LH/follicle-stimulating hormone (FSH) ratio (35.5%). FSH, LH/FSH ratio and age were reported to be significant predictors for acne vulgaris (p=0.01, p=0.04 and p=0.01, respectively).[23] It is worth noting that the study was limited by a lack of a control group to compare the PCOS patients, and the collection of data was done through a retrospective chart review of the electrical medical record system, limiting the ability to account for possible confounders.[23]

Fereidooni et al. studied 130 women with diagnosed PCOS in Iran, and found that a majority (83.85%) of the women had hirsutism.[25] Moreover, they also reported a significant association between hirsutism and female sexual functioning index (FSFI) scores. However, the study was limited by the absence of a control group, and its inability to conduct a clinical/biochemical analysis of parameters relevant to cutaneous manifestations and infertility.[25]

With respect to autoimmune disorders, dermatomyositis, a systemic autoimmune disease, is generally marked by cutaneous lesions and muscle inflammation.[30] With an incidence of approximately 1-6 per 100,000 individuals, dermatomyositis exhibits distinctive dermatological lesions, including heliotrope sign, Gottron's papules and Gottron's sign, nail-fold changes, scalp involvement, psoriasiform, mechanic hand, panniculitis and calcinosis.[31] Two Brazilian studies in the current systematic review, which assessed dermatological manifestations of dermatomyositis and their possible association with infertility.[18,19] Although these studies reported suboptimal ovarian reserves among females and spermatic abnormalities among males suffering from dermatomyositis, both of these studies were limited by small sample sizes, and suggested caution in the generalisability of their findings.

De Souza et al.[18] discussed dermatomyositis in the adult female population, while Moraes et al.[19] discussed cases of juvenile dermatomyositis in young post-pubertal males.

De Souza et al. included 39 females (16 cases of

Table: Description of the studies analysed.

Study Title	Author	Location	Participant	Inclusion exclusion criteria	Sample size	Study design	Data collected
Cutaneous Manifestations and Hormonal Changes Among Polycystic Ovary Syndrome Patients at a Tertiary Care Center	Aljefri et al. 2021[23]	Saudi Arabia	all PCOS female patients	Not mentioned	447 females	Cross sectional	socio-demo variables, cutaneous manifestations, hormonal profile, and comorbidities collected through self-constructed questionnaire
Reduction of ovarian reserve in adult patients with dermatomyositis.	De Souza et al. 2015[18]	Brazil	Females aged 18–42 with dermatomyositis	Inclusion: All patients fulfilled the Bohan and Peter classification criteria for the disease Exclusion: hormonal contraceptive use within the last six months , neoplasia associations, current pregnancy , gynaecological surgery, other autoimmune diseases and individual choice not to participate.	39 females	Case-control	clinical evaluation that included a standardised interview, Clinical and laboratory data. Disease status was assessed through the application of questionnaires and Medical Research Council scoring. Kendall Manual Muscle Testing. health assessment quality (HAQ) (17) and global assessment of the disease by the physician and the patient through the visual analogue scale (VAS) was performed. Autoantibodies levels and ovarian function tests were performed.
Relationship between semen production and medical comorbidity.	Eisenberg 2015[24]	USA	Men attending fertility clinic between 1994 and 2011	Not mentioned	9,387 men. Cases were selected from semen data base	Cross-sectional	Charlson comorbidity index, medical diagnoses by organ system
The Effective Factors on The Sexual Function of Polycystic Ovary Syndrome Women: A Cross-Sectional Study.	Fereidooni ET AL. 2022[25]	Iran	females with PCOs	The inclusion criteria for women were: age 18-45 years and married, not having non-classic adrenal hyperplasia, thyroid or metabolic disease, hyperprolactinemia, and not having psychiatric disorders. Pregnant women, breastfeeding mothers, and patients who received oral contraceptive pills (OCPS) or other hormonal medications that affect the hypothalamic-pituitarygonadal (HPG) axis 3 months ago were excluded.	130 females	Cross-sectional	demographic characteristics, hirsutism (Ferriman-Gallwey) score, and sexual function was assessed using the female sexual function index (FSFI)
Atopic Dermatitis and Infertility: A Nationwide Retrospective Cohort Study	Horev et al. 2022[22]	Israel	General population	being at least one documented diagnosis of AD registered in the medical records by a dermatologist between the years 2002 and 2018. Patients with conditions that might affect fertility, such as alcohol abuse, drug abuse, cystic fibrosis, hyperprolactinemia, pituitary adenomas, organ transplantation, cirrhosis, and malignancy, were excluded from the study.	127,150 patients with AD and 127,071 comparison enrollees	nationwide retrospective cohort study with matched control group. All cases of AD from 2002-2018 and matched control group	Data extracted from the CHS chronic diseases registry

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Study Title	Author	Location	Participant	Inclusion exclusion criteria	Sample size	Study design	Data collected
Minor Sperm abnormalities in young male post-pubertal patients with juvenile dermatomyositis	Moraes et al. 2008[19]	Brazil	post-pubertal males with juvenile dermatomyositis	Exclusion criteria were hydrocele, hypospadia, cryptorchidism, testicular infection (e.g., mumps), testicular cancer, orchitis, testicular vasculitis, urethral impairment, previous history of any scrotal or inguinal surgery (e.g., varicocelectomy, vasectomy, hernia repair), diabetes mellitus, previous or current history of alcohol or tobacco use, and refusal to collect sperm sample or incomplete evaluation	5 males	Case control	Clinical evaluation followed by previous clinical, lab, and treatment-related data. Childhood Health Assessment Questionnaire (CHAQ), Manual Muscle Testing, Childhood Myositis Assessment Scale (CMAS), and Disease Activity Score (DAS). Physician and patient assessments of global disease activity and damage were rated on a 10-cm visual analog scale (VAS) and physical functioning was assessed by the Medical Outcomes Study 36 Item Short-Form Health Survey
Effects of medical comorbidity on male infertility and comorbidity treatment on spermatogenesis	Shiraishi and Matsuyama 2018[20]	Japan	5,337 Japanese men who were consecutively assessed for male infertility between April 1995 and March 2017	men who provided more than two semen samples, had endocrinologic data based on morning samples, underwent scrotal evaluation, and had detailed data regarding past and current medical histories and general health checks within one year before infertility evaluation were included. For those lacking this information, weight, height, and blood pressure measurements, blood tests, and a chest X-ray were additionally assessed. Men who did not provide this information were excluded. Those with obstructive azoospermia, current cancer treatment, and sexual dysfunction without aberrant spermatogenesis were excluded. Men with hypogonadotropic hypogonadism were also excluded. Men younger than 45 years with normal results on semen analysis who underwent a fertility evaluation and those who underwent assisted insemination owing to female factor infertility were included as controls	3,328 infertile men and 452 men with normal results on semen examination were included	Retrospective case control	The Charlson Comorbidity Index (CCI) was used to score existing comorbidities. (BMI) was calculated. The testes volume was assessed using a punched-out orchidometer.
Fertility and pregnancy outcome in women with systemic sclerosis	Steen and Medsger 1999[21]	USA	Women with scleroderma diagnosed after 1972 were sent questionnaire in 1986	Women under the age of 45 years	214 women with scleroderma, 167 with Rheumatoid arthritis and 105 healthy controls	Case control	Self administered questionnaire

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Table: *Continued from previous page.*

Study Title	Author	Location	Participant	Inclusion exclusion criteria	Sample size	Study design	Data collected
Frequent testicular involvement in multibacillary leprosy	Gunawan et al. 2020[26]	Indonesia	men affected by leprosy	either receiving multi-drug therapy for leprosy or had been released from treatment Exclusion criteria were (1) patients with diabetes, tuberculosis, or a hepatic or renal disease, as determined through history-taking and physical examination; (2) patients with a history of chemotherapy or radiotherapy; and (3) patients who had a history of parotitis and testicular abnormalities due to a genetic disorder.	5 males32 men affected by leprosy and five healthy men as a control group	Cross-sectional	history-taking, physical examination, local genital examination, laboratory investigations, and testicular ultrasonography examination. Semen analysis.
Endocrinological Testicular Dysfunction in Patients with Lepromatous Leprosy and the Impact of Disease on Patient's Quality of Life.	Mohta et al. 2020[27]	India	Men with leprosy	Married male patients aged 18–59 years, diagnosed with Leprosy were included Unmarried patients or those with comorbidities like diabetes, renal or hepatic dysfunction, tuberculosis, immunosuppression, traumatic, surgical, or congenital testicular abnormalities were excluded.	43 men with leprosy	Cross-sectional	diagnosed with lepromatous leprosy based on clinical presentation, clinical tests, histopathological analysis, and slit skin smear examination. Serum concentrations of total testosterone, FSH, and LH were recorded. WHOQoL-BREF Hindi-validated questionnair

dermatomyositis and 23 healthy controls) of reproductive age in their cross-sectional study, and observed reduced ovarian reserves in the dermatomyositis cases. Moreover, anti-Müllerian hormone (AMH) values of ≤1ng/mL (p=0.027) and antral follicle counts (AFC) values (p=0.017) were significantly reduced in the cases relative to the controls, whereas serum oestradiol levels (p<0.001) were higher in the cases compared to the controls. Serum follicle stimulating hormone (FSH), inhibin-B, ovarian volumes and immunoglobulin G (IgG) anti-corpus luteum (anti-Col) antibody frequencies were found to be comparable in both the groups.[18] Despite being the first study to identify that the patients of dermatomyositis have a sub-clinical ovarian reserve at the reproductive age, the study of De Souza et al. was limited by a small sample size and the inclusion of dermatomyositis cases only from a single tertiary care centre, limiting the generalisability of their results.

Moraes et al. in 2008 studied post-pubertal males with juvenile dermatomyositis. Besides the skin lesions' associated with juvenile dermatomycosis, the males also had minor sperm abnormalities in the head, mid-piece and/or tail of the spermatozoids. However, all sperm parameters, testicular volume and hormones were similar in the cases and the controls, whereas, the frequency of anti-sperm antibodies was similar in both the groups. Similar to the study by De Souza et al. this study was also challenged by a small sample size, and the authors recommended serial semen analysis in larger study populations to further validate the findings.[19]

Also part of the current systematic review was a study by Steen et al. who compared 214 women aged <45 years suffering from scleroderma with two race-matched and age-matched control groups. There were 167 women with rheumatoid arthritis (RA) and 105 healthy controls.[21] The study did not find any significant difference in fertility between the patients and the controls, but the cases had more adverse pregnancy outcomes after the onset of disease. In terms of adverse pregnancy outcomes, including miscarriage, premature birth, small full-term birth, and neonatal death, there were no significant differences in the overall rates between the cases and the controls. Although a significantly greater number of women with systemic sclerosis reported never having been pregnant, there were no significant differences in the rates of infertility or frequency of never having been pregnant between the cases and the controls after adjusting for contributing factors. The authors concluded that infertility was not associated with systemic sclerosis, and the cases of systemic sclerosis should undergo the same evaluation and management methods for infertility as their disease-free counterparts.[21]

Case-control studies

1. Reduction of ovarian reserve in adult patients with dermatomyositis.

S.No	Assessment criteria	Yes	No	Unclear	Not applicable
1.	Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	√			
2.	Were cases and controls matched appropriately?	√			
3.	Were the same criteria used for identification of cases and controls?	√			
4.	Was exposure measured in a standard, valid and reliable way?	√			
5.	Was exposure measured in the same way for cases and controls?	√			
6.	Were confounding factors identified?	√			
7.	Were strategies to deal with confounding factors stated?	√			
8.	Were outcomes assessed in a standard, valid and reliable way for cases and controls?	√			
9.	Was the exposure period of interest long enough to be meaningful?	√			
10.	Was appropriate statistical analysis used?	√			

Overall appraisal: Include, exclude, seek further info

2. Minor Sperm abnormalities in young male post-pubertal patients with juvenile dermatomyositis.

S.No	Assessment criteria	Yes	No	Unclear	Not applicable
1.	Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	√			
2.	Were cases and controls matched appropriately?	√			
3.	Were the same criteria used for identification of cases and controls?	√			
4.	Was exposure measured in a standard, valid and reliable way?	√			
5.	Was exposure measured in the same way for cases and controls?	√			
6.	Were confounding factors identified?			√	
7.	Were strategies to deal with confounding factors stated?			√	
8.	Were outcomes assessed in a standard, valid and reliable way for cases and controls?	√			
9.	Was the exposure period of interest long enough to be meaningful?	√			
10.	Was appropriate statistical analysis used?	√			

Overall appraisal: Include, exclude, seek further info.

3. Effects of medical comorbidity on male infertility and comorbidity treatment on spermatogenesis.

S.No	Assessment criteria	Yes	No	Unclear	Not applicable
1.	Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	√			
2.	Were cases and controls matched appropriately?	√			
3.	Were the same criteria used for identification of cases and controls?	√			
4.	Was exposure measured in a standard, valid and reliable way?	√			
5.	Was exposure measured in the same way for cases and controls?	√			
6.	Were confounding factors identified?	√			
7.	Were strategies to deal with confounding factors stated?	√			
8.	Were outcomes assessed in a standard, valid and reliable way for cases and controls?	√			
9.	Was the exposure period of interest long enough to be meaningful?	√			
10.	Was appropriate statistical analysis used?	√			

Overall appraisal: Include, exclude, seek further info

4. Fertility and pregnancy outcome in women with systemic sclerosis.

S.No	Assessment criteria	Yes	No	Unclear	Not applicable
1.	Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	√			
2.	Were cases and controls matched appropriately?	√			
3.	Were the same criteria used for identification of cases and controls?	√			
4.	Was exposure measured in a standard, valid and reliable way?	√			
5.	Was exposure measured in the same way for cases and controls?	√			
6.	Were confounding factors identified?	√			
7.	Were strategies to deal with confounding factors stated?	√			
8.	Were outcomes assessed in a standard, valid and reliable way for cases and controls?	√			
9.	Was the exposure period of interest long enough to be meaningful?	√			
10.	Was appropriate statistical analysis used?	√			

Overall appraisal: Include, exclude, seek further info

Cohort studies

5. Atopic Dermatitis and Infertility: A Nationwide Retrospective Cohort Study.

S.No	Assessment criteria	Yes	No	Unclear	Not applicable
1.	Were the two groups similar and recruited from the same population?	√			
2.	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	√			
3.	Was exposure measured in a standard, valid and reliable way?	√			
4.	Were confounding factors identified?	√			
5.	Were strategies to deal with confounding factors stated?	√			
6.	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	√			
7.	Were the outcomes measured in a valid and reliable way?	√			
8.	Was the follow up time reported and sufficient to be long enough for outcome to occur?	√			
9.	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	√			
10.	Were strategies to address incomplete follow up utilised?	√			
11.	Was appropriate statistical analysis used?	√			

Overall appraisal: Include, exclude, seek further info

Cross sectional studies

6. Cutaneous Manifestations and Hormonal Changes Among Polycystic Ovary Syndrome Patients at a Tertiary Care Center.

S.No	Assessment criteria	Yes	No	Unclear	Not applicable
1.	Were the criteria for inclusion in the sample clearly defined?	√			
2.	Were the study subjects and the setting described in detail?	√			
3.	Was the exposure measured in a valid and reliable way?	√			
4.	Were objective, standard criteria used for measurement of the condition?	√			
5.	Were confounding factors identified?		√		
6.	Were strategies to deal with confounding factors stated?		√		
7.	Were outcomes measured in a valid and reliable way?	√			
8.	Was appropriate statistical analysis used?	√			

Overall appraisal: Include, exclude, seek further info

7. Relationship between semen production and medical comorbidity.

S.No	Assessment criteria	Yes	No	Unclear	Not applicable
1.	Were the criteria for inclusion in the sample clearly defined?	√			
2.	Were the study subjects and the setting described in detail?	√			
3.	Was the exposure measured in a valid and reliable way?	√			
4.	Were objective, standard criteria used for measurement of the condition?	√			
5.	Were confounding factors identified?			√	
6.	Were strategies to deal with confounding factors stated?			√	
7.	Were outcomes measured in a valid and reliable way?	√			
8.	Was appropriate statistical analysis used?	√			

Overall appraisal: Include, exclude, seek further info

8. The Effective Factors on The Sexual Function of Polycystic Ovary Syndrome Women: A Cross-Sectional Study.

S.No	Assessment criteria	Yes	No	Unclear	Not applicable
1.	Were the criteria for inclusion in the sample clearly defined?	√			
2.	Were the study subjects and the setting described in detail?	√			
3.	Was the exposure measured in a valid and reliable way?	√			
4.	Were objective, standard criteria used for measurement of the condition?	√			
5.	Were confounding factors identified?		√		
6.	Were strategies to deal with confounding factors stated?		√		
7.	Were outcomes measured in a valid and reliable way?	√			
8.	Was appropriate statistical analysis used?	√			

Overall appraisal: Include, exclude, seek further info

9. Frequent testicular involvement in multibacillary leprosy.

S.No	Assessment criteria	Yes	No	Unclear	Not applicable
1.	Were the criteria for inclusion in the sample clearly defined?	√			
2.	Were the study subjects and the setting described in detail?	√			
3.	Was the exposure measured in a valid and reliable way?	√			
4.	Were objective, standard criteria used for measurement of the condition?	√			
5.	Were confounding factors identified?		√		
6.	Were strategies to deal with confounding factors stated?		√		
7.	Were outcomes measured in a valid and reliable way?	√			
8.	Was appropriate statistical analysis used?	√			

Overall appraisal: Include, exclude, seek further info

10. Endocrinological Testicular Dysfunction in Patients with Lepromatous Leprosy and the Impact of Disease on Patient's Quality of Life.

S.No	Assessment criteria	Yes	No	Unclear	Not applicable
1.	Were the criteria for inclusion in the sample clearly defined?	√			
2.	Were the study subjects and the setting described in detail?	√			
3.	Was the exposure measured in a valid and reliable way?	√			
4.	Were objective, standard criteria used for measurement of the condition?	√			
5.	Were confounding factors identified?		√		
6.	Were strategies to deal with confounding factors stated?		√		
7.	Were outcomes measured in a valid and reliable way?	√			
8.	Was appropriate statistical analysis used?	√			

Overall appraisal: Include, exclude, seek further info

With respect to inflammatory disorders, atopic dermatitis is a chronic inflammatory skin disease with an estimated prevalence of 10-20% among children, and 1-3% among adults in developed countries.[32] A nationwide study included in the current systematic review identified the association of atopic dermatitis with infertility, but due to the retrospective nature of the study, the causative pathway remained unclear.[22] It is noteworthy that skin lesions, such as atopic dermatitis, may not only affect fertility directly, but can also be a manifestation of medications used for the treatment of atopic dermatitis, and thus more studies with longitudinal designs are needed.[33,34]

Horev et al. utilised a nationwide healthcare database and conducted a retrospective cohort study in Israel with 127,150 cases of atopic dermatitis and matched control group with 127,071 participants, enrolled over a period of 16 years.[22] This cohort study found that atopic dermatitis was associated with a higher prevalence of infertility when compared to the control group. Upon multivariate analysis for infertility, atopic dermatitis was identified as a key risk factor for infertility in both males and females having mild and moderate-to-severe atopic dermatitis. Despite providing credible proof of a significant association between atopic dermatitis and infertility, the study had the general limitations of a retrospective cohort study, including missing relevant data, and the inability to identify true cases of infertility and those not willing to conceive. Moreover, due to the retrospective nature of the data, the authors could not ascertain the degree of severity of the case of atopic dermatitis, which is usually measured through the Severity Scoring of Atopic Dermatitis Index, because it was not a part of the healthcare database from where the data had been derived. However, attempts were made to use a proxy estimation method based on healthcare services utilisation and the medicines prescribed for the treatment. Another limitation of the study was the unavailability of relevant information on improvement in the symptoms or recovery of patients of atopic dermatitis and its possible effect on infertility. Despite these limitations, the large sample size of the study contributed to the strength of the evidence on the association between atopic dermatitis and infertility.[22]

With respect to infectious diseases, 2 (20%) cross-sectional studies in the current systematic review analysed the association between Leprosy and infertility. Gunawan et al. in 2020 recruited 32 Indonesian men affected by leprosy and five healthy men as a control group.[26] After detailed history-taking, physical examination, local genital examination, laboratory investigations, semen analyses and testicular ultrasonography examination, testicular atrophy was observed in 94% of the patients. The authors reported that the clinical manifestations of testicular atrophy were loss of libido in 22% patients, female pubic hair pattern was observed in 9%, gynecomastia was seen in 6%, and secondary infertility was reported by 6% of the cases. The hormonal imbalance was seen in 16 patients, and all 10 cases who underwent semen analysis showed both qualitative and quantitative abnormalities. Although the study comprehensively assessed testicular atrophy in

the patients, a small sample size was recognised as a limitation of the study, and the findings should, therefore, be interpreted with caution.[26]

Mohata et al. also conducted a cross-sectional study in 2020 and reported similar findings. Their sample included 43 married Indian male patients aged 18-59 years who had been diagnosed with leprosy.[27] Similar to the study by Gunawan et al.[26] they also found that the most common clinical manifestation in their sample was reduction or loss in libido, and gynaecomastia. They reported a significant negative correlation between testosterone level and FSH and LH, and a significantly positive correlation between testicular volume and testosterone level.[27] This study was also limited by a small sample size and the lack of a control group.

Among the other studies in the current systematic review, 2 (20%) analysed the relationship involving cutaneous morbidities, their treatment and infertility,[20,24]Eisenberg et al. in 2015 conducted a cross-sectional study with 9,387 men in the United States. The subjects were men attending fertility clinics between 1994 and 2011 who were selected from a semen database.[24] Those with diseases of skin had significantly higher rates of semen abnormalities, either due to inflammatory or autoimmune conditions or treatments for such skin diseases. Since the participants were selected from a database and represented individuals seeking treatment for infertility rather than an unselected group of men, the findings could not be generalised.

Shiraishi and Matsuyama, on the other hand carried out a retrospective case-control study with 3,328 infertile Japanese men and 452 counterparts with normal results on semen examination, assessed for infertility between April 1995 and March 2017.[20] The authors reported that the prevalence of comorbidities was significantly higher among infertile men than among fertile men. For morbidities related to skin, atopic dermatitis was the most common dermatological morbidity, with its prevalence being significantly higher among the infertile males than their fertile counterparts. Moreover, the incidence of azoospermia was also significantly higher in men with skin disease than in men without it.[20]

Discussion

Dermatological manifestations may often serve as evidence to various underlying systemic health issues that may affect reproductive health and may be associated with infertility. Recognising these signs early by dermatologists may prove to be effective in prompt diagnosis and appropriate intervention to improve fertility outcomes, reducing healthcare costs, and enhancing overall quality of life. To the best of our knowledge, the current systematic review is the first to highlight the common dermatological manifestations and their possible association with infertility. Despite a limited number of studies eligible to be included in this systematic review, the findings indicate that certain skin disorders and their cutaneous manifestations are associated with infertility both in women and men. Due to the scarcity of literature reporting on the association between different dermatological manifestations and infertility, we did not filter out old studies reporting on such association, and thus studies ranging from a publication period of 1999-2022 were included in this review. The studies[18-27] reported on dermatological manifestations of PCOS, dermatomyositis, atopic dermatitis, systemic sclerosis, and leprosy, and their potential association with infertility. Significant positive associations between skin manifestations and infertility were found in the studies reporting on the dermatological manifestations of PCOS, dermatomyositis, atopic dermatitis and leprosy, whereas, the study reporting on the association between skin manifestation of systemic sclerosis did not report a significant result. However, the diversity in design, small sample sizes, limited geographic inclusivity, and inconsistent quality reporting warrants caution in drawing firm conclusions. Reporting limitations pose a significant risk of bias due to either a lack of most unadjusted confounders or no clear explanation on how they were dealt with.

Polycystic ovarian syndrome (PCOS) was the most common hormonal condition investigated. PCOS is a complex endocrine disorder with literature suggesting a pooled global prevalence of 22%, characterised by hyperandrogenism, insulin resistance and a constellation of dermatological features including hirsutism, acne, androgenic alopecia, and acanthosis nigricans.[35] The presence of cutaneous signs may represent an early clinical marker of PCOS and future infertility risk, as supported by recent literature.[36]

Autoimmune dermatological conditions like dermatomyositis and systemic sclerosis have also been assessed in terms of their association with infertility, and although the findings of these studies may indicate possible association between autoimmune skin conditions and sub-optimal reproductive outcomes, the singular center models with smaller sample sizes lessen the scope of these conclusions, but none the less warranting differentiation between infertility from other obstetric complications thorough fertility workups in affected individuals.[37] Similarly, Atopic dermatitis, an inflammatory condition, has been explored as a potential risk factor for infertility, literature suggests that chronic inflammation could impact reproductive function either directly or

through adverse complications from treatment.[38] However, the absence of severity indices in most of the studies included in this review and data on fertility intentions in retrospective datasets continues to pose significant challenges in establishing causality.

The scarcity of appropriate data restricted the ability to perform a meta-analysis to statistically combine the results of various studies. Majority of the studies presented epidemiological data, but did not validate their findings with credible laboratory investigations, which could have further strengthened their findings. Further research is, therefore, required to ascertain the prevalence of infertility associated with various skin disorders with distinctive dermatological manifestations, and studies with large sample sizes and better study designs, preferably cohort and randomised clinical trials, should be conducted to understand the temporal pathways of the link between infertility and various skin lesions of dermatological disorders for early identification of fertility issues, improve disease outcomes, and ensure a better quality of life for people suffering from dermatological disorders.

The current systematic review has its own limitations. As with other reviews, publication bias, which is the tendency of publishing studies only showing significant results or relationships, along with limited number of studies warrants caution in the interpretation of the current findings. Further high-quality systematic studies, regardless of the outcomes of the findings, are needed for more authentic and generalisable results. Moreover, since the database search was carried out since their inception till 31st December 2022, a number of studies included in this review precedes five year from the publication of this review. Considering the scarcity of literature to ascertain association between dermatological manifestations and infertility, these studies were included in this review. The focus of future studies should be on well-designed prospective studies with a well-defined control group, as well as uniform age, sex, and severity stratification for the dermatological and reproductive parameters. Solving the connection between skin diseases and infertility requires the input from not just dermatologists, but also endocrinologists and reproductive health specialists, which highlights the need for integrated screening and management pathways.

Conclusion

There is a potential association between cutaneous manifestations of various dermatological disorders and infertility. However, the studies analysed had several limitations affecting the generalizability of their findings.

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Author Contribution:

MS & MA: Design, guided methodology, reviewed, discussion, final approval and agreement to be accountable for all aspects of the work.

SA, SKF, MN & MD: Searching, selection, data extraction, wrote the first draft, final approval and agreement to be accountable for all aspects of the work.