Turkish Journal of Pediatric Surgery 2026;40(3):147-158
https://doi.org/10.62114/JTAPS.2026.277

Turkish Journal of Pediatric Surgery

Original Article

OPEN ACCESS

# Recurrence after manual separation for labial synechia in prepubertal girls: A two-center retrospective cohort study with center-specific maintenance protocols

Emine Bilaloğlu[1], Erol Can Külice[2]

Labial synechia is the clinical term used to describe superficial adherence or fusion of the medial margins of the labia minora. Although terms such as labial adhesion or vulvar synechia are also common in the literature, these designations generally denote more extensive involvement that includes fusion of the vulvar margins in addition to the labia minora.[1,2] The reported frequency of this condition ranges from 1.8 to 3.5%.[3-5] Labial synechia is seen predominantly in prepubertal girls between three months and six years of age, with the highest incidence identified in the period from one to 23 months.[6-8]

Although the exact etiology has not yet been clarified, it is widely accepted that the principal pathophysiological mechanism is low systemic estrogen levels (hypoestrogenism). This hormonal state leads to thinning of the vulvar epithelium

**Received:** May 22, 2026
**Accepted:** September 30, 2026
**Published online:** October 17, 2026

**Correspondence:** Emine Bilaloğlu, MD.

**E-mail:** dreminebilaloglu@gmail.com

[1]Department of Pediatric Surgery, Bayburt State Hospital, Bayburt, Türkiye
[2]Department of Pediatric Surgery, Antalya Training and Research Hospital, Antalya, Türkiye

**Citation:**

Bilaloğlu E, Külice EC. Recurrence after manual separation for labial synechia in prepubertal girls: A two-center retrospective cohort study with center-specific maintenance protocols. Turkish J Ped Surg 2026;40(3):147-158. doi: 10.62114/JTAPS.2026.277.

© 2026 Turkish Journal of Pediatric Surgery. This is an open access article published under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0), which permits non-commercial use, distribution, reproduction, and adaptation in any medium, provided the original work is properly cited. http://creativecommons.org/licenses/by-nc/4.0/

## Abstract

**Objectives:** This study aimed to compare recurrence following manual separation between two maintenance protocols, topical antibiotic alone versus antibiotic plus estrogen, and to evaluate additional risk factors associated with recurrence.

**Patients and methods:** This retrospective study was conducted by reviewing the medical records of pediatric patients presenting with labial synechia at two pediatric surgery centers between January 1, 2023, and December 15, 2025. Each center used one maintenance protocol (Center 1: antibiotic plus estrogen, n = 73; Center 2: antibiotic alone, n = 68), so protocol and center are completely collinear. All patients were followed for at least six months; recurrence was defined as re-approximation of ≥ 25% of the labial length. Firth penalized regression was used.

**Results:** A total of 141 female patients (median age: 1 year [IQR, 0-2 years]; range, 0 to 10 years) who underwent manual separation for labial synechia were analyzed. Recurrence developed in 30 of 141 patients (21.3%; mean 10.20 ± 8.10 weeks): 19.2% with the combined protocol and 23.5% with antibiotics alone (risk difference −4.4 points, 95% CI: −17.9 to 9.1; $p = 0.528$; adjusted odds ratio 0.38, 95% CI: 0.12-1.04). Recurrence was more frequent with fibrotic than thin adhesions (90.9% *vs.* 15.4%; risk ratio 5.91, 95% CI: 3.54-9.15; $p < 0.001$) and in both symptomatic patients ($p = 0.044$); fibrotic adhesion remained the strongest correlate after adjustment (adjusted odds ratio 63.40, 95% CI: 11.12-757.06). After repeat separation plus combined therapy, 27 of 30 did not recur.

**Conclusion:** Manual separation is an effective and rapid primary intervention. Recurrence did not differ significantly between the two protocols, and no adverse effect was seen with either; as the protocol was determined by the center, no superiority can be inferred, though both appear acceptable. Fibrotic adhesions warrant close follow-up.

***Keywords:*** Labial synechia, manual separation, pediatric gynecology, recurrence, topical estrogen.

and renders the tissue susceptible to inflammation triggered by local irritants such as poor hygiene, diaper dermatitis, infection, or trauma. The healing process that follows inflammation of the tissue results in adherence of the labial margins to one another.[9,10] Characterized by avascular re-epithelialization, these adhesions consist of layers of keratinized squamous epithelium. The diagnosis is typically made on physical examination, which reveals a very thin, translucent membrane occluding the vaginal orifice. Although it is most often detected incidentally, patients may present with findings such as pain or pruritus during physical activity, urinary tract infection, urinary retention, alteration of the urinary stream, or post-void dribbling.[11] Labial adhesions have also been described in children with genital trauma or sexual abuse, which should therefore be considered in the clinical assessment.[12,13]

Symptomatology varies according to the extent of the adhesion. Adhesions may be confined to the ventral, dorsal, or central regions of the labia minora or may present as complete fusion along the entire labial length. The severity and longitudinal extent of the adhesion are directly related to earlier onset of clinical complaints. In toilet-trained children, complete labial fusion may cause incontinence in the form of post-void dribbling; this may increase local inflammatory reactions and predispose the patient to urinary tract infection or nonspecific bacteriuria. The most frequent local clinical findings are vulvitis or vulvovaginitis, whereas complaints such as vaginal burning, pruritus, or dysuria are less common. In children with small adhesions, the condition is most often noticed during routine pediatric assessment, without any overt symptoms.[14,15] In one series of 151 girls with labial adhesions, 19.9% presented with urinary tract infection and 12.6% with post-void dribbling.[15] Vulvovaginitis is the most common gynecological complaint of childhood, and nonspecific irritation of the unestrogenized prepubertal epithelium, often related to hygiene, is its principal cause; counseling on vulvar hygiene is therefore a central element of management.[16-21]

The treatment spectrum for labial synechia ranges from the application of topical estrogen or corticosteroids to manual separation in the outpatient setting and surgical adhesiolysis under general anesthesia.[22,23] Although topical treatments show high initial success rates, these rates fall markedly in children older than five years. Topical estrogen has traditionally been the first-line medical treatment, although reported success rates vary widely between series and recurrence after estrogen therapy is common.[24-27] Topical betamethasone has been proposed as an alternative with fewer hormonal side effects, such as breast budding, vaginal bleeding, or labial enlargement,[15,28,29] and a randomized controlled trial comparing topical estrogen with an emollient, each combined with lateral traction, found no significant difference in complete resolution, although the reduction in severity was greater with estrogen.[30] A classification based on the location and thickness of the adhesion, with treatment tailored to each subtype, has also been proposed.[31] Manual separation is one of the widely accepted primary treatment options as it provides rapid clinical resolution, avoids systemic estrogen exposure, has a favorable safety profile, and is preferred by parents; it is additionally advantageous in settings where adherence to prolonged topical therapy may be limited.[32]

Whatever the initial treatment method, labial synechia is associated with high recurrence rates. We aimed to evaluate whether maintenance therapy combining topical antibiotic and estrogen reduces recurrence rates compared with topical antibiotic monotherapy following manual separation in prepubertal girls.

## PATIENTS AND METHODS

This retrospective study was conducted by reviewing the medical records of pediatric patients presenting with labial synechia to the Departments of Pediatric Surgery at Bayburt State Hospital and Antalya Training and Research Hospital between January 1, 2023, and December 15, 2025. Inclusion criteria comprised prepubertal girls aged 0 to 10 years with a clinically confirmed diagnosis of labial synechia who underwent manual separation as the primary treatment and had complete follow-up documentation. Exclusion criteria were cases of synechia secondary to another medical condition (e.g., congenital adrenal hyperplasia) and patients with incomplete medical records. The records of girls up to 18 years of age were screened, but all eligible patients proved to be prepubertal (age range, 0-10 years; median, 1 year; interquartile

range [IQR], 0-2 years), and no adolescent patient was treated during the study period; the stated inclusion age range was therefore narrowed to reflect the cohort actually studied. Owing to the retrospective nature of the study, the requirement for written informed consent was waived by the ethics board. Written informed consent for the publication of clinical photographs was obtained from the patients' parents or legal guardians. The study protocol was reviewed and approved by the Antalya Training and Research Hospital Medical Research Scientific Ethics Committee (Date: January 22, 2026; Decision/Approval No: 2/3), and the participating center gave institutional approval for the use of anonymized clinical records. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The following data were extracted and standardized from the electronic medical records and outpatient clinic logs: demographic data at the time of diagnosis (including age and diaper status); presenting symptoms (e.g., pruritus, post-void dribbling, dysuria, pain); comorbidities; urinalysis findings at diagnosis; and the degree (partial or complete) and type (thin or fibrotic) of the labial synechia. In addition, the medical treatments administered after manual separation and the duration of these therapies were recorded. Urine culture was not obtained in this cohort. Urinalysis findings were therefore classified as pyuria (≥ 5 leukocytes per high-power field on a clean-catch or bag-collected specimen) rather than as culture-confirmed urinary tract infection, and this variable is used descriptively throughout. Two patients met this definition at presentation. Given that bag-collected urine specimens carry a high risk of contamination, and pyuria in the absence of positive culture is insufficient to confirm infection, a diagnosis was not assigned to any patient in this study.

Manual separation was performed in the outpatient setting by applying gentle lateral traction with a lubricated blunt probe; no sharp dissection and no cutting instrument were used. A topical local anesthetic EMLA® cream 5%, lidocaine 25 mg/g and prilocaine 25 mg/g (VLD Danışmanlık Tıbbi Ürünler ve Tanıtım Hizmetleri A.Ş., İstanbul, Türkiye) was applied 30 min before the procedure, and sedation or systemic analgesia was not required in any case. After separation, families were advised to apply a protective emollient barrier (petrolatum) as part of home care. Following manual separation, the study population was divided into two groups according to the prescribed medical regimen: the first group received a topical antibiotic ointment containing bacitracin and neomycin alone (Thiocilline® dermal ointment, 30 g tube containing bacitracin 15,000 IU and neomycin sulfate 150 mg; Abdi İbrahim İlaç San. ve Tic. A.Ş., İstanbul, Türkiye) for two weeks, while the second group received topical estrogen (Estriol® 1 mg/g cream; Assos İlaç, Kimya, Gıda Ürünleri Üretim ve Tic. Ltd. Şti., İstanbul, Türkiye) twice daily for four weeks in addition to the same topical antibiotic. No treatment-related adverse effect was observed at either center. Whenever recurrence developed in either group, the combination therapy protocol was used for management.

The maintenance protocol was not randomized and was determined entirely by the center at which the child was treated: every patient treated at Center 1 received the antibiotic plus estrogen combination (n = 73), and every patient treated at Center 2 received topical antibiotic alone (n = 68). Maintenance protocol and treating center are therefore completely collinear, and the comparison of the two protocols cannot be separated from a comparison of the two centers. Baseline characteristics by center and protocol are given in Table 1: age, adhesion degree, symptoms, diaper use, and urinalysis were similar, whereas fibrotic adhesions (12.3% *vs.* 2.9%) and comorbidity (8.2% *vs.* 0%) were more frequent at Center 1, indicating a difference in case mix in addition to the difference in protocol.

Recurrence was defined, irrespective of symptoms, as re-approximation of the margins of the labia minora covering at least 25% of the total labial length at follow-up physical examination. Recurrence was assessed by the treating pediatric surgeon at each center using the same criteria, after which the records were reviewed jointly by both surgeons in order to reduce inter-observer variability. However, as each center applied a single protocol, the physician assessing each patient necessarily knew which protocol that patient had received. At both centers, patients were followed for a minimum of six months (26 weeks) after separation for the detection of recurrence. The timing of the first two documented review visits differed slightly between

Available online at https://journalpedsurg.org

**TABLE 1**

Baseline characteristics by treating center and maintenance protocol

| | | Center 2 – antibiotic alone (n = 68) | | | | | | Center 1 – antibiotic + estrogen (n = 73) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Characteristic | Subgroup | n | % | Mean ± SD | Median | IQR | Range | n | % | Mean ± SD | Median | IQR | Range | *p* |
| Age (year) | | | | | 1 | 1-1 | | | | | 1 | 0-2 | | 0.516[a] |
| Time to recurrence (weeks) | | | | 14.06 ± 8.93 | 10.5 | | 3-30 | | | 5.79 ± 3.89 | 4.5 | | 2-16 | -[b] |
| Age group | Infant (< 1 year) | 16 | 23.5 | | | | | 21 | 28.8 | | | | | 0.154[c] |
| | 1 year | 35 | 51.5 | | | | | 24 | 32.9 | | | | | |
| | 2 years | 10 | 14.7 | | | | | 16 | 21.9 | | | | | |
| | ≥ 3 years | 7 | 10.3 | | | | | 12 | 16.4 | | | | | |
| Synechia type | Thin | 66 | 97.1 | | | | | 64 | 87.7 | | | | | 0.057[d] |
| | Fibrotic | 2 | 2.9 | | | | | 9 | 12.3 | | | | | |
| Synechia extent | Partial | 66 | 97.1 | | | | | 70 | 95.9 | | | | | 1.000[d] |
| | Complete | 2 | 2.9 | | | | | 3 | 4.1 | | | | | |
| Symptoms | Asymptomatic | 67 | 98.5 | | | | | 72 | 98.6 | | | | | 1.000[d] |
| | Symptomatic | 1 | 1.5 | | | | | 1 | 1.4 | | | | | |
| Diaper use | Yes | 62 | 91.2 | | | | | 70 | 95.9 | | | | | 0.314[d] |
| | No | 6 | 8.8 | | | | | 3 | 4.1 | | | | | |
| Comorbidity | None | 68 | 100.0 | | | | | 67 | 91.8 | | | | | **0.029**[d] |
| | Present | 0 | 0.0 | | | | | 6 | 8.2 | | | | | |
| Urinalysis | Normal | 67 | 98.5 | | | | | 72 | 98.6 | | | | | 1.000[d] |
| | Pyuria | 1 | 1.5 | | | | | 1 | 1.4 | | | | | |
| Follow-up for recurrence | Duration | ≥ 6 months | | | | | | ≥ 6 months | | | | | | - |

SD, standard deviation; IQR, interquartile range; a Mann-Whitney U test; b Time to recurrence is presented descriptively only, as early review schedules differed between the centers (Center 1: 2 and 4 weeks; Center 2: 4 and 8 weeks), the difference may reflect the time to detection rather than the biological time to recurrence, and no statistical test was applied; c Pearson chi-square test; d Fisher's exact test, two-sided. The assignment was not randomized: every patient at Center 1 received the combined protocol, and every patient at Center 2 received antibiotic alone, so the maintenance protocol and treating center are completely collinear and cannot be separated. The centers also differed in case mix (fibrotic adhesions, comorbidity). Patients at both centers were followed for at least six months. Pyuria was defined as ≥5 leukocytes per high-power field on a clean-catch or bag-collected specimen; urine culture was not obtained, so no diagnosis of urinary tract infection is claimed.

the centers (Center 1: 2 weeks and a median of four weeks; Center 2: a median of four weeks and a median of 8 weeks), after which review continued to at least six months at both centers. Patients were additionally instructed to attend earlier if symptoms recurred, and recurrence was ascertained from all follow-up entries in the electronic record, whether scheduled or unscheduled. Two recurrences were detected shortly beyond the six-month point, at 28 and 30 weeks, at unscheduled visits prompted by parental concern; these were retained in the analysis, which is why the observed range of times to recurrence extends slightly beyond the nominal follow-up period.

### Statistical analysis

The distribution of demographic and clinical characteristics was summarized with descriptive statistics such as frequency (n) and percentage (%). Categorical variables were cross-tabulated and compared with Pearson's chi-square test. Where any expected cell count was below five, the two-sided Fisher's exact test was used instead, and the Fisher-Freeman-Halton exact test was applied to the 4 × 2 age-group comparison. All exact *p*-values are reported two-sided. Given that a nonsignificant *p*-value does not by itself constitute evidence of equivalence, the comparison of the two maintenance regimens is also presented as an absolute risk difference (Newcombe hybrid-score interval), a risk ratio, and an odds ratio, each with a 95% confidence interval. Antibiotic alone (Center 2) is used as the reference category in every comparison of the two regimens throughout the Abstract, Results, and Tables, so that a negative risk difference or a ratio below 1 indicates less recurrence with the combined protocol. Risk ratios are reported with Miettinen-Nurminen score-based 95% confidence intervals, which remain valid in small samples. For subgroups containing fewer than 10 patients, no effect estimate is reported; only the subgroup proportions and the exact *p*-value are given, and such findings are regarded as hypothesis-generating. Given that some subgroups were small and one cell was empty, Firth-penalized logistic regression was used for the multivariable analysis, with recurrence as the dependent variable and age in completed years, adhesion type, adhesion degree, symptomatic presentation, and maintenance regimen as covariates; adjusted odds ratios are reported with 95% confidence intervals obtained by the profile penalized-likelihood method and with penalized likelihood-ratio *p*-values. As the treating center and maintenance protocol are completely collinear, center could not be included in the model as a separate covariate; the corresponding term should be read as a combined center-and-protocol effect rather than as an effect of the topical agents alone. Descriptive and bivariate analyses were performed with IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA), and Microsoft Excel 2024; the penalized regression and the interval estimates were computed in R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria) using the logistf package. A two-sided p-value below 0.05 was considered statistically significant.

## RESULTS

A total of 141 female patients (median age: 1 year [IQR, 0-2 years]; range, 0 to 10 years) who underwent manual separation for labial synechia were included in the study. Analysis of the age distribution in the study cohort showed that the great majority



**Figure 1.** Partial labial synechia before manual separation. Partial labial synechia in a one-year-old girl before manual separation. The medial margins of the labia minora are joined by a thin, translucent, avascular membrane that occludes the upper part of the vaginal introitus; a patent opening is preserved anteriorly.

of cases were in early childhood. The highest frequency was in the 1-year age group (41.8%), followed by infants under 1 year of age (26.2%) and the 2-year age group (18.5%). Most participants had no comorbidity (95.7%), had normal urinalysis (98.6%), and were asymptomatic (98.6%). Diaper use was very common and was identified in 93.6% of patients. With regard to the type of labial synechia, most cases had thin adhesions (92.2%), whereas the proportion of fibrotic adhesions was low (7.8%). The degree of labial synechia was partial in 96.5% of cases (n = 136) and complete in 3.5% (n = 5), as shown in Figure 1. With regard to treatment distribution, approximately half of the patients (48.2%) received topical antibiotic ointment, and the remaining half (51.8%) received the combination of topical antibiotic and estrogen. Follow-up results showed normal healing in 78.7% of cases and recurrence in 21.3%, as shown in Table 2.

All patients completed at least six months of follow-up. Among those who developed recurrence, the mean time to recurrence was 10.20 ± 8.10 weeks (median 7.5 weeks; range 2-30), with 28 of the 30 recurrences detected within the first 26 weeks and the remaining two at 28 and 30 weeks. Descriptively, recurrences were detected earlier at Center 1 than at Center 2 (mean 5.79 ± 3.89 *vs.* 14.06 ± 8.93 weeks; median 4.5 [range 2-16] *vs.* 10.5 [range 3-30] weeks). As early review schedules differed between the centers, this difference may reflect the time to detection rather than the biological time to recurrence, and it was therefore not tested statistically. All cases with recurrence underwent repeat separation followed by the standard antibiotic plus estrogen protocol. Twenty-seven of these 30 patients (90.0%) had no further recurrence, whereas 3 (10.0%) recurred again. Given that every patient with

**TABLE 2**

Demographic and clinical profile of the patients with labial synechia (n = 141)

| Characteristic | Subgroup | n | % | Mean ± SD | Median | Range |
|---|---|---|---|---|---|---|
| Age group | Infant (< 1 year) | 37 | 26.2 | | | |
| | 1 year | 59 | 41.8 | | | |
| | 2 years | 26 | 18.5 | | | |
| | ≥ 3 years | 19 | 13.5 | | | |
| Clinical presentation | Asymptomatic | 139 | 98.6 | | | |
| | Symptomatic | 2 | 1.4 | | | |
| | Comorbidity present | 6 | 4.3 | | | |
| | Urinalysis: pyuria | 2 | 1.4 | | | |
| | Active diaper use | 132 | 93.6 | | | |
| Synechia morphology | Type: thin | 130 | 92.2 | | | |
| | Type: fibrotic | 11 | 7.8 | | | |
| | Degree: partial | 136 | 96.5 | | | |
| | Degree: complete | 5 | 3.5 | | | |
| Primary maintenance protocol | Topical antibiotic (Center 2) | 68 | 48.2 | | | |
| | Topical antibiotic + estrogen (Center 1) | 73 | 51.8 | | | |
| Initial follow-up outcome | No recurrence | 111 | 78.7 | | | |
| | Recurrence | 30 | 21.3 | | | |
| Recurrent patients (n = 30) | Time to recurrence (weeks) | | | 10.20 ± 8.10 | 7.5 | 2-30 |
| | Repeat manual separation | 30/30 | 100 | | | |
| | Secondary protocol (antibiotic + estrogen) | 30/30 | 100 | | | |
| Final outcome of recurrent patients (n = 30) | No further recurrence during follow-up | 27/30 | 90.0 | | | |
| | Further recurrence | 3/30 | 10.0 | | | |

SD, standard deviation. Pyuria was defined as ≥ 5 leukocytes per high-power field on a clean-catch or bag-collected specimen; urine culture was not obtained, so no diagnosis of urinary tract infection is claimed. Percentages in the first six blocks are calculated on the whole cohort (n = 141). Percentages in the "Recurrent patients" and "Final outcome" blocks are calculated on the 30 patients who developed recurrence, as indicated by the explicit denominators. n, number of patients.

recurrence underwent surgical re-separation first and combination therapy afterwards, this proportion reflects the combined effect of the two interventions and cannot be attributed to the medical regimen alone.

In the comparisons according to recurrence status, no statistically significant difference was found between the age groups (Fisher-Freeman-Halton exact test $p = 0.448$). No age-related effect could be demonstrated. Likewise, no significant difference was observed between the groups with regard to the presence of comorbidity, urinalysis findings, or diaper use (comorbidity $p = 0.608$; urinalysis $p = 0.381$; diaper use $p = 1.000$; all two-sided Fisher's exact tests), as shown in Table 3.

By contrast, a statistically significant association was identified between symptomatic presentation and recurrence ($p = 0.044$). Recurrence developed in both of the symptomatic patients (2/2, 100%) and in 28 of the 139 asymptomatic patients (20.1%). As this comparison rests on only two symptomatic children, no effect estimate is reported, and the finding should be regarded as a hypothesis-generating observation rather than as evidence that symptoms predict recurrence. The strongest association was between adhesion type and recurrence. Recurrence developed in 20 of 130 thin adhesions (15.4%; 95% CI: 10.2-22.6) and in 10 of 11 fibrotic adhesions (90.9%; 95% CI: 62.3-98.4), corresponding to an absolute risk difference of 75.5 percentage points (95% CI: 46.0-84.6) and a

**TABLE 3**
Comparison of demographic and clinical characteristics according to recurrence status (n = 141)

| | | No recurrence (n = 111) | | Recurrence (n = 30) | | | | |
|---|---|---|---|---|---|---|---|---|
| Variable | Subgroup | n | % | n | % | Risk ratio | 95% CI[c] | *p* |
| Age group | Infant (< 1 year) | 30 | 81.1 | 7 | 18.9 | Reference | | 0.448[a] |
| | 1 year | 43 | 72.9 | 16 | 27.1 | 1.43 | 0.68-3.17 | |
| | 2 years | 21 | 80.8 | 5 | 19.2 | 1.02 | 0.37-2.73 | |
| | ≥ 3 years | 17 | 89.5 | 2 | 10.5 | 0.56 | 0.14-2.07 | |
| Comorbidity | None | 107 | 79.3 | 28 | 20.7 | - | - | 0.608[b] |
| | Present | 4 | 66.7 | 2 | 33.3 | -[d] | -[d] | |
| Urinalysis | Normal | 110 | 79.1 | 29 | 20.9 | - | - | 0.381[b] |
| | Pyuria | 1 | 50.0 | 1 | 50.0 | -[d] | -[d] | |
| Symptoms | Asymptomatic | 111 | 79.9 | 28 | 20.1 | - | - | **0.044**[b] |
| | Symptomatic | 0 | 0.0 | 2 | 100.0 | -[d] | -[d] | |
| Diaper use | No | 7 | 77.8 | 2 | 22.2 | - | - | 1.000[b] |
| | Yes | 104 | 78.8 | 28 | 21.2 | -[d] | -[d] | |
| Synechia type | Thin | 110 | 84.6 | 20 | 15.4 | Reference | | **< 0.001**[b] |
| | Fibrotic | 1 | 9.1 | 10 | 90.9 | 5.91 | 3.54-9.15 | |
| Synechia extent | Partial | 109 | 80.1 | 27 | 19.9 | - | - | 0.065[b] |
| | Complete | 2 | 40.0 | 3 | 60.0 | -[d] | -[d] | |
| Maintenance protocol (= treating center) | Center 2: antibiotic alone | 52 | 76.5 | 16 | 23.5 | Reference | | 0.528[e] |
| | Center 1: antibiotic + estrogen | 59 | 80.8 | 14 | 19.2 | 0.82 | 0.43-1.53 | |

CI, confidence interval; [a], Fisher-Freeman-Halton exact test (4 × 2 table; the chi-square test is not appropriate given that the smallest expected count was 4.04); [b], Fisher's exact test, two-sided; [c], Miettinen-Nurminen score-based 95% confidence interval; [d], No effect estimate is reported, as the variable contains a subgroup of fewer than 10 patients (comorbidity present, n = 6; pyuria, n = 2; symptomatic, n = 2; no diaper use, n = 9; complete fusion, n = 5); the subgroup proportions and the exact p-value are given instead, and these findings should be regarded as hypothesis-generating; [e], Pearson chi-square test (all expected counts ≥5). This row compares the two centers as much as the two protocols, since each center used one protocol exclusively. Antibiotic alone (Center 2) is the reference category, so a risk ratio below 1 indicates less recurrence with the combined protocol; the same direction is used in the text and in Table 4. Significant *p*-values ($p < 0.05$) are shown in bold. Pyuria was defined as ≥ 5 leukocytes per high-power field on a clean-catch or bag-collected specimen; urine culture was not obtained, so no diagnosis of urinary tract infection is claimed. Percentages are row percentages, that is, the proportion of each subgroup that did or did not develop recurrence. All *p* values are two-sided.

**TABLE 4**
Firth penalized logistic regression for factors associated with recurrence (n = 141, 30 events)

| Covariate | Adjusted odds ratio | 95% CI | *p* |
|---|---|---|---|
| Age (per additional completed year) | 0.69 | 0.38-1.04 | 0.083 |
| Fibrotic *vs.* thin adhesion | 63.40 | 11.12-757.06 | **< 0.001** |
| Complete *vs.* partial fusion | 1.56 | 0.07-19.95 | 0.751 |
| Symptomatic *vs.* asymptomatic presentation | 62.05 | 4.00-9376.22 | **0.003** |
| Center 1 / antibiotic + estrogen *vs.* Center 2 / antibiotic alone | 0.38 | 0.12-1.04 | 0.059 |

CI, confidence interval. Firth penalized maximum-likelihood logistic regression was used given that one cell of the symptoms × recurrence table is empty, and several subgroups are small; confidence intervals are profile penalized-likelihood intervals, and *p* values are penalized likelihood-ratio *p* values. Treating center cannot be entered as a separate covariate since it is identical to the maintenance protocol; the last row must therefore be read as a combined center-and-protocol term rather than as an effect of the topical agents alone. Antibiotic alone (Center 2) is the reference category, as in Table 3. The extremely wide interval for symptomatic presentation reflects the fact that only two patients were symptomatic and should not be used for clinical prediction. Significant *p* values ($p < 0.05$) are shown in bold.

risk ratio of 5.91 (95% CI: 3.54-9.15; $p < 0.001$). Although this finding suggests that fibrotic adhesion is associated with a markedly higher risk of recurrence, the fibrotic subgroup is small (n = 11).

When the degree of labial synechia was evaluated, recurrence occurred in three of five patients with complete fusion (60.0%) and in 27 of 136 with partial fusion (19.9%); this difference did not reach statistical significance (Fisher's exact $p = 0.065$), and given that only five patients had complete fusion, no effect estimate is reported. Recurrence developed in 14 of the 73 patients (19.2%) who received antibiotic–estrogen therapy at Center 1 and in 16 of the 68 patients (23.5%) who received antibiotic monotherapy at Center 2. With antibiotic alone as the reference, this corresponds to an absolute risk difference of −4.4 percentage points (95% CI: −17.9 to 9.1), a risk ratio of 0.82 (95% CI: 0.43-1.53), and an odds ratio of 0.77 (95% CI: 0.34-1.73; $p = 0.528$; Table 3).

In the Firth penalized logistic regression including age, adhesion type, adhesion degree, symptomatic presentation, and maintenance regimen, fibrotic adhesion remained strongly associated with recurrence (adjusted odds ratio 63.40; 95% CI: 11.12-757.06; $p < 0.001$), as shown in Table 4. A similar association was found for symptomatic presentation, although with an extremely wide interval reflecting only two patients (adjusted odds ratio 62.05; 95% CI: 4.00-9376.22; $p = 0.003$). After adjustment, the Center 1/combined-protocol term was associated with lower odds of recurrence, although the interval included unity (adjusted odds ratio 0.38; 95% CI: 0.12-1.04; $p = 0.059$). Age (adjusted odds ratio 0.69 per year; 95% CI: 0.38-1.04; $p = 0.083$) and complete fusion (adjusted odds ratio 1.56; 95% CI: 0.07-19.95; $p = 0.751$) were not independently associated with recurrence.

## DISCUSSION

In the present study, we evaluated recurrence after manual separation for labial synechia in 141 prepubertal girls managed at two centers, each of which applied a single maintenance protocol. Our study results showed that recurrence occurred in 21.3% of patients and was strongly associated with the fibrotic rather than the thin type of adhesion, whereas recurrence rates did not differ significantly between the two maintenance protocols. These findings suggest that the character of the adhesion is more informative than the choice of topical maintenance agent; however, as the protocol was determined entirely by the treating center, protocol and center cannot be separated in these data, and no inference of superiority can be drawn.

Labial synechia occurs most frequently in the period from three to 23 months.[3-6] In the present study, the highest frequency was observed in the 1-year age group, followed by infants under one year of age, and this finding is consistent with the established literature. The true prevalence may be even higher, since a substantial proportion of cases are asymptomatic and therefore under-reported.[32] The fact that most of our patients were diagnosed during routine assessments underlines the critical importance of regular pediatric physical examination.

The etiology of labial synechia is generally attributed to a combination of low estrogen levels and local irritation.[9] The strikingly high rate of diaper use in our cohort (93.6%) supports the role of chronic irritation, due to the moist environment created by urine and feces and to possible diaper dermatitis, in the formation of labial adhesions. Local irritation and inadequate hygiene are also the principal causes of nonspecific vulvovaginitis in this age group.[19,21]

The management spectrum for labial synechia is broad, ranging from conservative observation to surgical intervention. Manual separation is a globally accepted primary treatment option, as it provides rapid clinical resolution, has high immediate success, avoids systemic estrogen exposure, and is preferred by parents; it is also useful in situations where adherence to prolonged topical therapy may be limited. There is as yet no definitive consensus in the literature regarding the optimal treatment of prepubertal labial synechia. Many authors advocate topical treatments containing estriol and report success rates between 50% and 90%.[1,3,24,29] Other series have reported considerably lower success, around 15%, with either estrogen or betamethasone alone,[28] and recurrence after both topical and surgical treatment has been described repeatedly.[23,26,33,34] By contrast, studies using manual separation report immediate success in almost all cases, since the adhesions are mechanically resolved. This method is frequently preferred due to its rapid therapeutic effect, high resolution rates, and recurrence rates comparable to those of topical treatments.[35,36] Wejde et al.[37] showed that manual separation was more successful than topical estrogen on the basis of both primary treatment outcomes and the analysis of recurrence treatments. They also noted that, according to parental reports, manual separation showed a tendency towards better long-term outcomes, but that recurrence rates remained high for both modalities in retrospective records as well as in parental feedback. Rahman Dhaiban and Chaudhary,[32] using manual separation followed by one week of topical antibiotic and local hygiene in 48 girls, reported complete release in all cases and no recurrence at six months, a regimen that corresponds closely to the antibiotic-alone protocol used at Center 2 in our cohort. In our study, we preferred manual separation given its shorter treatment duration, immediate result, and suitability for patients with low treatment adherence. Although the great majority of patients in this cohort were asymptomatic, manual separation was preferred owing to the need for a rapid result, parental preference, and the reduction of the risk of developing symptoms. The retrospective design of our study did not allow direct demonstration that early separation prevents fibrotic transformation; we consider this a hypothesis that could be tested prospectively.

According to the literature, approximately three-quarters of patients treated for labial synechia (some sources report rates up to 45% specifically for asymptomatic cases) have no symptoms.[38] Management of the asymptomatic child is genuinely contested. Some authors argue that most adhesions separate spontaneously around puberty as endogenous estrogen rises. They suggest that observation with vulvar hygiene measures, including avoidance of irritant soaps and bubble baths, timely diaper changes, gentle drying, and application of an emollient barrier, is sufficient and that no treatment is required.[22,36,39] In a cohort of 114 girls, resolution occurred in 85% of those managed by observation alone, compared with all of those treated with topical estrogen.[40] Others suggest that earlier treatment may be preferable, as adhesions tend to become denser and more fibrotic over time. Our data do not allow us to adjudicate between these two positions: we have no untreated comparison group, and the association we observed between fibrotic tissue and recurrence is cross-sectional rather than temporal. In this cohort, the decision to separate asymptomatic children rested on parental preference and on the immediacy of the result; this decision should be presented as such rather than as evidence-based prophylaxis. Recurrence rates reported in the literature range from 14% to 34%, and our findings lie within this range.[22,37,38] In our cohort, no association was found between recurrence and age, comorbidity, or diaper use, which is consistent with the findings of Acer et al.,[41] who observed no correlation between hygiene products, diaper dermatitis, or infection and the recurrence of labial fusion. The fact that recurrence developed in both of the two symptomatic patients may point to a more resistant clinical phenotype; given that only two

children are involved, this observation is anecdotal and cannot support the use of symptoms as a prognostic marker.

The clearest finding of our study is the association between adhesion type and recurrence. The recurrence rate was 15.4% for thin adhesions and 90.9% for fibrotic adhesions, and fibrotic tissue remained the strongest correlate of recurrence after adjustment. Although this supports an association between tissue character and recurrence risk, a causal prognostic role cannot be confirmed in a retrospective design. Adhesion thickness is also one of the defining features of the classification proposed by Huseynov and Hakalmaz,[31] in which treatment is tailored to the subtype. This finding may support consideration of earlier intervention before adhesions undergo fibrotic change; however, our retrospective data cannot establish that early treatment prevents fibrosis. In addition, although not statistically significant, we observed a higher tendency to recurrence in cases with complete fusion, which suggests that the extent of the adhesion warrants close follow-up.

To our knowledge, there is no study in the literature that specifically compares maintenance protocols aimed at preventing recurrence after manual separation. In our study, we compared topical antibiotic monotherapy with the combination of topical estrogen and antibiotic. We found no statistically significant difference in recurrence rates between the two regimens (19.2% with the combination versus 23.5% with antibiotic alone; risk difference −4.4 percentage points, 95% CI −17.9 to 9.1; risk ratio 0.82, 95% CI: 0.43-1.53). The numerically lower rate in the combination group is compatible with a supportive effect of estrogen on epithelial healing, but the confidence interval is wide and does not exclude a difference in either direction; moreover, as each center used a single protocol, the comparison cannot be separated from a comparison of the two centers, and the difference between the groups may equally reflect differences in case mix, in operator technique, or in the thoroughness of parental counseling. We therefore draw no inference of superiority in either direction. The 90.0% recurrence-free rate achieved after secondary surgical separation followed by the standard antibiotic-estrogen protocol is consistent with the effectiveness of that approach in resistant cases, although it reflects the combined effect of both interventions. No treatment-related adverse effect was observed with either regimen. Within the limits of this design, both maintenance protocols therefore appear to be acceptable options after manual separation, and a randomized comparison within centers, with a common follow-up schedule and blinded outcome assessment, would be required to determine whether either is superior.

Our study has several limitations that should be taken into account. First, its retrospective nature entails selection and documentation biases. Second, although the study is multicenter, the sample size is relatively small, particularly in certain clinical subgroups such as the symptomatic and fibrotic cases; estimates for these subgroups are therefore imprecise and are reported with wide confidence intervals. Third, the maintenance protocol was determined entirely by the treating center, so protocol and center are completely collinear; no statistical adjustment can separate them, and the two groups also differed in case mix (fibrotic adhesions 12.3% *vs.* 2.9%; comorbidity 8.2% *vs.* 0%). The comparison of the two regimens should therefore be read as a comparison of two centers as much as of two topical protocols. Fourth, as each center delivered a single protocol, the surgeon assessing recurrence was necessarily aware of the regimen the patient had received; outcome ascertainment was therefore not blinded and could not be blinded retrospectively. Fifth, urine culture was not obtained; hence pyuria on urinalysis could not be confirmed as a urinary tract infection, and this variable is subject to misclassification in both directions.

In conclusion, manual separation is an effective and rapid method for treating labial synechia. Clinicians should be aware of the higher recurrence rates observed in patients with fibrotic adhesions, while the apparent association with symptomatic presentation should be interpreted cautiously given the very small symptomatic subgroup. Recurrence did not differ significantly between topical antibiotic alone and combined antibiotic-estrogen maintenance, and no adverse effect was observed with either; since the treatment protocol was determined by the treating center rather than by the individual patient, however, our data do not demonstrate the superiority of either regimen, and

both appear to be acceptable options within the limits of this design. Our findings show an association between fibrotic adhesions and recurrence, and this association is robust to adjustment. By contrast, they do not establish that early treatment prevents fibrosis. Prospective randomized studies are needed to determine the optimal maintenance protocol after manual separation.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Author Contributions:** E.B., E.K.: Concept, design, supervision, data collection and/or processing, analysis and/or interpretation, critical review; E.B.: Literature search, writing. All authors approved the final version of the manuscript.

**Conflict of Interest:** The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

**Funding:** The authors received no financial support for the research and/or authorship of this article.

**AI Disclosure:** The authors declare that artificial intelligence (AI) tools were not used, or were used solely for language editing, and had no role in data analysis, interpretation, or the formulation of conclusions. All scientific content, data interpretation, and conclusions are the sole responsibility of the authors. The authors further confirm that AI tools were not used to generate, fabricate, or 'hallucinate' references, and that all references have been carefully verified for accuracy.

## REFERENCES

1. Heinz M. Symptome und Erkrankungen des äußeren Genitale und der Brust bei Mädchen. Gynakologe 2011;44:452-62. doi: 10.1007/s00129-010-2748-5.
2. Vilano SE, Robbins CL. Common prepubertal vulvar conditions. Curr Opin Obstet Gynecol 2016;28:359-65. doi: 10.1097/GCO.0000000000000309.
3. Eyk NV, Allen L, Giesbrecht E, Jamieson MA, Kives S, Morris M, et al. Pediatric vulvovaginal disorders: A diagnostic approach and review of the literature. J Obstet Gynaecol Can 2009;31:850-62. doi: 10.1016/S1701-2163(16)34304-3.
4. Leung AK, Robson WL, Tay-Uyboco J. The incidence of labial fusion in children. J Paediatr Child Health 1993;29:235-6. doi: 10.1111/j.1440-1754.1993.tb00495.x.
5. Lee IO, Pak HY, Chung JE. Demographic characteristics of labial adhesion in South Korea: A population-based study from 2010 to 2014. BMJ Paediatr Open 2018;2:e000276. doi: 10.1136/bmjpo-2018-000276.
6. Muram D. Treatment of prepubertal girls with labial adhesions. J Pediatr Adolesc Gynecol 1999;12:67-70. doi: 10.1016/s1083-3188(00)86629-2.
7. Capraro VJ, Greenberg H. Adhesions of the labia minora. A study of 50 patients. Obstet Gynecol 1972;39:65-9.
8. Rubinstein A, Rahman G, Risso P, Ocampo D. Labial adhesions: Experience in a children's hospital. Arch Argent Pediatr 2018;116:65-8. doi: 10.5546/aap.2018.eng.65.
9. Schober J, Dulabon L, Martin-Alguacil N, Kow LM, Pfaff D. Significance of topical estrogens to labial fusion and vaginal introital integrity. J Pediatr Adolesc Gynecol 2006;19:337-9. doi: 10.1016/j.jpag.2006.06.004.
10. Cağlar MK. Serum estradiol levels in infants with and without labial adhesions: The role of estrogen in the etiology and treatment. Pediatr Dermatol 2007;24:373-5. doi: 10.1111/j.1525-1470.2007.00493.x.
11. Bacon JL. Prepubertal labial adhesions: evaluation of a referral population. Am J Obstet Gynecol 2002;187:327-31. doi: 10.1067/mob.2002.126201.
12. McCann J, Voris J, Simon M. Labial adhesions and posterior fourchette injuries in childhood sexual abuse. Am J Dis Child 1988;142:659-63. doi: 10.1001/archpedi.1988.02150060093040.
13. Muram D. Labial adhesions in sexually abused children. JAMA 1988;259:352-3. doi: 10.1001/jama.1988.03720030020016.
14. Leung AK, Robson WL. Labial fusion and asymptomatic bacteriuria. Eur J Pediatr 1993;152:250-1. doi: 10.1007/BF01956155.
15. Myers JB, Sorensen CM, Wisner BP, Furness PD 3rd, Passamaneck M, Koyle MA. Betamethasone cream for the treatment of prepubertal labial adhesions. J Pediatr Adolesc Gynecol 2006;19:407-11. doi: 10.1016/j.jpag.2006.09.005.
16. Stricker T, Navratil F, Sennhauser FH. Vulvovaginitis in prepubertal girls. Arch Dis Child 2003;88:324-6. doi: 10.1136/adc.88.4.324.
17. Jaquiery A, Stylianopoulos A, Hogg G, Grover S. Vulvovaginitis: Clinical features, aetiology, and microbiology of the genital tract. Arch Dis Child 1999;81:64-7. doi: 10.1136/adc.81.1.64.
18. Yilmaz AE, Celik N, Soylu G, Donmez A, Yuksel C. Comparison of clinical and microbiological features of vulvovaginitis in prepubertal and pubertal girls. J Formos Med Assoc 2012;111:392-6. doi: 10.1016/j.jfma.2011.05.013.
19. Zuckerman A, Romano M. Clinical recommendation: Vulvovaginitis. J Pediatr Adolesc Gynecol 2016;29:673-9. doi: 10.1016/j.jpag.2016.08.002.
20. Beyitler İ, Kavukcu S. Clinical presentation, diagnosis and treatment of vulvovaginitis in girls: A current approach and review of the literature. World J Pediatr 2017;13:101-5. doi: 10.1007/s12519-016-0078-y.
21. Cemek F, Odabaş D, Şenel Ü, Kocaman AT. Personal hygiene and vulvovaginitis in prepubertal children. J Pediatr Adolesc Gynecol 2016;29:223-7. doi: 10.1016/j.jpag.2015.07.002.
22. Bacon JL, Romano ME, Quint EH. Clinical recommendation: Labial adhesions. J Pediatr Adolesc Gynecol 2015;28:405-9. doi: 10.1016/j.jpag.2015.04.010.
23. Nurzia MJ, Eickhorst KM, Ankem MK, Barone JG. The surgical treatment of labial adhesions in pre-pubertal girls. J Pediatr Adolesc Gynecol 2003;16:21-3. doi: 10.1016/s1083-3188(02)00208-5.
24. Leung AK, Robson WL, Kao CP, Liu EK, Fong JH. Treatment of labial fusion with topical estrogen therapy. Clin Pediatr (Phila) 2005;44:245-7. doi: 10.1177/000992280504400308.
25. Soyer T. Topical estrogen therapy in labial adhesions in children: Therapeutic or prophylactic? J Pediatr Adolesc Gynecol 2007;20:241-4. doi: 10.1016/j.jpag.2006.09.015.
26. Kumetz LM, Quint EH, Fisseha S, Smith YR. Estrogen treatment success in recurrent and persistent labial agglutination. J Pediatr Adolesc Gynecol 2006;19:381-4. doi: 10.1016/j.jpag.2006.09.008.

27. Tebruegge M, Misra I, Nerminathan V. Is the topical application of oestrogen cream an effective intervention in girls suffering from labial adhesions? Arch Dis Child 2007;92:268-71. doi: 10.1136/adc.2006.110528.
28. Eroğlu E, Yip M, Oktar T, Kayiran SM, Mocan H. How should we treat prepubertal labial adhesions? Retrospective comparison of topical treatments: Estrogen only, betamethasone only, and combination estrogen and betamethasone. J Pediatr Adolesc Gynecol 2011;24:389-91. doi: 10.1016/j.jpag.2011.07.015.
29. Ertürk N. Comparison of estrogen and betamethasone in the topical treatment of labial adhesions in prepubertal girls. Turk J Med Sci 2014;44:1103-7. doi: 10.3906/sag-1312-3.
30. Dowlut-McElroy T, Higgins J, Williams KB, Strickland JL. Treatment of prepubertal labial adhesions: A randomized controlled trial. J Pediatr Adolesc Gynecol 2019;32:259-63. doi: 10.1016/j.jpag.2018.10.006.
31. Huseynov M, Hakalmaz AE. Labial adhesion: New classification and treatment protocol. J Pediatr Adolesc Gynecol 2020;33:343-8. doi: 10.1016/j.jpag.2020.03.005.
32. Rahman Dhaiban MA, Chaudhary MA. Manual separation of labial synechiae: A cost-effective method in prepubertal girls. Afr J Paediatr Surg 2021;18:139-42. doi: 10.4103/ajps.AJPS_34_20.
33. Mayoglou L, Dulabon L, Martin-Alguacil N, Pfaff D, Schober J. Success of treatment modalities for labial fusion: A retrospective evaluation of topical and surgical treatments. J Pediatr Adolesc Gynecol 2009;22:247-50. doi: 10.1016/j.jpag.2008.09.003.
34. Granada C, Sokkary N, Sangi-Haghpeykar H, Dietrich JE. Labial adhesions and outcomes of office management. J Pediatr Adolesc Gynecol 2015;28:109-13. doi: 10.1016/j.jpag.2014.06.004.
35. Watanabe T, Matsubara S, Fujinaga Y, Asada K, Ohmaru T, Suzuki M. Manual separation followed by local cleanliness for pediatric labial adhesion. J Obstet Gynaecol Res 2010;36:667-70. doi: 10.1111/j.1447-0756.2010.01192.x.
36. Thibaud E, Duflos C. Plea for child: labial agglutination should not be treated. Arch Pediatr 2003;10:465-6. doi: 10.1016/s0929-693x(03)00099-x.
37. Wejde E, Ekmark AN, Stenström P. Treatment with oestrogen or manual separation for labial adhesions - initial outcome and long-term follow-up. BMC Pediatr 2018;18:104. doi: 10.1186/s12887-018-1018-x.
38. Bussen S, Eckert A, Schmidt U, Sütterlin M. Comparison of conservative and surgical therapy concepts for synechia of the labia in pre-pubertal girls. Geburtshilfe Frauenheilkd 2016;76:390-5. doi: 10.1055/s-0035-1558101.
39. Norris JE, Elder CV, Dunford AM, Rampal D, Cheung C, Grover SR. Spontaneous resolution of labial adhesions in pre-pubertal girls. J Paediatr Child Health 2018;54:748-53. doi: 10.1111/jpc.13847.
40. Kim SW, Han JY, Han SJ, Kim H, Ku SY. Effect of topical estrogen cream compared with observation in prepubertal girls with labial adhesions. J Pediatr Urol 2023;19:403.e1-6. doi: 10.1016/j.jpurol.2023.01.006.
41. Acer T, Otgün I, Oztürk O, Kocabaş T, Tezcan AY, Cirak A, et al. Do hygienic factors affect labial fusion recurrence? A search for possible related etiologic factors. J Pediatr Surg 2012;47:1913-8. doi: 10.1016/j.jpedsurg.2012.05.005.