

Prevalence and risk factors of diaper dermatitis among newborn babies to two years of age in Al-Baha region, Saudi Arabia

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Abstract

Introduction: Diaper dermatitis is the most common dermatological condition which affects the pediatric age group. A variety of factors contribute to the pathophysiology. Diaper dermatitis presents as an erythematous rash, papules, scaling, and erosions around the thighs, scrotum, suprapubic area, and buttocks, characteristically where skin creases. The primary treatment is to keep the skin around the diaper area as dry as possible by frequent diaper changes together with careful selection of the diaper type. Some creams (barrier creams) and mild topical corticosteroid treatments are also available to protect the infant's thin skin and to reduce any inflammation.

Methods: This was a cross sectional study of 389 parents using structural questionnaires. The study was conducted in the Al-Baha region, Saudi Arabia from January to July 2022. We used bivariate and multivariate logistic regression analyses to analyze our data and test the association between the prevalence of diaper dermatitis and its possible risk factors.

Results: The prevalence of diaper dermatitis was 39.33% (153/389). The highest prevalence was among children who were 19-24 months old (65%). When comparing gender groups, females had a higher prevalence (44.4%) compared to males (34.7%) ($p=0.005$). Preterm babies had a slightly lower prevalence than term babies.

Conclusion: Multiple factors are involved in diaper dermatitis which most commonly affect infants and toddlers. The highest prevalence was among children who were 19-24 months old and there was more prevalence among females.

Keywords: Diaper dermatitis, Prevalence, Al-Baha, Saudi Arabia

Introduction

Diaper dermatitis is a dermatological condition that affects the diaper area. It manifests as skin eruptions such as an erythematous rash, papules, scaling, and erosions around the thighs, scrotum, suprapubic area, and buttocks (1). More than 50% of infants experience diaper dermatitis at least once during their diaper-wearing phase (2).

Although diaper dermatitis has a complex pathophysiology, it could be a type of irritant contact dermatitis. This type of dermatitis develops in areas covered by the diaper as a result of prolonged skin contact with faeces as the primary factor and urine as a secondary factor. Most diaper dermatitis patients experience mild symptoms; only 5% of cases are severe (3).

Generally, skin eruptions in the diaper area are cases of irritant contact dermatitis and are treated with topical treatments in conjunction with parental education about proper diaper use. Therefore, it is important to distinguish whether a skin eruption in the diaper area is directly caused by improper diaper use and resembles a flare-up of a more diffuse diaper-induced skin condition or is caused by a condition that has accidentally appeared in the diaper area but is unrelated to it (4).

The prevalence of diaper dermatitis varies greatly in different studies and countries. In the United States, diaper dermatitis is the most common skin disease that affects infants, accounting for over 1 million hospital visits per year, and less than 10% of those affected experience severe diaper dermatitis (5).

The prevalence of diaper dermatitis among children was found to be 87% in Japan, 75% in the United States, 25% in the United Kingdom, and 15% in Italy (6).

Previous studies have shown that diaper dermatitis is more common in children aged 1–24 months, with most cases occurring in infants younger than 1 year (2,7). Two recent studies from Ethiopia and Thailand demonstrated that the risk factors of diaper dermatitis have a strong correlation to parental factors (8,9).

Poor compliance to treatment advice is the main cause of failure in diaper dermatitis management. There are different causes of non-compliance, including apprehension about possible side effects, under prescription, the inability to promptly refill prescribed drugs, insufficient time, and a child's rejection of the treatment (1).

The most significant risk factors for diaper dermatitis include parents with low educational levels, parents who are unemployed, and individuals who belong to low socioeconomic classes (9-11).

According to a previous study, mothers have insufficient knowledge of diaper dermatitis prevention and management in infants. This study demonstrated a statistically significant improvement in mothers' knowledge after the administration of a structured teaching programme. A comparison of the pre-education and post-education

programme test results revealed a significant difference in mothers' general knowledge of diaper dermatitis (1).

Therefore, the goal of this study aimed to determine the prevalence of diaper dermatitis, levels of parental knowledge, attitudes toward the disease, and the risk factors associated with the disease in society.

Subjects and Methods

Study Setting

A total of 389 parents from Al-Baha region, the capital of Saudi Arabia's southern province, participated in this cross-sectional survey from January to July 2022.

Sampling Method

The sample size was calculated using the Fisher sample size formula ($N = Z^2 P(1 - P)/d^2$) with a 95% confidence interval and a 5% margin of error. A minimum sample size of 384 parents was requested based on the population of Al-Baha region (487,108), with a 5% margin of error and a 95% confidence interval. This sample size is appropriate for determining the prevalence of diaper dermatitis and its causative factors in children aged 0 to 24 months in Al-Baha region of Saudi Arabia. The ethical conduct of this study was approved by the Scientific Research and Ethics Committee of the Faculty of Medicine at Al-Baha University.

Data Collection

We used a structured electronic survey for data collection. The participants were informed about the objectives of the study before enrolment. In this study, an anonymous self-administered, reliable, prevalidated, and modified electronic questionnaire was obtained from previous studies and used to collect data (12,8). Parents who agreed to participate in the study were asked to complete the questionnaire assessing their knowledge and attitude toward diaper dermatitis. The questionnaire was translated into Arabic. We assessed the associations between diaper rash as a dependent variable and sociodemographic, socioeconomic, educational, and child health status as the independent variables. This study only included parents who had a child aged 0–24 months, parents who lived in Al-Baha region of Saudi Arabia, and parents who agreed to participate in the current survey. This study excluded parents who had not completed the questionnaire, parents who had children older than 24 months, parents who did not live in Al-Baha region, and parents who did not consent to participate. Parents whose responses met at least one of the exclusion criteria were not considered for this study.

Questionnaire Development and Testing

We used a reliable, prevalidated, and modified electronic questionnaire from previous studies (8,12). The questionnaire was divided into two sections. The first section consisted of sociodemographic and personal clinical questions. The second section consisted of 15 questions that assessed diaper dermatitis prevalence in infants (0–24 months), its risk factors, and its related parental factors.

Study Variables

The independent factors in this study included the caregiver's gender, child's gender, child's age, child's weight, child's nationality, caregiver's educational level, child's gestational age, presence of congenital abnormalities, and child's skin type and colour. Contrarily, the dependent variable was diaper rash.

Statistical Analysis

Microsoft Excel 16.0 was used to enter, manage, and code the data. Statistical analyses were performed, and tables were created using IBM SPSS 25.0 (Statistical Package for the Social Sciences (Inc, Chicago, IL, United States). For descriptive data, frequencies and percentages were used to present the information. In order to investigate potential correlations between the categorical variables, Pearson's Chi-square test was used. The relationship between diaper dermatitis and other risk factors was assessed using mixed-model logistic regression analysis. Statistical significance is defined as a value of 0.05 or lower.

Results

A cross-sectional survey was conducted on 389 parents from Al-Baha region to determine the prevalence of diaper dermatitis, parents' attitudes toward the disease, and its risk factors.

Sociodemographic Characteristics

This study included 389 children aged 0–24 months, of which 202 (51.9%) were males and 287 (48.1%) were females. Almost half of the children (43.2%) were under 24 months old, while the remaining (56.8%) were over 24 months old. The Fitzpatrick scale for skin type revealed that 57.6% of the children had type III skin, whereas 33.2% had type IV skin (Table 1).

Characteristics of the Childcare Providers

Most of the participants (98.2%) claimed to be the primary childcare provider, while the remaining participants claimed that their housekeepers or relatives were the primary childcare providers. Most of the parents (75.6%) had a university degree, 17.5% had only a high school degree, 3.3% had only an intermediate school degree, and the remaining parents were either illiterate or had only an elementary school education (Table 2).

The practice of childcare provider regarding diaper and cleaning agent use

Approximately half of the childcare providers (48.3%) changed their child's diaper more than three times per day, followed by 126 childcare providers (32.4%) who changed it three times per day, 61 childcare providers (15.7%) who changed it twice per day, and 14 childcare providers (3.6%) who changed it once per day. Furthermore, 183 childcare providers (47%) used only water as a cleaning agent, followed by 97 (24.9%) who used water and tissue paper or wet wipes, 71 (18.3%) who used water and soap, and finally 7 (1.8%) who used only alcohol sanitizers. Additionally, 138 childcare providers (35.5%) used a combination of regular moisturizers, Vaseline,

baby powder, and diaper creams in the diaper area, and 46 childcare providers (11.8%) used nothing in the diaper area (Table 3).

Prevalence of diaper dermatitis among children

The prevalence of diaper dermatitis was 39.33% (153/389). Children aged 19–24 months (65%) had the highest prevalence, followed by children aged 0–6 months (37.5%), children aged 7–12 months (61.5%), and children aged 13–18 months (53.1%). Children older than 24 months (28.1%) had the lowest prevalence (Figure 1). Regarding gender, females had a higher prevalence (44.4%) than males (34.7%) ($p = 0.005$). Children born before the 37th week of gestation had a slightly lower prevalence (34.7%) than those born at or after the 37th week of gestation (40.9%). In terms of whether or not the child had an existing skin disease, there was no significant difference in diaper dermatitis prevalence between the two groups. Children with no known allergic diseases had a slightly lower diaper dermatitis prevalence than those with an existing allergic disease (Table 4).

Children without prior episodes of diaper dermatitis were highly associated with a low prevalence ($p \leq 0.001$). In terms of the frequency of diaper changes at night, there was no significant difference in prevalence between the groups. However, in terms of diaper change during the day, children who had their diapers changed twice had a low prevalence ($p = 0.019$). At the time of diaper dermatitis, children who consumed a regular mixed diet had a low diaper dermatitis prevalence ($p = 0.008$); however, there was no significant difference in diaper dermatitis prevalence between children who were exclusively breastfeeding, exclusively formula milk, breastfeeding and formula milk, or on a regular diet with milk (Table 4).

Other factors listed in Table 4 that have no association with increased prevalence of diaper dermatitis include the childcare provider, educational level of the childcare provider, underlying gastrointestinal disease, cleaning agents used, agents used on the diaper area regularly, and Fitzpatrick skin type.

Bivariate logistic regression results

Bivariate analysis revealed that diaper dermatitis was highly related to four factors: gender, the number of prior incidents of diaper dermatitis, the frequency of diaper change during the day, and the food consumed by the child at the time of diaper dermatitis.

Multivariate logistic regression

Forward logistic regression was used to fit the bivariate logistic regression factors with p -values of <0.05 into multivariate logistic regression. Only two of the four factors were significantly linked to diaper dermatitis: the child's gender ($p = 0.025$) and the food consumed by children when they developed diaper dermatitis ($p = 0.015$) (Table 5).

Table 1: Participants' demographic characteristics

Variable	N=389	%
Age of child in months		
0-6 months	40	10.3
7-12 months	39	10
13-18 months	49	12.6
19-24 months	40	10.3
Older than 24 months	221	56.8
Sex of the child		
Male	202	51.9
Female	187	48.1
Fitzpatrick skin type		
Type I	0	0
Type II	2	0.5
Type III	224	57.6
Type IV	129	33.2
Type V	33	8.5
Type VI	1	0.2

Table 2: Characteristics of childcare provider

Variable	N=389	%
Main childcare provider		
Parents	382	98.2
Housemaid	4	1
Brothers	3	0.8
Educational level		
Uneducated	3	0.8
Elementary school	11	2.8
Intermediate school	13	3.3
High school	68	17.5
Higher education	294	75.6

Table 3: Practice of childcare provider's diaper and cleaning agents use

Variable	N=389	%
Frequency of diaper change during daytime		
Once	14	3.6
Twice	61	15.7
Three times	126	32.4
More than three times	188	48.3
Frequency of diaper change during nighttime		
Once	152	39.1
Twice	159	40.9
Three times	58	14.9
More than three times	20	5.1
Cleaning agents		
Water	183	47
Paper tissue or wet wipes	31	8
Water and paper tissue or wet wipes	97	24.9
Water and soap	71	18.3
Alcohol sanitizers	7	1.8
Agents applied on diaper area regularly		
Nothing	46	11.8
Generic moisturizers or Vaseline	71	18.3
Baby powder	39	10
Diaper creams	95	24.4
More than one	138	35.5
Number of previous diaper rash episodes		
Once	62	15.9
Twice	75	19.3
More than twice	109	28
None	143	36.8
If your child has a diaper rash, when will you take them to the doctor?		
As soon as possible	75	19.3
If it does not improve within 2 days	180	46.3
If it does not improve within 7 days	105	27
If it does not improve within 14 days	29	7.5
How do you treat diaper rash for your child?		
Doctor's prescription	157	40.4
Vaseline	151	38.8
Baby powder	88	22.6
Topical zinc oxide cream	167	42.9
Topical dexpanthenol ointment	8	2.1
Topical cornstarch	25	6.4
Topical olive oil	19	4.9
Nothing	13	3.3

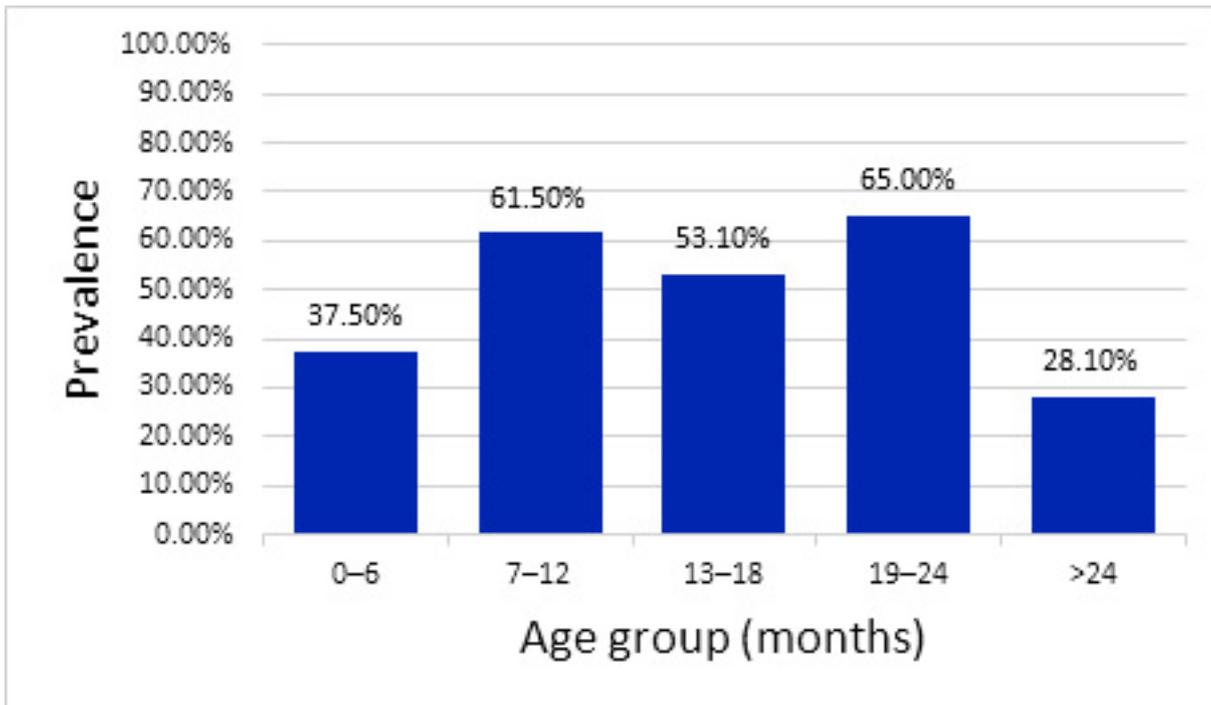
Figure 1: Prevalence of diaper dermatitis among different age groups

Table 4: Summary of the risk factors for diaper dermatitis in the study population.

Variable	Diaper dermatitis		Bivariate logistic regression		
	No n=236	Yes n=153	Odds ratio	95% Confidence interval	p-value
Age					
0-6 months	25 (62.5)	15 (37.5)	1		
7-12 months	15 (38.5)	24 (61.5)	1.19	0.29, 4.87	0.814
13-18 months	23 (46.9)	26 (53.1)	0.63	0.17, 2.35	0.489
19-24 months	14 (35)	26 (65)	2.31	0.52, 10.21	0.279
Older than 24 months	159 (71.9)	62 (28.1)	0.325	0.10, 1.02	0.054
Gender					
Male	132 (65.3)	70 (34.7)	1		
Female	104 (55.6)	83 (44.4)	2.61	1.34, 5.10	0.005*
Birth gestational age					
< 37 weeks	64 (65.3)	34 (34.7)	1		
≥ 37 weeks	172 (59.1)	119 (40.9)	0.830	0.38, 1.81	0.640
Children with birth defects					
No	233 (61.5)	146 (38.5)	1		
Yes	3 (30)	7 (70)	3.32	0.29, 37.64	0.334
Childcare provider					
Parents	230 (60.2)	152 (39.8)	1		
Housemaid	4 (100)	0 (0)	0	0, 0	0.999
Brothers	2 (66.7)	1 (33.3)	4.63	0.05, 442.74	0.510
Educational level of the childcare provider					
Uneducated	2 (66.7)	1 (33.3)	1		
Elementary school	8 (72.7)	3 (27.3)	0.15	0, 16.24	0.428
Intermediate school	8 (61.5)	5 (38.5)	1.84	0.01, 287.83	0.813
High school	39 (57.4)	29 (42.6)	0.15	0, 12.40	0.401
Higher education	179 (60.9)	115 (39.1)	0.07	0, 5.3	0.226
Children with underlying skin disease					
No	215 (62.1)	131 (37.9)	1		
Yes	21 (48.8)	22 (51.2)	0.64	0.17, 2.32	0.493
Children with underlying allergic disease					
None	183 (65.1)	98 (34.9)	1		
Skin	30 (48.4)	32 (51.6)	1.64	0.54, 5.03	0.385
Respiratory	23 (50)	23 (50)	1.58	0.60, 4.18	0.355
Previous episodes of diaper dermatitis					
Once	29 (46.8)	33 (53.2)	1		
Twice	29 (38.7)	46 (61.3)	1.49	0.56, 2.64	0.627
More than twice	37 (33.9)	72 (66.1)	2.45	0.92, 4.21	0.079
None	141 (98.6)	2 (1.4)	0.01	0, 0.03	<0.001*

Table 4: Summary of the risk factors for diaper dermatitis in the study population (continued)

Variable	Diaper dermatitis		Bivariate logistic regression		
	No n=236	Yes n=153	Odds ratio	95% Confidence interval	p-value
Diaper dermatitis appeared with a GIT disease					
No	188 (67.6)	90 (32.4)	1		
Yes	48 (43.2)	63 (56.8)	1.16	0.58, 2.30	0.679
Frequency of diaper change during daytime					
Once	9 (64.3)	5 (35.7)	1		
Twice	38 (62.3)	23 (37.7)	0.076	0.01, 0.65	0.019*
Three times	77 (61.1)	49 (38.9)	0.243	0.03, 1.85	0.172
More than threetimes	112 (59.6)	76 (40.4)	0.250	0.03, 1.85	0.175
Frequency of diaper change during nighttime					
Once	84 (55.3)	68 (44.7)	1		
Twice	107 (67.3)	52 (32.7)	0.90	0.44, 1.18	0.757
Three times	33 (56.9)	25 (43.1)	1.17	0.42, 3.22	0.766
More than threetimes	12 (60)	8 (40)	1.90	0.30, 12.06	0.498
Food consumed by child at time of diaper rash					
Exclusive breastfeeding	39 (73.6)	14 (26.4)	1		
Exclusive formulamilk	32 (54.2)	27 (45.8)	0.27	0.07, 1.10	0.068
Breastfeeding and formula milk	17 (65.4)	9 (34.6)	0.43	0.09, 2.17	0.307
Milk and normal diet	81 (50.6)	79 (49.4)	0.37	0.11, 1.28	0.117
Normal diet	67 (73.6)	24 (26.4)	0.17	0.05, 0.64	0.008*
Cleaning agents used					
Water	112 (61.2)	71 (38.8)	1		
Paper tissue or wet wipes	20 (64.5)	11 (35.5)	0.27	0.07, 1.10	0.994
Water and paper tissue or wet wipes	65 (67)	32 (33)	0.43	0.9, 2.17	0.170
Water and soup	36 (50.7)	35 (49.3)	0.37	0.11, 1.28	0.972
Alcohol sanitizers	3 (42.9)	4 (57.1)	0.17	0.05, 0.64	0.525
Agents applied on diaper area regularly					
Nothing	33 (71.7)	13 (28.3)	1		
Generic moisturizers or Vaseline	44 (62)	27 (38)	1.47	0.45, 4.87	0.527
Baby powder	26 (66.7)	13 (33.3)	1.11	0.27, 4.52	0.886
Diaper creams	57 (60)	38 (40)	1.68	0.57, 4.94	0.350
More than one	76 (55.1)	62 (44.9)	1.96	0.69, 5.59	0.210
Fitzpatrick skin type					
Type III	135 (60.3)	89 (39.7)	1		
Type IV	82 (63.6)	47 (36.4)	0.65	0.33, 1.28	0.213

*p-value <0.05 was considered statistically significant.

Table 5: Factors associated with diaper dermatitis on multivariate logistic regression.

Variable	Multivariate logistic regression		
	Odds ratio	95% Confidence interval	p-value
Gender			
Male	1		
Female	1.92	0.11, 0.17	0.25*
Previous episodes of diaper dermatitis			
Once	1		
Twice	1.71	-0.03, 0.23	0.130
More than twice	2.16	0.03, 0.27	0.016
None	0.01	-0.62, -0.39	<0.001
Frequency of diaper change during daytime			
Once	1		
Twice	0.18	-0.42, 0.04	0.108
Three times	0.25	-0.35, 0.09	0.239
More than three times	0.34	-0.31, 0.12	0.400
Food consumed by child at time of diaper rash			
Exclusive breastfeeding	1		
Exclusive formulamilk	0.68	-0.17, 0.13	0.761
Breastfeeding and formula milk	0.50	-0.27, 0.10	0.386
Milk and normal diet	0.75	-0.13, 0.12	0.927
Normal diet	0.26	-0.30, -0.03	0.015*

*p-value <0.05 was considered statistically significant

Discussion

Diaper dermatitis is an inflammatory skin eruption that develops in the diaper area. It typically affects infants and toddlers, but it can affect anyone who wears a diaper (1). It has been noted that more than 50% of infants are likely to experience at least a single episode of diaper dermatitis (2).

The primary factor that contributes to the etiology of diaper dermatitis is prolonged skin contact with faeces, and the secondary factor is prolonged skin contact with urine.

Many studies have suggested that low parental educational status, unemployment, and belonging to a lower socioeconomic class are related to the incidence of diaper dermatitis (9-11).

This study is the first to examine the prevalence and risk factors of diaper dermatitis in Al-Baha children. In this study, we assessed diaper dermatitis prevalence among children younger than 24 months because diaper dermatitis can result from poor parental education and knowledge. We studied the risk factors for diaper dermatitis as well as parental knowledge and practice regarding diaper dermatitis.

Diaper dermatitis prevalence has been reported in numerous studies in the literature. In our study, the prevalence of diaper dermatitis reached 39.33% (153/389). Our study findings revealed that diaper dermatitis prevalence in Al-Baha is lower than that in the United States (75%), Mauritius (79.7%), Japan (87%), and Ethiopia (62.5%). Our study findings also revealed that the prevalence of diaper rash is higher than that reported in similar studies that were conducted in Italy (15%), the United Kingdom (25%), and Kenya (27.3%) (9).

Another study that included the entire population of Saudi Arabia discovered that children aged 0–24 months old who were diaper-dependent during the study had a diaper rash prevalence of 44%. This percentage is significantly higher than the prevalence percentage of children older than the age of 2 (12).

Several studies have claimed that there is no significant difference in diaper dermatitis prevalence between genders, while other studies have claimed that diaper dermatitis is significantly more common in females. In our study, females had a higher diaper dermatitis prevalence (44.4%) than males (34.7%) (p=0.005). Contrary to our study, some other studies have reported that there is no significant difference in diaper dermatitis prevalence

between male and female children (8,15,17). In another study, female gender was considered an independent risk factor for diaper dermatitis ($p = 0.001$) (12). There is no conclusive evidence in the literature that suggests a rationale for the difference in the prevalence of diaper dermatitis between genders; however, differences in research outcomes could be related to differences in the number of participants.

In terms of age, most studies have agreed that diaper dermatitis is more prevalent in children younger than 24 months than in older children. However, many studies have disagreed about the most common age group for children younger than 24 months. In this study, our analysis results revealed that children aged 19–24 months had the highest prevalence (65%), which is consistent with the results of another study conducted in China (7). Some studies from Saudi Arabia and Indonesia have reported that the most common age group is children younger than 12 months (12,17). Two studies from Thailand and Kenya reported that the most common age group is under 7 months old (8,9), whereas a study from Ethiopia reported that the most common age group is 13–18 months old (9).

Consistent with this study, previous studies have also revealed that infants with a history of skin allergies or a gestational age older than 37 weeks have a relatively high prevalence of diaper dermatitis (2,12).

The analysis of diaper dermatitis in relation to the Fitzpatrick skin type revealed that infants with Fitzpatrick type III had the highest prevalence of diaper dermatitis, followed by those with types I, II, and IV, which is consistent with a previous finding (18). Nevertheless, our study findings were not statistically significant.

Infants who were exclusively breastfed during the time of this study had the lowest diaper dermatitis prevalence. This prevalence was similar to that of infants fed with a regular diet, as shown in Table 4. Additionally, other studies in the literature support the idea that infants who are exclusively breastfed have a low incidence of diaper dermatitis. Two previous studies conducted in the United States and Turkey have shown that infants fed with milk formula have a significantly higher prevalence of diaper dermatitis than those who are exclusively breastfed (3,15).

In fact, studies have shown that infants who are exclusively breastfed have low levels of organisms that contain the urease enzyme. Additionally, these infants have a relatively low pH and low levels of faecal protease and lipase enzymes. Therefore, their diaper areas exhibit less irritation.

Furthermore, we evaluated how changing an infant's diaper during the day versus changing it at night affects the prevalence of diaper dermatitis. We discovered that infants whose diapers were changed more than three times during the day had a significantly lower prevalence of diaper dermatitis than infants whose diapers were changed less than three times during the day. This finding is consistent

with a previous finding that revealed that diaper dermatitis is reduced by frequent diaper changes (8). However, the increase in the diaper-changing frequency at night did not exhibit an increase in diaper dermatitis prevalence.

This study has some limitations since it is the first in the area and is one of the few studies conducted across the country. Additionally, all the factors associated with diaper rash may not have been considered. However, there is no doubt that this study will contribute to the literature and provide epidemiological data on the prevalence of diaper dermatitis and its associated risk factors.

Conclusion

The findings of this study, which is the first report on the prevalence of diaper dermatitis in Al-Baha, demonstrated a high prevalence of diaper rash in children aged 0–24 months. Children aged 19–24 months were found to have the highest diaper dermatitis prevalence, followed by children aged 7–12 months.

This study demonstrated that diaper dermatitis is significantly linked to four factors: gender, the number of prior episodes of diaper dermatitis, the frequency of diaper change during the day, and the food consumed by children at the time of diaper dermatitis. Thus, campaigns, hospital visits, and educational materials could all be used to educate parents and caregivers about the modifiable risk factors of diaper dermatitis.

Ethical approval and consent to participate

The study was approved by the research ethics committee in the Faculty of Medicine, Al-Baha University (Number of approval REC/MED/BU-FM/2022/14). Written informed consent was obtained from all participants included in the study.

Data availability

All data associated with this study are included in the article. Further inquiries can be directed to the corresponding author.

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