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ORIGINAL RESEARCH

Cow's Milk Allergy and Associated Factors Among Children in Abha City, Saudi Arabia – A Retrospective Case Control Study

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Introduction: Cow's Milk Allergy (CMA) is the most common food allergy among children. The global prevalence of CMA ranges from 1.8% to 7.5% among children. Data regarding CMA is scarce and only a few studies have been conducted in Saudi Arabia. Therefore, this study was undertaken to determine the factors associated with CMA among children in Abha city and to explore the knowledge and practice regarding CMA among parents in Abha city.

Methods: This retrospective one-year case control study was conducted amongst children with CMA (cases) and healthy children without CMA (controls) and their parents attending Abha Maternity and Children Hospital, Saudi Arabia. Data regarding CMA was extracted from the hospital medical records. A validated questionnaire was used to collect detailed information from the identified cases and controls after obtaining informed consent. SPSS software was used for data analysis.

Results: The study groups consisted of 31 cases and 37 controls. Children between 0 and 36 months of age were included. The male-to-female ratio was 1:1. The parent's knowledge level was good regarding the association between early introduction of cow's milk and increased risk of CMA (Mean Score: 3.96). Having a sibling with a CMA is actually a risk factor for developing CMA (P-value = 0.03).

Conclusion: To reduce the risk of CMA, the study recommends dietary strategies that exclude CMA allergens and the use of suitable alternative milk formulas. It highlights the protective role of breastfeeding and advises against the early introduction of cow's milk formulas during infancy. Furthermore, the study advocates for hospital nurseries and new parents to refrain from administering artificial milk formulas to newborns.

Keywords: Cow's milk allergy, children, infants, risk factors, knowledge, practice, parents

Introduction

The American Academy of Pediatrics and the American College of Allergy, Asthma, and Immunology define Cow's Milk Allergy (CMA) as a hypersensitivity reaction that typically affects infants and young children, with responses that can be either IgE-mediated or non-IgE-mediated. IgE-Mediated CMA results in immediate allergic reactions, typically diagnosed through skin prick tests or specific IgE blood tests. In contrast, Non-IgE-Mediated CMA presents with delayed reactions, primarily affecting the gastrointestinal system and skin.[1–3]

CMA is a prevalent food allergy among infants and young children, affecting approximately 1.8% to 7.5% of this population. The prevalence varies by region and diagnostic approach[4–11] The increase in allergic cases, which is caused by

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cows milk protein such as atopic dermatitis, appears to have plateaued in Westernized countries, while in low and middle-income countries have been increasing.[4]

It is universally acknowledged that breastfeeding is the best and ultimate way for the development and growth of infants and a source of ideal food.[12] Infants should exclusively be breastfed for at least the first 6 months of age in order to receive optimal benefits for the growth and development of health as recommended by WHO.[5,14]. The best method to prevent CMA is breastfeeding as shown in a study of German Infant Nutrition Intervention atopic dermatitis is significantly prevented by breastfeeding when compared with other artificial formula.[10] Numerous studies have shown that early exposure to cow's milk formula may decrease the risk of CMA.[12–14] According to the United States of Federal Food, Drug, and Cosmetic Act, an infant formula is a food simulating human milk or its quality as an entire or partial substitute for human milk that is exclusively used as a special diet for babies.[5] By definition, a milk formula could be a substitute for human milk, which is the optimal supply of nutrition for an infant.[6] Since human milk is the gold standard, the primary infant formulas were developed to be similar or close to the macronutrient composition of human milk using cow's milk.[6] Infant formula has been carefully modified and diluted to meet the nutrients found in breast milk.[4] Most importantly, CMA is affecting the quality of life and the social and economic burden of the population. In addition, the symptoms caused by CMA can lead to anaphylaxis reactions. This study aims to keep in view the seriousness of the issue, especially among the group of affected infants and families. Additionally, an extensive literature review revealed that no such prior study has been conducted in the Aseer region.

Although various health problems of infants and young children have been addressed, there is a paucity of data regarding CMA particularly in Abha city. With the above background, this study was undertaken to determine the associated factors that lead to CMA among infants in Abha city, assess the parent's knowledge, and practices regarding CMA and suggest suitable preventive measures to the study population. This study provides insights for future researchers, clinicians, and public health experts to better understand the associated factors of CMA among infants and develop effective preventive measures.

Material and Methods

Study Design, Area and Setting

This retrospective preliminary case control study was conducted amongst children with CMA (cases) and healthy children without CMA (controls) and their parents attending Abha Maternity and Children Hospital, Almahala, Abha city, Kingdom of Saudi Arabia. This hospital is managed by the Ministry of Health (MOH). Abha is the capital city of the Aseer Region and is situated on the slopes of the Sarawat Mountains in the Southern Region of Saudi Arabia with an estimated population of 1,093,705 according to the 2021 estimated census. We hypothesized that cow's milk allergy (CMA) among children in Abha city is likely associated with certain factors within the study population, and that the knowledge and practices of their parents regarding CMA are likely to be inadequate. The research questions are: What factors are associated with CMA among children in Abha city? "What are the knowledge and practices of parents towards CMA in their children in Abha city"?

Study Population and Eligibility Criteria

Age and gender matching of the cases and the controls was done to diminish the potential confounding effect(s). The study included a group of children with confirmed CMA using oral food challenge and their controls relatively close in number from the same hospital. The control group consisted of healthy children without a diagnosis of CMA, CMA sensitivity, or CMA symptoms, and were not using milk formulas for CMA symptoms They were recruited from the Departments of Pediatrics, Abha maternity and children hospital.

Inclusion Criteria

Cases

Children diagnosed with CMA at Abha Maternity and Children Hospital.

Children aged up to 3 years.

Parents or guardians who provided written consent.

Confirmation of CMA according to the following guidelines: A proper diagnosis of CMA started with an "allergy-focused clinical history" and a complete physical examination. The diagnosis was further confirmed or excluded by an

allergen elimination and challenge procedure. An oral food challenge (OFC) is the gold standard for confirming non-IgE-mediated CMA. It is conducted in a controlled medical environment, following a structured protocol of incremental dosing and careful observation for symptoms. This approach ensures the safety and accuracy of the diagnosis, providing valuable information for the ongoing management of the patient.

Controls

Healthy children without a diagnosis of CMA, CMA sensitivity, CMA symptoms, physician diagnosis of CMA from outpatient clinics.

Children aged up to 3 years.

Parents or guardians who provided written consent.

Exclusion Criteria

Cases

Children with incomplete medical records.

Children with other significant allergies or chronic conditions that could confound the results.

Parents or guardians who did not provide written consent.

Controls

Children with incomplete medical records.

Children with any diagnosis of CMA, CMA sensitivity, CMA symptoms, or other significant allergies or chronic conditions.

Parents or guardians who did not provide written consent.

Children with any serious health condition such as anomalies and heart defects that might affect the study.

Data Collection Tool

The questionnaire was structured based on an extensive literature review to ensure it encompassed all relevant aspects of the study objectives. The initial draft of the questionnaire was reviewed by a panel of experts in the field of pediatrics, allergy, and biostatistics. Their feedback was instrumental in refining the questions for clarity, relevance, and comprehensiveness.

An online questionnaire was developed based on the study criteria to gather data from both cases and controls. It was designed to align with the study objectives and was available in both English and Arabic through Google Forms. To facilitate data collection, the questionnaire was shared via social media and email. A certified bilingual expert translated the questionnaire from English to Arabic to ensure clarity and minimize bias. Before its final use, a pretest was conducted among randomly selected parents in the region to assess its reliability and applicability. However, the results from this pilot study were excluded from the final analysis.

Sampling/Data Collection Technique

The selection of subjects in this retrospective case-control study was systematically conducted using available hospital records. Cases were identified from existing records of children diagnosed with CMA, while controls were selected as every alternate participant (child) without CMA. Both groups were contacted via mobile phone and included only after obtaining written consent.

Data collection included parents' age, parental income, number of siblings, and consumption of cow's milk products. This information was gathered through a detailed questionnaire administered to both cases and controls.

Sample Size Calculation

Sixty-eight children (31 cases and 37 controls) identified during the study period were included in the study as per inclusion criteria. Each child corresponded to one mother. The desired sample size was 30 cases and 30 controls, respectively.

Sample sizes Determination:

$$n = \frac{2\left(Z_{\alpha/2} - Z_{1-\beta}\right)^2}{\left(\frac{\mu_1-\mu_2}{\sigma}\right)^2} = \frac{2(1.96 - 0.84)^2}{\left(\frac{\Delta}{\sigma}\right)^2}$$

$$n = \frac{15.68}{(\delta)^2} \approx \frac{16}{(\delta)^2}$$

$Z_\beta = Z_{0.20} = 0.842$ from (Z table) 80% power.

$Z_{\alpha/2} = Z_{0.05/2} = 1.96$ (Z table) at type I error of 5%

Effect size (δ) = 0.75 Following Allen's (2011) guidelines, a large effect size (δ=0.75) was assumed.[15]

The sample size is 30 in each group.

Study Variables

The study focused on the presence or absence of CMA in children as the dependent variable. Within this framework, "case" indicated children diagnosed with CMA, while "control" denoted those without a CMA diagnosis. Each child in the study was represented by their mother, and thus each mother corresponded to one child, which ensures the clarity and accuracy of the study's representation of the population. The investigation encompassed various social demographic factors as independent variables. Several factors associated with CMA risk and caregiving practices were considered. The knowledge of families regarding CMA was evaluated through specific questions addressing beliefs about early milk introduction, the role of casein in triggering CMA, potential cross-reactivity between cow's milk and soy proteins, the use of alternative animal milk, and dietary considerations for individuals with lactose intolerance. Parental knowledge regarding CMA, utilizing mean scores was divided into three categories (Poor, Intermediate, and Good) and cut off values were 1.0–2.4 (Poor), 2.5–3.4 (Intermediate) and 3.5–5.0 (Good).

Determination of Likert Scale Total Scores

Each response is given a numerical value, known as a score, ranging from one to five. For instance, "Strongly Disagree" is assigned a score of 1, "Disagree" a score of 2, "Neutral/Undecided" a score of 3, "Agree" a score of 4, and "Strongly Agree" a score of 5. The total score on the Likert scale is determined by multiplying the frequency of each response by its corresponding score. The formula used is: Total Score = Σ (fi × Likert Scale Score). Where fi represents the number of respondents selecting each option.

For example, the total score for the statement "Early introduction of cow's milk increases the risk of developing a cow's milk protein allergy" is calculated using this method.

(17*5) + (34*4) + (15*3) + (1*2) + (1*1) = 269

Determination of Likert Scale Mean Scores

The mean score is calculated by dividing the total scores by the total number of respondents.

Mean Score = Σ(fi × Likert Item Score) ÷ Number of Respondents

For instance, the mean score of the first statement as shown in the table is as follows: Mean Score = [(17*5) + (34*4) + (15*3) + (1*2) + (1*1)] ÷ 68

Mean Score = 3.96

Data Entry and Statistical Analysis

Data were entered into an MS-Excel spreadsheet (Microsoft Office Excel 2010) and were analyzed by using the SPSS package 16.0 version (SPSS Inc., Chicago, Illinois, USA). By conducting univariate analysis, we aimed to explore the isolated influence of each variable on the likelihood of children being diagnosed with CMA. Binary logistic regression analysis was employed to investigate the relationship between the dependent variable, which was the diagnosis of CMA in children, and several identified significant risk factors in univariate analysis. In this context, the analysis aimed to

ascertain which factors significantly contribute to the likelihood of children being diagnosed with CMA. The logistic regression analysis provided odds ratios and associated p-values, offering insights into the strength and statistical significance of these associations. A p-value of less than 0.05 was considered statistically significant for variable calculations. To account for multiple testing, False Discovery Rate (FDR) adjustments were applied.

Ethical Considerations

This study was approved by the Research Ethics Committee at King Khalid University (ECM#2023-2112) and by MOH (H-06-B-091). This study was further permitted by the Director of the Academic Affairs and Training Department at Abha Maternity and Children's Hospital (AMC-2023- 010). The research's objectives, anticipated duration, and the nature of any interventions or trials were disclosed to the participants or their authorized substitutes to acquire their informed permission. The study complies with the Declaration of Helsinki.

Results

Background Information

There was an equal distribution between female[16] and male[16] children, with each gender representing 50.0% of the total sample. The number of cases was 31 (45.59%) and controls were 37(54.41%).

The most notable representation is the age range of 13 to 15 months, constituting 22.1% of the sample. (Figure 1)

The data reveals that 34 (50.0%) parents used milk formula to manage CMA and the other 34 (50.0%) did not use milk formula for this purpose.

Table 1 presents the gender distribution and family history of CMA among cases and controls. The data indicates no significant association between the gender of the child and the diagnosis of CMA, with p = 0.808. A significant association was found regarding siblings with CMA: 68.6% of controls had no siblings with CMA, while 88.2% of

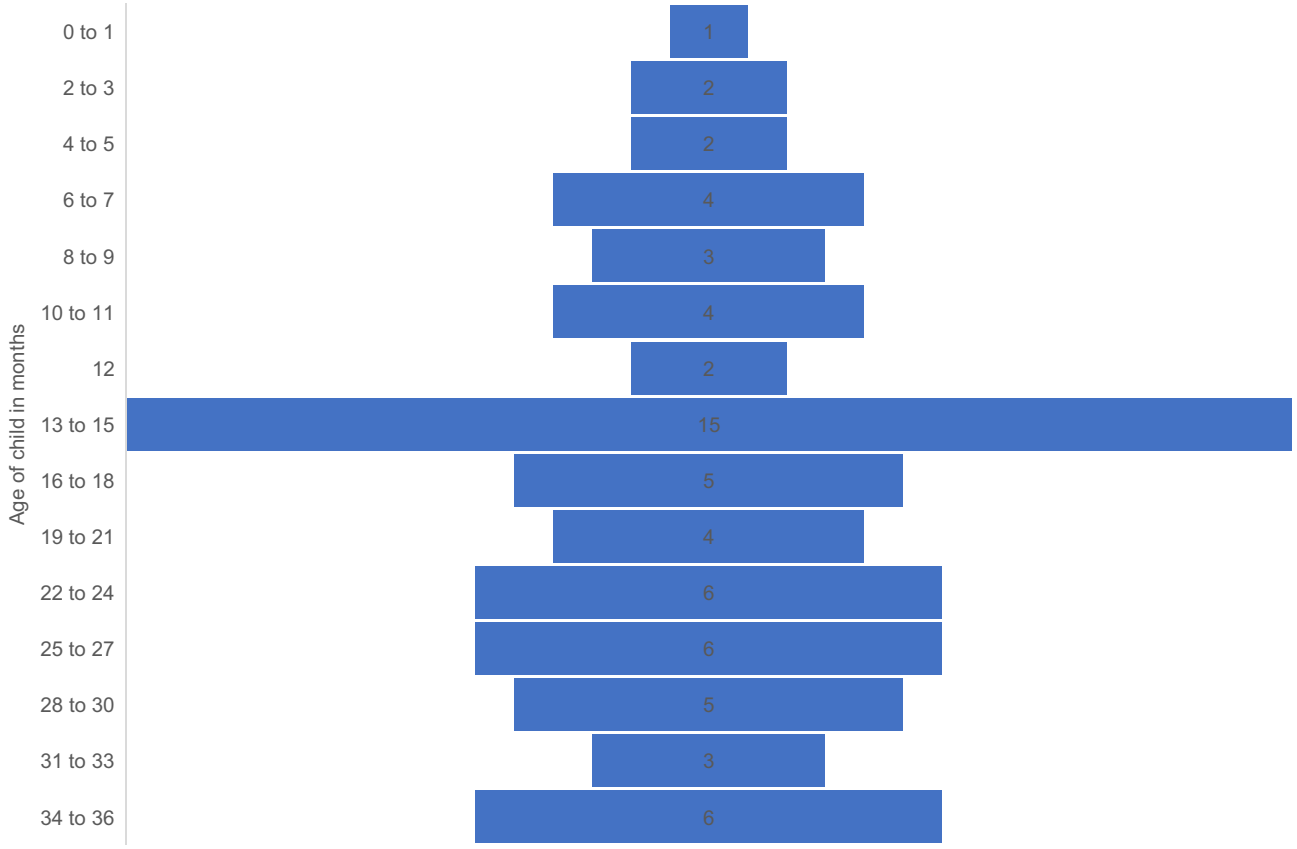

Figure 1 Age distribution of the children (months).

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Table 1 Gender Distribution and Family History of CMA Among Cases and Controls

Gender of the Child		Control (n=37)	Case (n=31)	Total	Chi Square, P value	O.R (95% CI)
Female		18	16	34	0.059, 0.808	1.13 (0.43 to 2.92)
		52.9%	47.1%	100.0%		
Male		19	15	34		
		55.9%	44.1%	100.0%		
Family history of CMA		**Case (n=31)**	**Control (n=37)**	**Total**	**Chi square, P value**	**O.R (95% CI)**
Does any of sibling have CMA?	No	16	35	51	16.620, 0.001	–
		31.4%	68.6%	100.0%		
	Yes	15	2	17		0.06 (0.012 to 0.29)
		88.2%	11.8%	100.0%		
Does the mother have a history of CMA?	No	28	35	63	0.452, 0.501	–
		44.4%	55.6%	100.0%		
	Yes	3	2	5		0.53 (0.08 to 3.41)
		60.0%	40.0%	100.0%		
Does the father have a history of CMA?	No	29	37	66	2.459, 0.117	–
		43.9%	56.1%	100.0%		
	Yes	2	0	2		0.15 (0.01 to 3.40)
		100.0%	0.0%	100.0%		
Does your child have any other food allergy than CMA?	No	24	27	51	0.178,	–
		47.1%	52.9%	100.0%	0.673	
	Yes	7	10	17		1.26 (0.41 to 3.85)
		41.2%	58.8%	100.0%		

cases had siblings with CMA (p = 0.001). No significant associations were found for maternal or paternal history of CMA, nor for the presence of other food allergies in the child.

Table 2 shows that there was no significant association between the educational level of mothers and the diagnosis of CMA in children (p-value = 0.105). However, the odds ratio suggested that children of mothers with low educational levels had a lower risk of developing CMA (OR = 0.52, 95% CI: 0.41–0.66). Similarly, the educational level of fathers was also found to have no

Table 2 Correlation of Parental Education and Income Levels with CMA Diagnosis in Children

Characteristics		Case (n=31)	Control (n=37)	Total	Chi Square, P Value	O.R (95% CI)
Educational level of the mothers	Low	0	3	3	2.63, 0.105	0.52 (0.41–0.66)
		0.0%	100.0%	100.0%		
	High	31	34	65		
		47.7%	52.3%	100.0%		

(*Continued*)

Table 2 (Continued).

Characteristics		Case (n=31)	Control (n=37)	Total	Chi Square, P Value	O.R (95% CI)
Educational level of the fathers	Low	0	2	2	1.72, 0.189	0.53(0.42–0.66)
		0.0%	100.0%	100.0%		
	High	31	35	66		
		46.9%	53.1%	100.0%		
Income of the mothers	Less than 6000 SAR	17	24	41	0.708, 0.4	–
		41.50%	58.50%	100.00%		
	More than 6000 SAR	14	13	27		1.52 (0.57 to 4.04)
		51.90%	48.10%	100.00%		
Income of the fathers	Less than 6000 SAR	0	5	5	4.52, 0.033	–
		0.00%	100.00%	100.00%		
	More than 6000 SAR	31	32	63		0.508 (0.39 to 0.65)
		49.20%	50.80%	100.00%		

significant association with the diagnosis of CMA in children (p-value = 0.189). Nevertheless, the odds ratio indicated that children of fathers with low educational levels had a lower risk of developing CMA (OR = 0.53, 95% CI: 0.42–0.66). Table 2 shows that there was no significant association between the income of mothers and the diagnosis of CMA in children (p-value = 0.4). Although the odds ratio suggested that children of mothers with higher incomes (>6000 SAR) had a slightly higher risk of developing CMA, the association was not significant. In contrast, the income of fathers was found to be significantly associated with the diagnosis of CMA in children (p-value = 0.033). Notably, the odds ratio indicated that children of fathers with higher incomes (>6000 SAR) had a significantly lower risk of developing CMA (OR = 0.508, 95% CI: 0.39–0.65).

Knowledge and Practices of Parents Regarding CMA

The majority of parents (n = 14) used a partially hydrolyzed formula. One parent uses a combination of a partially hydrolyzed formula and an amino acids-based formula (Figure 2).

The results show the level of understanding among parents on specific aspects. Notably, there is a solid consensus among parents, indicating a good level of knowledge, regarding the association between early introduction of cow's milk and an increased risk of developing a cow's milk protein allergy (Mean Score: 3.96). Similarly, parents exhibit a good level of awareness concerning the involvement of casein in triggering cow's milk protein allergy (Mean Score: 3.72). On the other hand, the understanding of parents on the potential development of cow's milk protein allergy in exclusively breastfed infants falls into the Intermediate category (Mean Score: 3.38). The same Intermediate level of knowledge is observed regarding the cross-reactivity of a child allergic to cow's milk protein with soy proteins (Mean Score: 2.97) and the use of alternative animal milk as a substitute for cow's milk (Mean Score: 3.37). Moreover, a good level of knowledge is demonstrated in the consensus among parents that patients with lactose intolerance should exclude all foods containing cow's milk protein from their diet (Mean Score: 3.51). Finally, an Intermediate level of understanding is seen in the recommendation that other allergenic foods should be eliminated from the diet of children with cow's milk allergy as a preventive measure. (Mean Score: 3.09). To minimize the risk of allergic reactions, it is also advisable for these children to avoid other common allergens, including soy, eggs, fish, and peanuts. The findings reflect varying levels of parental knowledge across different aspects of CMA (Table 3).

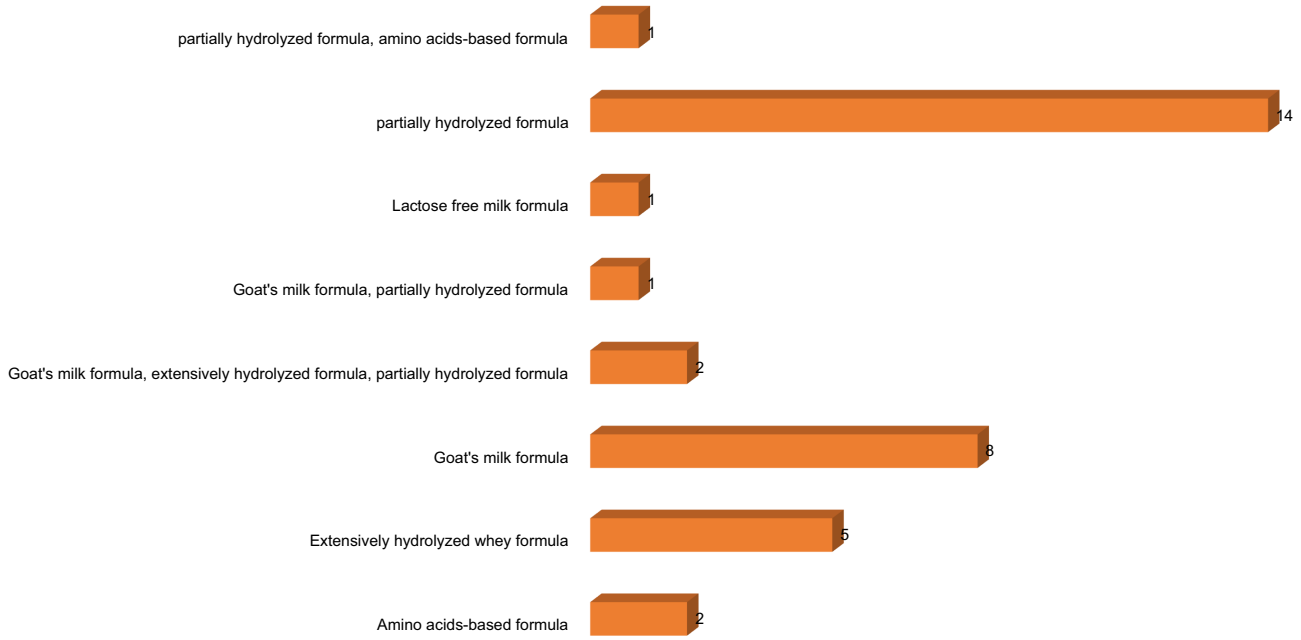

Figure 2 Type of milk formula used by the participants (n=34).

Source of Information, Reasons for Artificial Formula Feeding

Among all, twenty-five respondents relied on information provided by doctors (Figure 3).

Six parents use both feeding methods (breastfeeding and formula) due to school or work commitments. Twenty-two parents perceive insufficient milk supply as a reason for using formula. Three parents use formula because their baby is sick or unable to suckle. Eleven parents reported not using artificial formula feeding (Figure 4).

Table 3 presents an assessment of parent's knowledge regarding CMA. The responses are categorized into five levels ranging from "Strongly Agree" to "Strongly Disagree."

Table 3 Assessment of Parent's Knowledge Regarding CMA

Parent's Knowledge Regarding CMA	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Total Score	Mean Score	Knowledge Level
Early introduction of cow's milk increases the risk of developing CMA	17	34	15	1	1	269	3.96	Good
Casein is a milk protein that is involved in the triggering of a CMA	10	32	24	1	1	253	3.72	Good
Exclusively breastfed infants can develop CMA	8	30	13	14	3	230	3.38	Intermediate
Children allergic to cow's milk protein may cross-react with soy proteins	3	13	33	17	2	202	2.97	Intermediate
Goat's milk and other animal-derived milks, such as sheep, mare, or donkey milk, can serve as alternatives to cow's milk for children with CMA.	2	41	11	8	6	229	3.37	Intermediate

(*Continued*)

Table 3 (Continued).

Parent's Knowledge Regarding CMA	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Total Score	Mean Score	Knowledge Level
Individuals with lactose intolerance should eliminate all foods that contain cow's milk protein from their diet.	15	23	13	16	1	239	3.51	Good
To prevent allergic reactions, children with cow's milk allergy should also avoid other common allergens such as soy, eggs, fish, and peanuts.	7	20	15	24	2	210	3.09	Intermediate

Early Introduction of Cow's Milk

The majority of respondents, with 34 agreeing and 17 strongly agreeing, acknowledge that early introduction of cow's milk increases the risk of developing a cow's milk protein allergy.

Involvement of Casein in Triggering CMA

Respondents generally recognize the role of casein in triggering cow's milk protein allergy, with 32 agreeing and 10 strongly agreeing.

Exclusively Breastfed Infants and CMA

There is variation in responses regarding the belief that exclusively breastfed infants can develop cow's milk protein allergy, with 30 agreeing and 8 strongly agreeing. However, a considerable portion, 14, disagrees.

Cross-Reactivity With Soy Proteins

A mixed response is observed regarding the statement that a child allergic to cow's milk protein may cross-react with soy proteins, with 13 agreeing and 3 strongly agreeing, while 17 disagree.

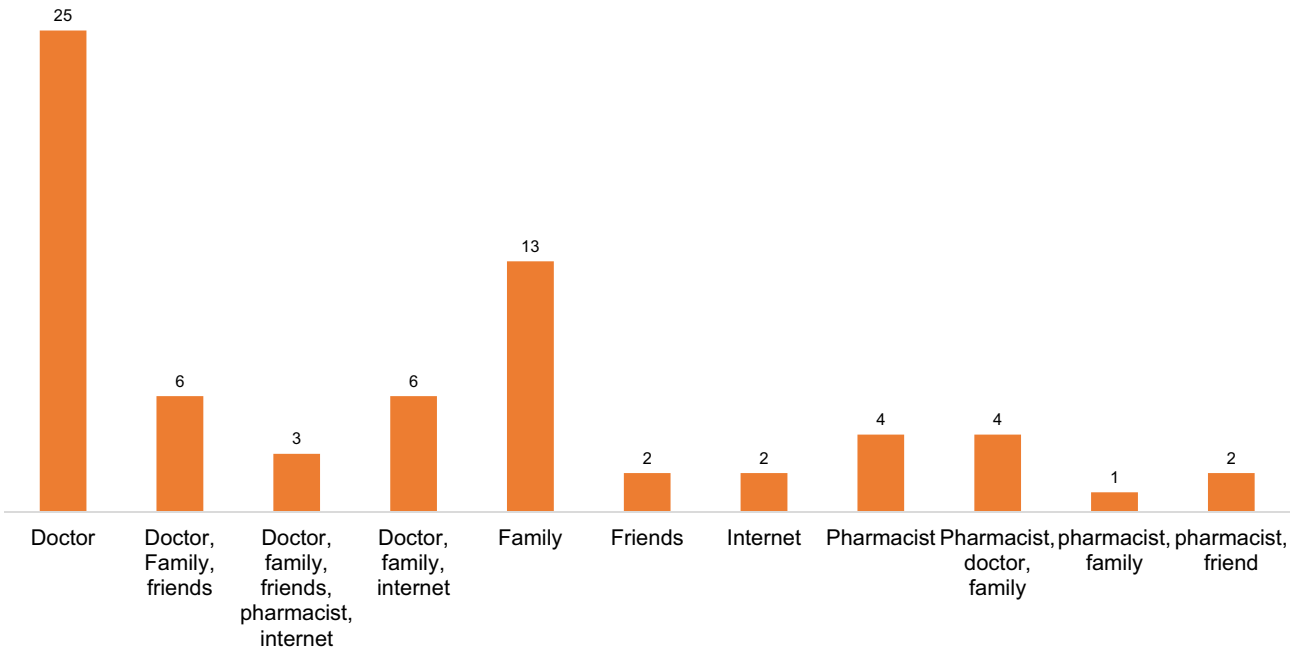

Figure 3 Source of information about the artificial formula feeding among the respondents.

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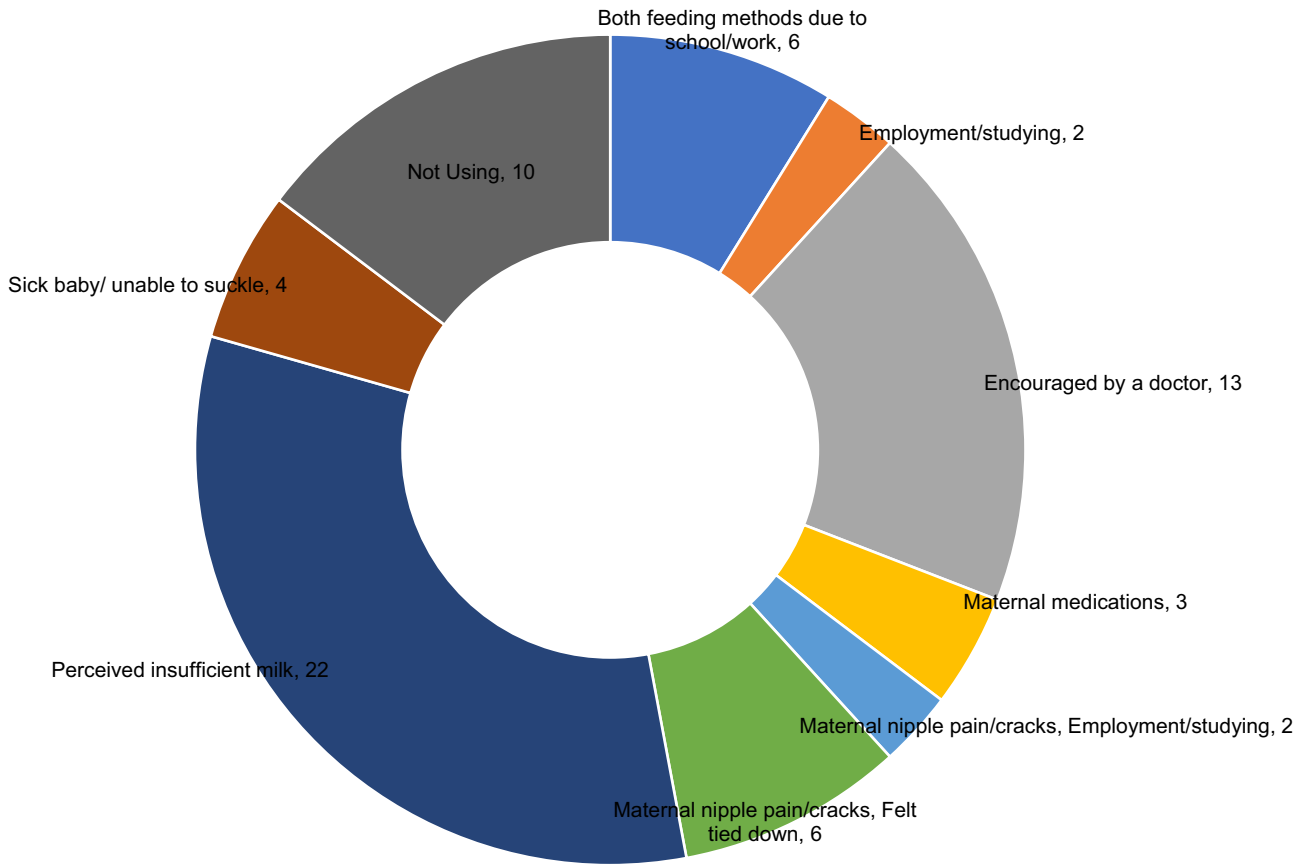

Figure 4 Reasons for using artificial formula feeding among the study participants (n=68).

Substitute for Cow's Milk

Regarding the use of goat's milk or other animal milk as a substitute for children with cow's milk protein allergy, the majority 41 agree, while 2 strongly agree. However, a notable portion of 8 disagrees.

Lactose Intolerance and Diet

Respondents generally acknowledge that patients with lactose intolerance should exclude all foods containing cow's milk protein from their diet, with 23 agreeing and 15 strongly agreeing.

Elimination of Other Allergenic Foods

Regarding the elimination of other allergenic foods for children with cow's milk allergy as a preventive measure, responses vary. Twenty percent agree, while 7% strongly agree. However, a significant portion of 24 disagrees.

The main findings from Table 4 indicate no significant difference in exclusively breastfeeding during the first 6 months between controls (47.5%) and cases (33.3%), suggesting no strong association with CMA. However, a significant association exists between exclusive use of cow's milk formula and CMA diagnosis, with 65.5% of cases exclusively using cow's milk formula compared to 69.2% of controls who did not. Additionally, the combined practice of breastfeeding and cow's milk formula shows a significant association, with 72.7% of cases following this method versus 45.7% of controls. Initiating breastfeeding within the first month shows a borderline significant association with CMA, as 58.6% of cases did not start breastfeeding in the first month compared to 35.9% of controls.

Symptoms and Age of Onset for CMA in Children

Thirty-six respondents reported vomiting, crying or colic, constipation, and flatulence (Figure 5).

Table 4 Type of Child Feeding Prior to Diagnosis of CMA in Relation to Children Diagnosed with CMA

Type of Child Feeding		Case (n=31)	Control (n=37)	Total	Chi Square, P Value	O.R (95% CI)
Exclusively breastfed children for the first 6 months of age (only breastmilk without any additional milk formula, food or drink, not even water)	No	28	31	59	0.628, 0.428	–
		47.5%	52.5%	100.0%		
	Yes	3	6	9		1.80 (0.41 to 7.91)
		33.3%	66.7%	100.0%		
Exclusive use of cow'smilk formula as a source of feeding	No	12	27	39	8.096, **0.004**	–
		30.8%	69.2%	100.0%		
	Yes	19	10	29		0.23 (0.08 to 0.65)
		65.5%	34.5%	100.0%		
Breastfeeding and also using cow's milk formulas a supplementary source	No	25	21	46	4.398, **0.036**	–
		54.3%	45.7%	100.0%		
	Yes	6	16	22		3.17 (1.05 to 9.56)
		27.3%	72.7%	100.0%		
Breastfeeding initiated in the first month	No	17	12	29	3.462, **0.063**	–
		58.6%	41.4%	100.0%		
	Yes	14	25	39		2.52 (0.94 to 6.78)
		35.9%	64.1%	100.0%		

Notes: The data presented in bold in the table signifies statistically significant results, p-value of less than 0.05 was regarded as statistically significant.

In Figure 6, at 1 month, 56.0% of children with symptoms were diagnosed with CMA, At 2 months, 42.3% of cases were diagnosed with CMA, At 4 months, 62.5% of children with symptoms were diagnosed with CMA. At 5 months, only 20.0% of children with symptoms were diagnosed with CMA.

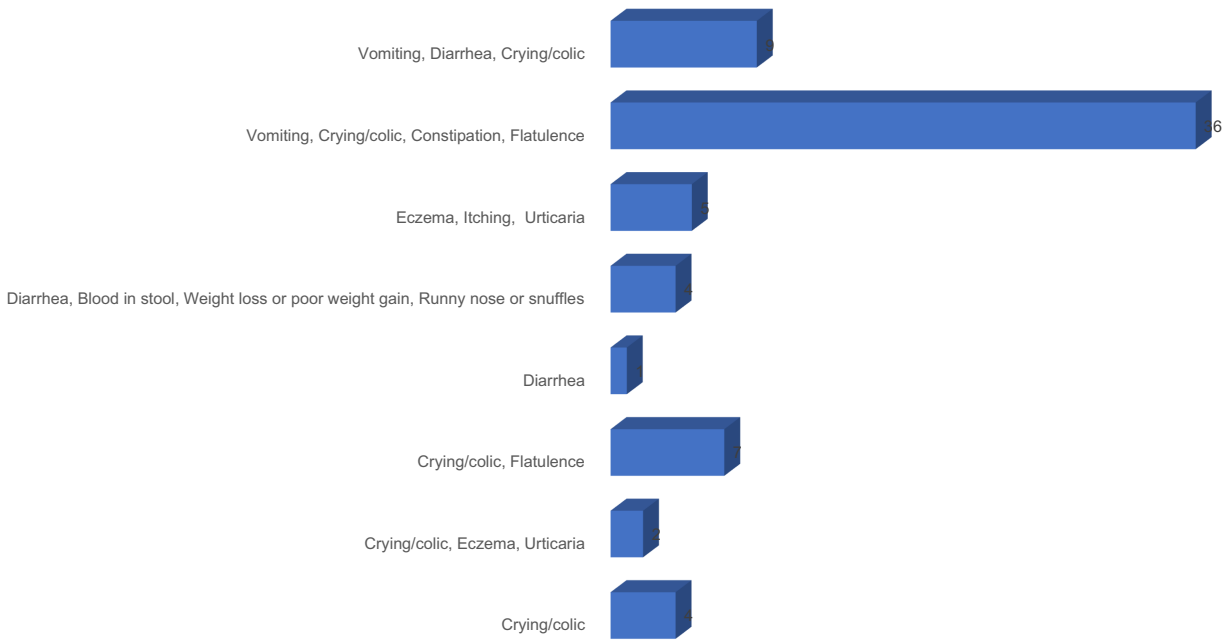

Figure 5 Cow's milk allergy symptoms in children.

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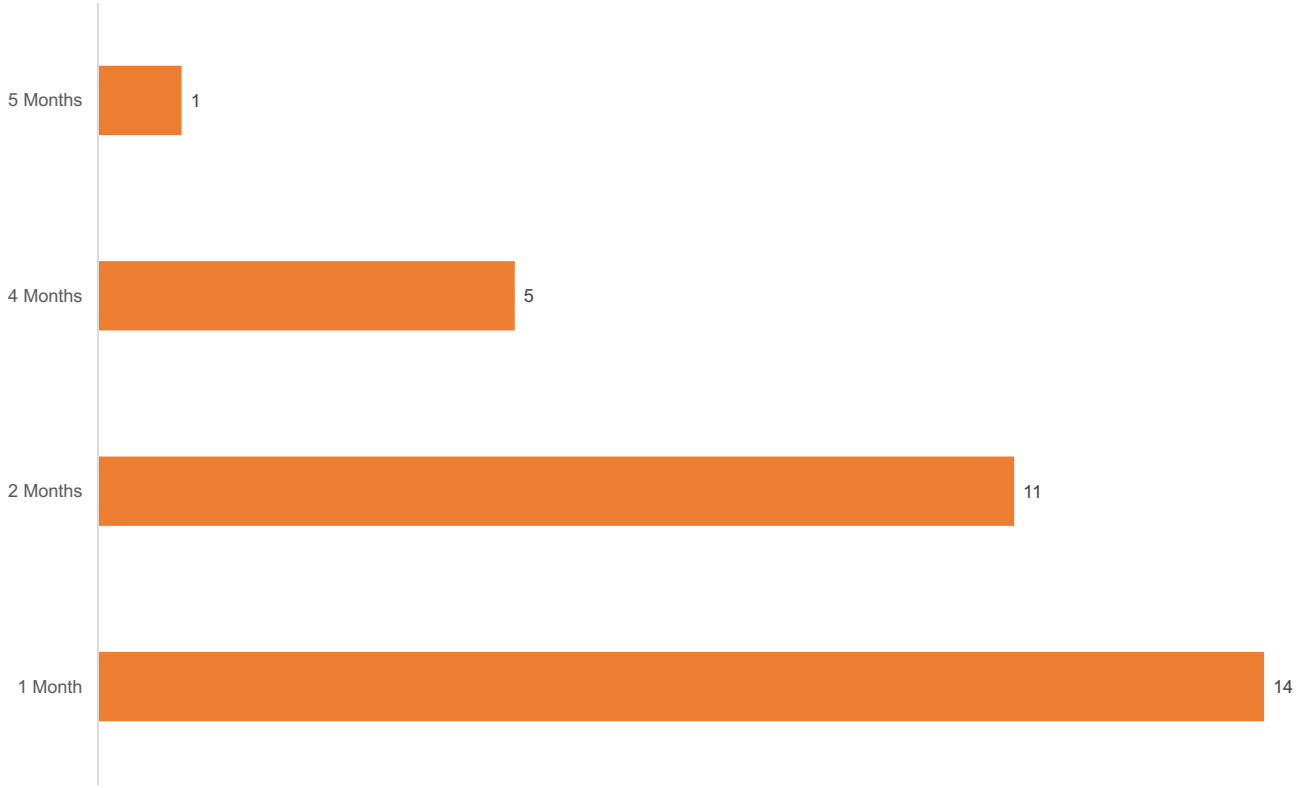

Figure 6 Age of appearance of CMA symptoms among cases.

Figure 7 highlights the timing of cow's milk formula introduction and CMA diagnosis. In the first month: 71.4% of cases were diagnosed with CMA. At less than one month: 61.8% of cases were diagnosed with CMA. At 3 months: 100.0% of cases were diagnosed with CMA At 4 months: 50.0% of cases were diagnosed with CMA. At 6 months: No diagnoses in the case group. Between 13 to 24 months: the case group had 100.0%. Between 25 to 36 months: the case group had 22.20%.

Cost and Frequency of Milk Formula Usage

The main findings from Table 5 reveal a highly significant association between the sources of milk formula used to manage CMA and the diagnostic status of children ($p = <0.0001$). Children not using specified sources of milk formula were predominantly controls (88.2%), while those using these specific formulas were mostly cases (79.4%).

Table 6 shows that, in the control group, 77.8% did not use artificial milk formula, suggesting a potential protective factor against CMA. Lower costs (<300 riyals/month) were associated with artificial milk formula usage. Changing artificial milk formula more than 6 times was significantly more common in the case group (42.9%) than the control group (33.3%), indicating a potential link with CMA.

Regression Analysis

The binary logistic regression analysis aimed to identify significant associated factors with CMA in children. The dependent variable was the presence or absence of CMA in children, and several independent variables were examined for their predictive value. The results revealed that having a sibling with CMA is actually a risk factor for developing CMA, demonstrating a statistically significant association. On the other hand, factors such as exclusively using cow's milk formula, breastfeeding while using cow's milk formula as a supplementary source, and the timing or frequency of introducing and changing artificial milk formula did not show statistical significance in predicting CMA diagnosis (Table 7).

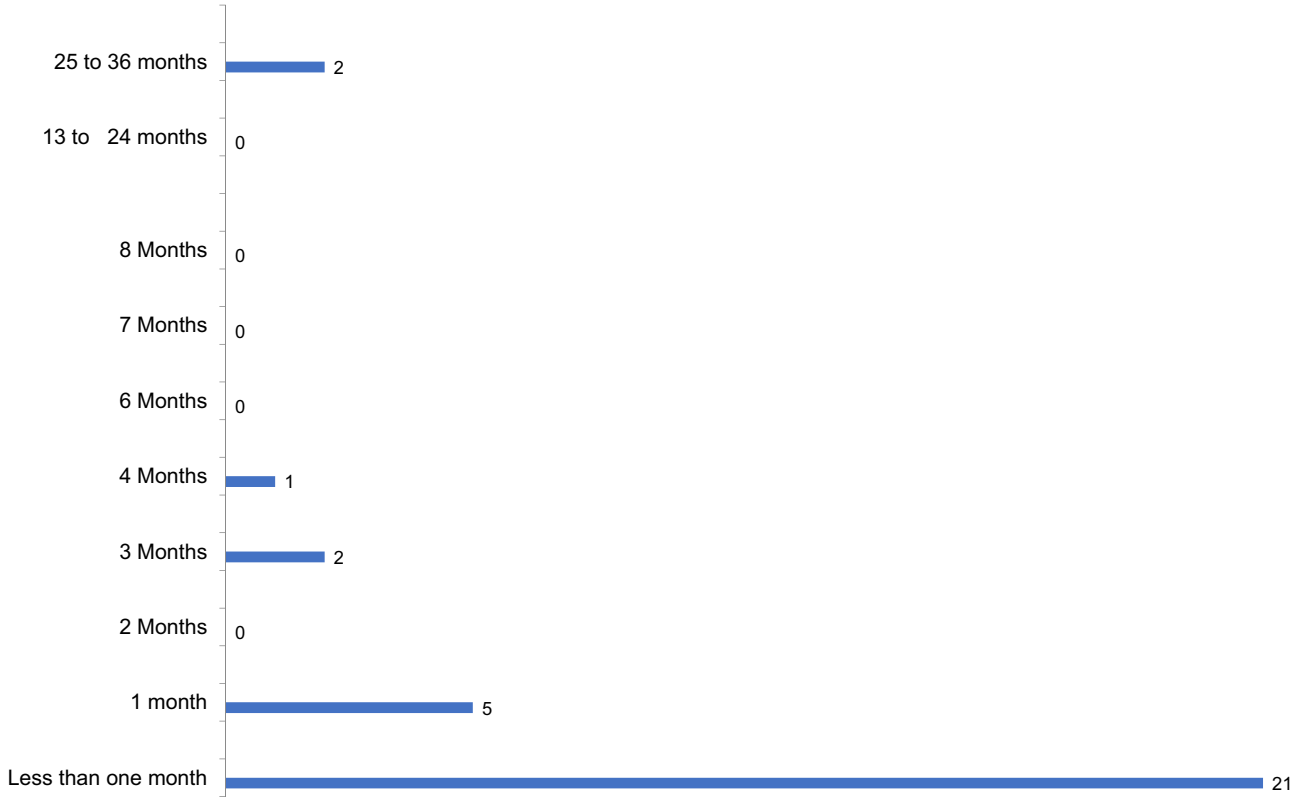

Figure 7 Timings of cow's milk formula introduction and CMA diagnosis.

Discussion

CMA affects 1.8% to 7.5% of infants and young children, making it one of the most prevalent food allergies in this age group.[4,9,11,12,17] A study in Lebanon found that the prevalence of food allergies was 4.1% in infants and children and 3.2% in adults.[11] The prevalence of CMA can vary depending on regional factors and diagnostic methods.[5,6,8] The current case-control study was carried out among children with CMA (cases) and healthy children without CMA (controls) and their parents, all attending Abha Maternity and Children Hospital in Abha, Kingdom of Saudi Arabia. However, case-control studies do not offer insights into the incidence or prevalence of diseases, as they do not involve measurements from population-based samples. We found consistent results with another study that shows an insignificant correlation with CMA development among children.[18] Our finding illustrated that the educational level of parents may not be a decisive factor in predicting or influencing the likelihood of their children being diagnosed with CMA. However, another study has shown that there is a higher chance of developing asthma, wheezing, and eczema development in children with higher educational level among parents.[18] This could be due to the increased awareness among such educated parents of the risks of poor hygiene as well as too hygienic conditions.

Table 5 Usage of Different Milk Formulas to Manage CMA (Extensively Hydrolyzed Whey Formula, Soy Protein-Based Formula, Amino Acids-Based Formula, Lactose-Free Milk Formula, and Partially Hydrolyzed Formula)

Sources of Milk Formula	Case (n=31)	Control (n=37)	Total	Chi-Square, P Value	O.R (95% CI)
No	4	30	34	31.362, <0.0001	-
	11.8%	88.2%	100.0%		
Yes	27	7	34		0.03 (0.01 to 0.13)
	79.4%	20.6%	100.0%		

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Table 6 Cost and Frequency of Artificial Milk Formula Used Among Cases and Controls

Characteristics		Case (n=31)	Control (n=37)	Total	Chi-Square, P Value	O.R (95% CI)
Monthly costs (SAR)* of artificial milk formula (a breastmilk substitute) (1SAR=0.27 USD)	Less than 300 riyals a month	0	7	7	12.347, 0.090	-
		0.0%	100.0%	100.0%		
	300–599 riyals a month	5	6	11		0.07 (0.01 to 1.71)
		45.5%	54.5%	100.0%		
	600–899 riyals a month	6	7	13		0.07 (0.01 to 1.62)
		46.2%	53.8%	100.0%		
	900–1199 riyals a month	8	5	13		0.04 (0.00 to 0.91)
		61.5%	38.5%	100.0%		
	1200–1499 riyals a month	6	2	8		0.03 (0.00 to 0.63)
		75.0%	25.0%	100.0%		
	1500 and above riyals a month	4	3	7		0.05 (0.00 to 1.25)
		57.1%	42.9%	100.0%		
	Not applicable	2	7	9		0.20 (0.01 to 4.90)
		22.2%	77.8%	100.0%		
The frequency of artificial milk formula changed before finding a suitable one	Once	0	6	6	15.532, **0.016**	-
		0.0%	100.0%	100.0%		
	Twice	6	8	14		0.10 (0.00 to 2.12)
		42.9%	57.1%	100.0%		
	Thrice	7	5	12		0.05 (0.00 to 1.22)
		58.3%	41.7%	100.0%		
	4 times	10	3	13		0.03 (0.00 to 0.58)
		76.9%	23.1%	100.0%		
	5 times	2	5	7		0.17 (0.01 to 4.32)
		28.6%	71.4%	100.0%		
	More than 6 times	4	2	6		0.04 (0.00 to 1.11)
		66.7%	33.3%	100.0%		
	Never used	2	8	10		0.26 (0.01 to 6.43)
		20.0%	80.0%	100.0%		

Notes: *1 SAR is equivalent to 0.27 USD. The data presented in bold in the table signifies statistically significant results, p-value of less than 0.05 was regarded as statistically significant.

Regarding the relationship between parental income and children diagnosed with CMA in this study, the result was not significant, however, while fathers earning less than 6000 SAR had 100.0% controls and 0.0% cases and those with incomes exceeding 6000 SAR displayed 50.8% controls and 49.2% cases. This could indicate that low income can be a barrier for parents to get proper medical consultation and diagnoses for their children. Moreover, gender did not show any differential result in the development of CMA. However, a Lebanese study showed 35% of patients having food

Table 7 Binary Logistic Regression Analysis for Dependent Variables (Children Diagnosed with CMA) and Significant Associated Factors

Variables	B	S.E.	Wald	df	P Value	Odds Ratio	95% C.I. for Odds Ratio	
							Lower	Upper
Does any of your other children have CMA? (yes)	**2.31**	**1.08**	**4.61**	**1.00**	**0.03**	10.07	1.22	82.94
Are you using cow's milk formula exclusively as a source of feeding? (yes)	−0.65	1.00	0.42	1.00	0.52	0.53	0.07	3.73
Are you breastfeeding and using cow's milk formula as a supplementary source? (yes)	−0.39	1.12	0.12	1.00	0.73	0.68	0.08	6.14
When did you introduce cow's milk formula in feeding? (Never; Ref.)			3.57	2.00	0.17			
When did you introduce cow's milk formula in feeding? (< one month)	0.28	1.88	0.02	1.00	0.88	1.33	0.03	53.26
When did you introduce cow's milk formula in feeding? (≥ one month)	2.60	2.18	1.42	1.00	0.23	13.48	0.19	973.78
How many times did you have to Change artificial milk formula until you found a suitable one. (Never used; Ref)			0.05	2.00	0.97			
How many times did you have to change artificial milk formula until you found a suitable one? (≤ 3 times)	0.35	1.97	0.03	1.00	0.86	1.43	0.03	67.18
How many times did you have to change artificial milk formula until you found a suitable one? (> 3 times)	0.19	1.88	0.01	1.00	0.92	1.20	0.03	47.99
Constant	−3.82	2.14	3.20	1.00	0.07	0.02		

Notes: The data presented in bold in the table signifies statistically significant results, p-value of less than 0.05 was regarded as statistically significant.

allergies are males and 65% are females.[19] The number of child's siblings and CMA diagnoses was not found significant in this study. This is similar to the finding of the Poland study.[18]

Family history did not show any significant association with children with CMA in this study. Another study, however, indicates that infants with a family history of atopy (such as having parents or siblings with allergic conditions) are at a higher risk of developing allergies, with family history being a significant factor in allergy development.[4] Children with atopic dermatitis who consumed cow's milk, or its by-products tend to have a higher total of IgE and eosinophil counts than children who did not consume it.[20] Additionally, if one of the parents has a food allergy, the chance is 40% for the child to have a food allergy and it increases to 80% if both parents have any allergic disease.[21]

In this study, out of sixty-eight participants (infants and their parents), twenty-five respondents relied on information provided by doctors. However, there was a deficiency in healthcare practitioners' knowledge of CMA as reported in a recent Saudi Arabian study. Poor understanding of the disease was found in 77.4% of healthcare practitioners, and only 22.6% had good knowledge levels.[22]

The source of milk formula is significantly associated with symptom resolution in children with Cow's Milk Allergy (CMA) ($P = 0.0001$). Notably, children administered extensively hydrolyzed whey formula exhibited a higher likelihood of symptom resolution compared to those receiving partially hydrolyzed formulas or goat's milk formula. This observation aligns with current guidelines advocating the use of extensively hydrolyzed formulas (eHF) and amino acid-based formulas (AAF) as first-line treatment options for CMA, particularly in moderate to severe cases or when symptoms persist despite dietary elimination. In our study, 79.4% of children in the CMA group were prescribed specialized formulas, with extensively hydrolyzed whey and amino acid-based formulas being the most frequently utilized. In contrast, only 20.6% of the control group used specialized formulas, where standard or lactose-free formulas were more common. These findings

underscore the targeted application of eHF and AAF in managing CMA, as opposed to general nutritional support. While some studies have suggested that extensively hydrolyzed formulas may assist in the primary prevention of CMA, the current evidence remains inconclusive. Various authors point out that the potential preventive effects of extremely hydrolyzed formulas are supported by low-quality evidence.[4,23] Furthermore, there is no consistent evidence endorsing the routine use of partially or extremely hydrolyzed formulas for allergy prevention in children.[24,25] However, regarding treatment rather than prevention, our findings corroborate previous research indicating that extensively hydrolyzed and amino acid-based formulas are effective alternatives for achieving symptom resolution and minimizing allergen exposure in sensitized children.[12,26,27] Supporting this, additional studies have shown that extensively hydrolyzed formulas and amino acid-based formulas are the most effective alternative milk formula options for avoiding cow's milk allergy (CMA), whereas partially hydrolyzed formulas are ineffective for this condition.[2,26,27] This distinction is crucial for helping parents and healthcare providers make informed choices regarding allergy management. Moreover, a study conducted in Saudi Arabia illustrated most common food allergies associated with CMA were cashews, eggs, wheat, and peanuts.[20] Alkhateeb's study in Saudi Arabia found that the most common allergies in children under five years old were cow's milk, oats, and other foods.[28] The American College of Allergy, Asthma, and Immunology (ACAAI) emphasizes that guidelines on food allergy management should adapt in light of emerging research.[2] Recent landmark studies, such as the LEAP (Learning Early About Peanut Allergy) and EAT (Enquiring About Tolerance) trials, indicate that the early introduction of certain allergenic foods could promote tolerance rather than increasing the risk of developing allergies.[29,30] As a result, while earlier recommendations suggested a strict avoidance of multiple allergens for children with CMA, current evidence supports a more balanced approach, advocating for competent monitoring of potential allergens like soy, eggs, fish, and peanuts rather than their complete elimination from the diet.[31]

We examined the type of child feeding with children diagnosed with CMA which are exclusively breastfed, exclusively formula fed, and mix-fed children. Those who were exclusively breastfed did not show significant results. That could be due to a small proportion of the sample population which consists of 16.2% of controls and 9.7% of cases. In this study, a higher percentage (58.6%) of cases were never breastfed, showing a possible association between no breastfeeding and the development of CMA ($P = 0.063$). Another study suggests that exclusive breastfeeding is the best method to prevent all sources of allergies.[10] It has been also reported that breastfeeding decreases the total level of IgE and increases the level of protective cytokines. Moreover, following a proper pharmacologic drug regimen and immunotherapy would create an effective treatment for CMA.[32] In the current study, those children who exclusively used cow's milk formula showed consistent results in developing CMA ($P = 0.004$).[3] Similarly, the practice of mixed feeding method was significantly higher in controls. This can be due to the fact that a higher proportion of controls (72.7%) are involved in the practice of the mixed feeding method. However, a Randomized Controlled Trial done in Japan did not report any intergroup difference among the subjects (breastfeeding vs cow's milk formula feeding).[14] Several studies have looked into how early exposure to cow's milk formula might affect the risk of developing CMA. Some research suggests that introducing cow's milk protein during infancy could help lower the risk, especially for infants with a family history of allergies.[12,15,16] However, the results are mixed; while some studies support this idea, others indicate that early exposure might not significantly impact the risk or could even increase it for certain groups. Factors like timing, amount of exposure, and individual genetics all influence how infants react to cow's milk. Overall, while there is some evidence that early exposure may be beneficial, more research is needed.

This study found an insignificant association between cow's milk products consumed during pregnancy and breastfeeding with CMA among children and is consistent with the findings of other studies.[10,16] In this study, 80% of cases showed CMA symptoms in the first two months of age. Another study reported that the development of CMA is affected by exposure time to CMA, especially among those children whose CMA was withheld up to the age of 4 to 6 months and were at a high risk of developing CMA.[12] On the contrary, few studies showed no differences in the development of CMA with the early introduction of milk formula and recommended avoiding cow's milk in the first three days after birth.[10,16] In this research, the monthly cost of cow's milk formula consumption ranges from 300 to $\geq$ 1500 SAR among cases. This cost burden could impact the quality of life of individuals and their families. However, it is significant about the individual who had to change the formula and its association with CMA. People with food allergies tend to utilize healthcare services more frequently, resulting in significant economic costs, in addition to the physical

health impact caused by anaphylaxis. In a recent review among children, allergic diseases burden the socioeconomic status, especially food allergies affect the quality of life and cost directly or indirectly.[16,33]

The data shows a relatively balanced distribution, with 52.9% of female controls and 47.1% female cases. Similarly, among males, there were 55.9% controls and 44.1% cases which suggests no statistically significant association between the gender of the child and the diagnosis of CMA (P = 0.808). Another Saudi Arabian study showed that there are no gender differences in response to food IgE-mediated reactions.[34] An insignificant association of Pre-lacteal feeding with CMA was found in this study (p=0.340). However, a larger sample size may add further insight into this matter. Many studies suggest that solid foods should be introduced after 6 months of age.[35] The increasing number of children with CMA contributes to a rising burden on healthcare systems, parents, and families, highlighting the need for continued research in this area. Gaining a better understanding of the molecular mechanisms behind CMA could help identify new therapeutic targets in the future.A deeper understanding of how cow's milk protein allergy develops can also improve existing prevention strategies.

Limitations and Strengths

Our study did not gather data about the financial government supportive programs for CMA which can be included in future studies for better understanding. Furthermore, it is important to note that this study was performed at a single health facility, and the majority of the participants were from Abha and its vicinity, which may limit its generalizability. This study also has limitations, such as the small sample size of CMA patients and the retrospective nature of data collection, which led to missing clinical information in some patient records. The current study was conducted within specific constraints, including time and resource limitations. We understand that a larger sample size would provide more comprehensive data and improve the statistical power of our comparisons. We hope in the future to have all the required resources to do multicentric/nationwide studies with a larger cohort to validate and expand upon our current findings. The study's lack of a breastfed control group is a limitation, as breastfeeding is linked to a reduced risk of allergies, including CMA. Including this group in future studies would enhance the understanding of infant feeding practices' role in CMA development. Limiting the study to children up to three years may overlook the evolving nature of CMA. Non-IgE-mediated allergies often resolve earlier, while IgE-mediated ones may persist. A broader age range could provide a more comprehensive view of CMA. Involving parents in developing and pilot testing the questionnaire could improve its relevance and clarity. Their insights might identify gaps and enhance understanding of practical CMA management. While assessing parental knowledge is important, it may be more beneficial to examine healthcare providers' advice on CMA management. Understanding HCP recommendations can offer valuable insights into effective management strategies. Addressing these points in future research could enhance the understanding of cow's milk allergy and improve the support provided to families navigating this condition.

We did not explore parents' perspectives on the study's findings. Understanding these viewpoints could enhance data interpretation and help identify gaps in knowledge and practices related to cow's milk allergy (CMA) management.

The study was the first of its kind to be undertaken to determine the associated factors with CMA among children Maternity and Child Hospital in Abha city, Saudi Arabia. A representative sample including children and their parents is the strength of our study. Our research addresses a significant gap in CMA data specific to Abha, highlighting that having a sibling with CMA is a notable risk factor (p-value = 0.03). This localized context can inform tailored interventions and improve outcomes for affected families. Additionally, our study reveals varying levels of parental knowledge about CMA, which can help direct educational initiatives. We employed a robust methodology, ensuring the reliability of our findings, and acknowledge our study's limitations while laying the groundwork for future research. The findings emphasize the importance of education, genetics, and dietary choices in managing and preventing CMA, providing valuable insights for healthcare practitioners and policymakers. Overall, we believe our work contributes valuable insights into CMA, informing public health and clinical practice.

Conclusions and Recommendations

The study on CMA in children from Abha city identified several risk factors, particularly that having a sibling with CMA significantly increases the likelihood of developing the condition. It also highlighted varying levels of parental knowledge regarding CMA. The primary recommendation for prevention is a diet free from CMA allergens, with suitable

alternative milk formulas, while mothers are encouraged to prioritize breastfeeding and avoid using supplementary cow's milk formulas for newborns. Exclusive breastfeeding is strongly advised for the first six months. The study underscores the need for further research and clinical trials to better understand pediatric CMA and its risk factors, aiding in the development of effective prevention and control strategies. Medical professionals should implement standardized protocols for suspected CMA cases, including comprehensive histories from parents and appropriate laboratory tests for all newborns and infants.

The economic burden of CMA is rising due to increased healthcare costs and medication needs, adversely affecting the quality of life for children and their families. Effective management strategies include an elimination diet and immunotherapy, which involves temporarily removing cow's milk protein from a child's diet to monitor symptom changes. While extensively hydrolyzed and amino acid-based formulas are effective, more comprehensive clinical trials are necessary to explore additional therapeutic options. Overall, policymakers are urged to prioritize the importance of timely diagnosis, prompt management, and cost-effective treatment strategies for CMA to better support affected children and families.

Data Sharing Statement

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

Institutional Review Board Statement

This study was approved by the Research Ethics Committee at King Khalid University (ECM#2023-2112) on 21 December 2023 and by MOH (H-06-B-091) on 31 December 2023. This study was further permitted by the Director of the Academic Affairs and Training Department at Abha Maternity and Children's Hospital (AMC-2023- 010).

Informed Consent Statement

The research's objectives, anticipated duration, and the nature of any interventions or trials were disclosed to the participants or their authorized substitutes to acquire their informed permission.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors declare no conflicts of interest.

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