

Treatment of Prepubertal Labial Adhesions: A Randomized Controlled Trial



Tazim Dowlut-McElroy MD, MS^{1,2,*}, Jeanette Higgins RN, CPNP¹, Karen B. Williams PhD³, Julie L. Strickland MD, MPH^{1,2}

¹ Department of Surgery, Children's Mercy Hospitals, Kansas City, Missouri

² Department of Obstetrics and Gynecology, University of Missouri-Kansas City, Kansas City, Missouri

³ Department of Biomedical and Health Informatics, University of Missouri-Kansas City, Kansas City, Missouri

ABSTRACT

Study Objective: Although various treatment options have been proposed for the treatment of labial adhesions, there are currently no clearly outlined limits on the duration of topical therapy, amount of lateral traction to apply, and methods to decrease the recurrence. This clinical trial was undertaken to assess the need for estrogen for treatment of prepubertal labial adhesions.

Design: Randomized, double-blinded, controlled trial.

Setting: Pediatric and Adolescent Gynecology Clinic at a children's hospital in a metropolitan area.

Participants: Prepubertal girls ages 3 months to 12 years with labial adhesions.

Interventions: Lateral traction with topical estrogen or topical emollient.

Main Outcome Measures: The primary outcome was resolution of labial adhesions. The secondary outcome was the change in severity of labial adhesions over time between the 2 groups.

Results: Forty-three girls were enrolled and 38 (88%) completed the study. The difference in complete resolution between the topical emollient group (19%) and the topical estrogen group (36%) was not statistically significant ($P = .21$). There was a statistically significant decrease in severity of labial adhesions over time, with the magnitude of improvement favoring the topical estrogen group.

Conclusion: Although labial adhesion severity decreased when treated with lateral traction and topical emollient or topical estrogen, the magnitude of the effect was significantly greater for topical estrogen.

Key Words: Labial adhesion, Labial agglutination, Fused labia, Topical estrogen

Introduction

Labial adhesions are an acquired condition of prepubertal girls in which the labia are fused over the vaginal opening and/or urethra. Labial adhesions are estimated to occur in 22% of prepubertal girls and are most frequent in ages 3 months to 6 years.¹⁻³ Because labial adhesions typically resolve spontaneously with estrogen production at puberty, treatment is recommended only for prepubertal girls who are symptomatic.¹ Symptoms are related to the accumulation of urine behind partially fused labia and include recurrent urinary tract infections and vulvovaginitis, pain with activity, post-void dripping of urine and, in cases of complete fusion of the labia, urinary retention.¹

The etiology of labial adhesions is unclear but is presumably related to hypoestrogenism in combination with vulvar irritation.¹ First-line treatment for labial adhesions in prepubertal girls has traditionally been topical estrogen.

This method of treatment is not without risk because estrogen is systemically absorbed. There have been infrequent reports of breast budding, vulvar hyperpigmentation, and vaginal bleeding, all of which were transient and resolved with discontinuation of topical estrogen.⁴⁻⁶

The primary aim of this randomized clinical trial was to compare the effectiveness of topical emollient with lateral traction compared with topical estrogen with lateral traction on the resolution of labial adhesions in prepubertal girls. The secondary aim of this study was to evaluate the change in severity of labial adhesion over time between the 2 groups.

Materials and Methods

This project was approved by the institutional review board of Children's Mercy Hospitals, Kansas City, Missouri and was registered on [ClinicalTrials.gov](https://clinicaltrials.gov) (identifier: NCT02218463). Between August 2014 and April 2016, a single-site, randomized, double-blinded clinical trial was completed to evaluate the comparative effectiveness of topical emollient with lateral traction vs topical estrogen with lateral traction for the treatment of labial adhesions in prepubertal girls.

Potential subjects meeting inclusion/exclusion criteria were invited to participate and written consent was obtained from a parent or legal guardian. Inclusion criteria

Julie L. Strickland, MD, MPH is a Nexplanon instructor and receives an honorarium from Merck. The remaining authors indicate no conflicts of interest.

The findings of this study were presented, in part, at the 31st Annual Clinical and Research Meeting of the North American Society for Pediatric and Adolescent Gynecology, Chicago, Illinois, April 20, 2017.

* Address correspondence to: Tazim Dowlut-McElroy, MD, MS, Department of Obstetrics and Gynecology, University of Missouri-Kansas City, 2301 Holmes, #713, Kansas City, MO 64108; Phone: (816) 404-5150

E-mail address: dowlutmcelroy@umkc.edu (T. Dowlut-McElroy).

were as follows: prepubertal girls ages 3 months to 12 years with labial adhesions. Exclusion criteria were as follows: presence of underlying dermatologic conditions such as lichen sclerosus, severe atopic dermatitis, psoriasis, or vitiligo; presence of systemic conditions that can have vulvar manifestations such as Crohn's disease and Behçet disease; presence of disorders requiring immunosuppressant treatment; and previous surgical separation of labial adhesions. Although treatment was only recommended for symptomatic girls, those whose families requested treatment because of concern about the appearance of the child's genitalia were not excluded from the study.

After baseline measurements, study participants were randomly assigned to either the topical estrogen with traction group or the topical emollient with traction group. A block randomization design with blocks of 10 was generated using SPSS software (version 22.0; IBM Corp, Armonk, NY) and used to maintain balance of treatment assignments. Treatment allocation was directed by a list of participant study identification numbers and corresponding random assignments prepared in advance by the study statistician and followed by the investigational drug services pharmacy as each new participant enrolled and was assigned the subsequent study identification number. Only the statistician and the pharmacy staff were aware of the assignments. The principal investigator, study staff, and patients were blinded throughout the trial. Group 1 received Estrace Cream (Estrace vaginal cream, USP, 0.01%; Warner Chilcott). Group 2 received Cetaphil Moisturizing Cream (Galderma). Cetaphil Moisturizing Cream (Galderma) was chosen because the consistency and color of this emollient resembles that of Estrace Cream (Warner Chilcott). Study medication was packaged in identical containers, placed in brown paper bags, and dispensed directly to the participant's parent or legal guardian by the investigational drug services pharmacy staff.

The participants' parent or legal guardian was instructed to apply the preparation to the labial adhesion twice daily with lateral traction to the point of discomfort but not pain. The length of time that traction should be applied was not specified because of the concern that excessive discomfort might cause the child to refuse subsequent treatment. The technique for application of the topical preparation as well as the technique for lateral traction was demonstrated to the participants' parent or legal guardian and written instructions were provided (Fig. 1). After randomization and baseline evaluation, participants returned for assessments at 3 and 6 weeks. The evaluation time frame was chosen on the basis of a previous report that 50% of labial adhesions resolve in 2–3 weeks and most labial adhesions resolve with 6 weeks of treatment with topical estrogen.¹

At the initial evaluation and at each of the subsequent evaluations, severity and thickness of the labial adhesion was determined by examination by either the principal investigator or the gynecology advanced practice nurse practitioner. Before study initiation, examiners were calibrated on the use of severity and thickness scales. Rating of closure of the introitus was assigned values of 0 = resolved, 1 = 25%, 2 = 50%, 3 = 75%, and 4 = 100%. A value of 4 was assigned to denote the presence of only a pinpoint opening

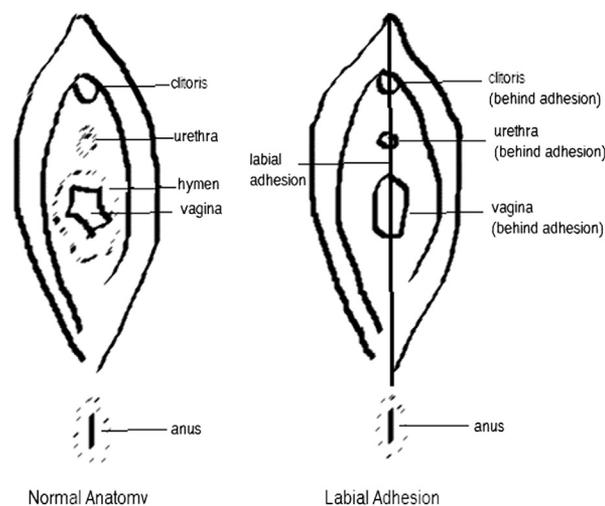


Fig. 1. Instructions for application of cream and traction.

of the adhesion that allowed passage of urine. Thickness of the labial adhesion was measured in a similar fashion with values assigned as 0 = resolved, 1 = thin, 2 = intermediate, or 3 = thick. Because response to treatment is dependent not only upon the size of the adhesion but also the thickness, a composite severity scale was created to incorporate both measurements into a single scale for analysis. For example, a participant with 100% closure (ordinal value of 4) and an adhesion of intermediate thickness (ordinal value of 2) would receive a composite score of 6 (4 + 2). Thus, higher composite scores corresponded to more severe labial adhesions.

Statistical Analyses

At the time of study initiation, there were no meaningful data from which to estimate the potential effect size between the 2 treatment groups. Therefore, a clinically meaningful failure rate was used for the power analysis. Previous data suggested that 50% of labial adhesions treated with estrogen resolve within the 3-week study period.¹ A meaningful failure rate for the emollient was deemed a rate of only 10% resolution at 3 weeks. Therefore, a sample size of 20 completed participants per group was determined to have 80% power to detect a difference in resolution of that magnitude in labial adhesions between the 2 groups at the 3-week follow-up point.

Statistical analyses were performed using STATA/SE version 14.2 (StataCorp LLC). Descriptive analyses characterized the 2 treatment groups at baseline. An intention to treat analysis was conducted for the primary outcome. For the primary outcome of complete resolution, dropouts were assigned as not completely resolved. To assess the primary outcome, complete resolution of labial adhesions between the 2 treatment arms, Fisher exact test was used because 1 cell had counts of less than 5. A *P* value of less than .05 was considered significant.

For the secondary outcome, severity of labial adhesion, a mixed effects model was used (participant as random effect, identity covariance structure), to assess the effect of treatment group over time. Because the effect of participant age

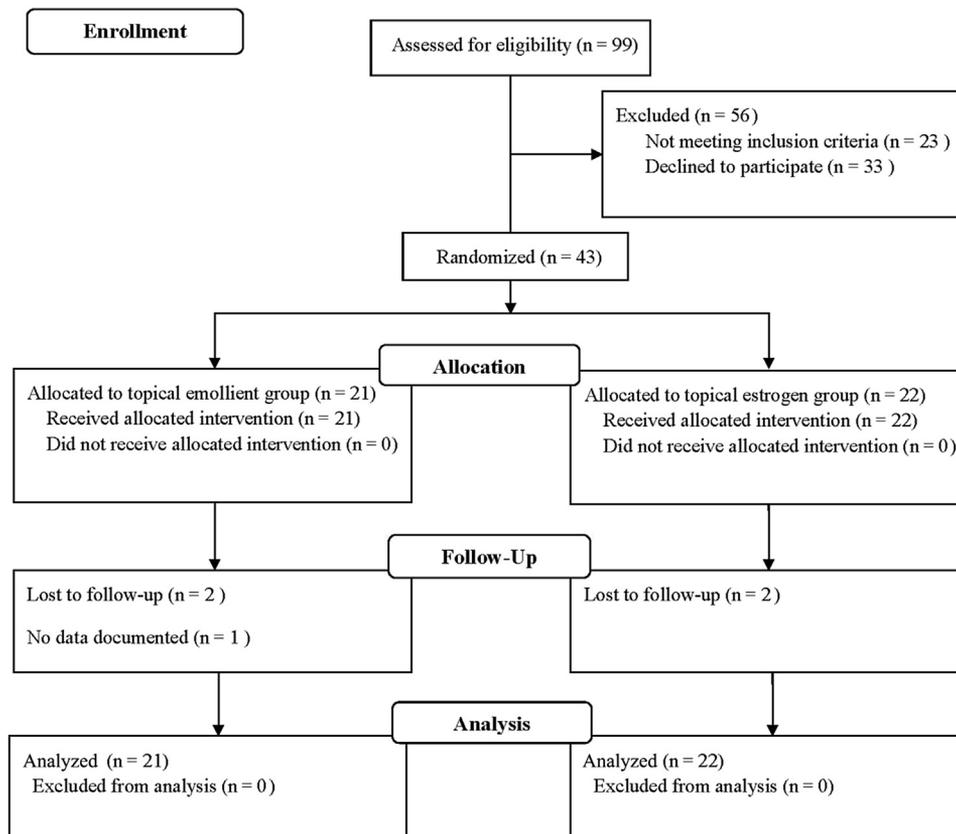


Fig. 2. Participant flow diagram including enrollment, random assignment, and follow-up.

was considered as a potential confounder, preliminary models included age as a covariate. In these initial models, age had no main effect nor 2- and 3-way interaction effects with treatment group and/or time; thus, it was subsequently eliminated from the final analysis. For these analyses, a P value of less than .05 was considered significant.

Results

A total of 99 children were assessed for eligibility. Of these children, 76 were eligible for the study, 43 were randomized and 38 (88%) completed the study (Fig. 2). Two study participants dropped out after randomization and 2 study participants dropped out after the 3-week assessment. Of these 4 dropouts, 2 had been randomized to the topical estrogen group and 2 to the topical emollient group. One study participant, who had been randomized to the topical emollient group, had no data recorded at her 6-week visit although her records indicated that she had been examined.

Table 1 shows the baseline characteristics of study participants in each of the treatment groups. Study participants ranged in ages from 4 months to 9 years and all were Tanner stage 1 with prepubertal appearance. The difference in mean age between the 2 groups was not statistically significant ($P = .31$). There were no reported side effects of breast budding, vulvar hyperpigmentation, or vaginal bleeding through the study period. Two patients, 1 randomized to each study group, reported vulvar irritation only

at 6 weeks post intervention. There were no serious adverse events during the trial.

The difference in complete resolution at 6 weeks between participants randomized to the topical emollient with lateral traction group compared with those randomized to the topical estrogen with lateral traction group is depicted in Table 2. Only 8 of 22 participants treated with estrogen and 4 of the 21 participants treated with emollient had complete resolution of the labial adhesion. Although almost twice as many patients treated with estrogen (36%) had complete resolution of the labial adhesion compared with those treated with emollient (19%), this difference was

Table 1
Demographic Characteristics and Baseline Measurements

Characteristic	Topical Emollient (n = 21)	Topical Estrogen (n = 22)
Mean age in months (SD)	33 (20)	26 (21)
Introital closure		
25%	1 (5)	0 (0)
50%	5 (24)	4 (18)
75%	4 (19)	7 (32)
100%	11 (52)	11 (50)
Thickness of labial adhesion		
Thin	5 (24)	4 (18)
Intermediate	14 (67)	17 (77)
Thick	2 (10)	1 (5)
Urinary tract infection	0 (0)	2 (9)
Vulvovaginitis	0 (0)	0 (0)
Pain with activity	1 (5)	1 (5)
Postvoid dribbling	1 (5)	0 (0)

Data are presented as n (%) except where otherwise noted.

Table 2
Complete Resolution of Labial Adhesion

Complete Resolution	Topical Emollient (n = 21)	Topical Estrogen (n = 22)	P
Yes	4 (19)	8 (36)	.21
No	17 (81)	14 (64)	

Data are presented as n (%) except where otherwise noted.

not statistically significant ($P = .21$). Of the 22 participants with almost complete occlusion (rating of closure assigned a value of 4), only 1 of 11 randomized to the emollient group and 4 of 11 randomized to the estrogen group had complete resolution of the labial adhesion. This difference was also not statistically significant ($P = .311$).

The composite severity scale created by summing the ordinal value assigned to introital closure and thickness of the adhesion for each of the 3 study visits allowed for comparison of treatment effect between each study group over time. A lower composite severity score corresponded to a less severe labial adhesion. Results from the random coefficients models showed that there was a statistically significant decrease in severity of labial adhesions over time, with the magnitude of the improvement over time favoring the estrogen group (Table 3). Labial adhesion severity decreased in both groups; however, the magnitude of effect was significantly greater for topical estrogen, which decreased from 4.2 to 1.6, compared with the topical emollient, which decreased from 3.9 to 2.5 (Fig. 3).

Discussion

Although the exact etiology of prepubertal labial adhesions is unknown, vulvar inflammation in a hypoestrogenic milieu is the prevailing hypothesis.^{5,7} However, investigators have found no difference in estrogen levels in prepubertal girls with and without labial adhesions.⁸ In addition, labial adhesion in association with premature thelarche has been reported, suggesting factors other than estrogen insufficiency as the etiology.⁹ Although the traditional treatment for labial adhesions has been the application of topical estrogen, there have been recent reports of the use of topical betamethasone with similar, albeit relatively low, efficacy. In a retrospective study, Eroglu et al reported a success rate of only 15% with the treatment of labial adhesion with topical estrogen or topical betamethasone.¹⁰ The success rate increased to 28% with the combination of estrogen and betamethasone. A recent study also reported a 40% resolution rate of prepubertal labial adhesions without treatment.¹¹ This raises the

Table 3
Composite Severity Scale of Labial Adhesion over Time (Random Coefficients Model)

Variable	Topical Emollient (n = 21)	Topical Estrogen (n = 22)	P
Composite severity scale			Treatment: .24 Time: < .001 (.75) Interaction: .013
Baseline	3.9 (1.5)	4.2 (1.0)	
3 Weeks	3.2 (1.5)	2.7 (1.5)	
6 Weeks	2.5 (2.0)	1.6 (1.7)	

Data presented as mean (SD) except where otherwise noted.

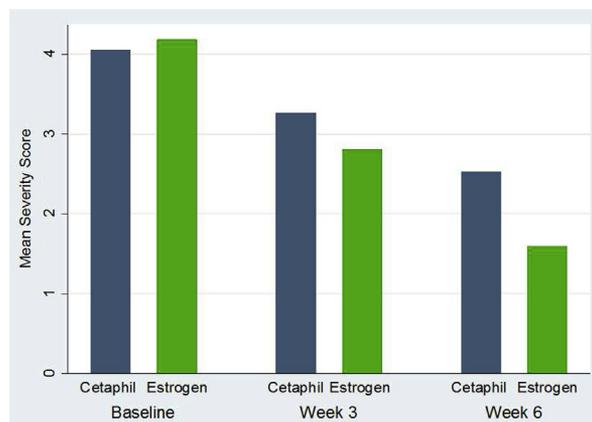


Fig. 3. Mean severity score for treatment groups over time.

question of optimal recommendations for the treatment of prepubertal labial adhesions. Our clinical trial was primarily undertaken to assess whether lateral traction with a topical emollient would have results comparable with lateral traction with topical estrogen.

In our study, only 36% had complete resolution of labial adhesions. This is considerably lower than previously reported resolution rates as high as 100% with use of topical estrogen.¹² Capraro and Greenburg described a retrospective case series of 50 premenarchal girls with a mean age of 2.5 years including 66% of patients with adhesions “involving the entire length of the labia minora.”³ Forty-two of 47 patients (89%) had good results with a 2- to 4-week course of once daily topical estrogen. However, included in the success rate were an unreported number of patients with “fine adhesions” who were treated with manual separation. Aribarg reported a prospective cohort study of girls with labial adhesions between the ages of 2 months to 2 years in which 22 of 25 patients (88%) were successfully treated with once daily topical estrogen for 1–4 weeks.⁶ All patients had adhesions “involving the entire length of the labia minora.” This study, however, lacked blinding of treatment method and the control group consisted of only 5 patients treated with a topical emollient for 1 month. Leung et al described a prospective case series of 20 patients with a mean age 13.2 months with labial adhesions in which all patients (100%) had complete resolution with topical estrogen applied twice daily.¹² Although the authors described the severity of the adhesions as covering at least 50% of the vaginal opening, the lower rate of complete resolution of labial adhesions in our study might be attributable to a higher percentage of more severe labial adhesions among our population. Because patients in the series from Leung et al were treated with topical estrogen for up to 14 weeks compared with up to only 6 weeks of treatment in our trial, the higher rate of complete resolution of labial adhesion in that series might also be due to prolonged treatment with topical estrogen.

In a retrospective case series of 259 prepubertal girls with labial adhesions wherein patients were treated with topical estrogen for 10–14 days, Muram reported a success rate of only 47% despite the fact that 76% of these girls were reported to have thin, translucent labial adhesions.¹ The

36% complete resolution rate in our study might be due to a much smaller percentage of patients (21%) with thin adhesions. The relative difference in results between these 2 studies reflects the importance of using thickness as well as size of labial adhesions as a measure of severity in assessing treatment response.

This study has several limitations. Adherence to treatment was obtained through parent report. The lack of a statistically significant difference in the severity of labial adhesions when evaluating treatment effect alone (ie, topical emollient with lateral traction vs topical estrogen with lateral traction) might reflect lack of adherence to the recommended frequency of treatment. The lower complete resolution rates of labial adhesions described in our study might also be a function of lack of adherence to the treatment protocol. In addition, although all study participants were evaluated by 1 of 2 investigators, and neither intra- nor interobserver variability in the assessment of labial adhesions were assessed, the measurements must be considered subjective. However, blinding of the investigators as to the treatment allocation reduced potential bias in assigning labial adhesion severity scores and reduced differential assessment of outcomes. The use of the intent to treat analysis also decreased potential bias in treatment comparisons between the 2 treatment groups. Last, the relatively small sample size of this study likely contributed to the inability to obtain statistically significant results for a relatively small difference in complete resolution of labial adhesion between the 2 treatment groups.

When comparing the relative effect of treatment with topical estrogen with lateral traction compared with topical emollient with lateral traction in our trial, use of the composite severity score showed that although labial adhesions decreased in severity in both treatment groups, the magnitude of the effect was significantly greater for topical estrogen. Investigators have previously proposed that the mechanical effect of labial traction as well as the softening effects of substances other than estrogen in topical preparations should be taken into consideration when evaluating the effect of topical estrogen.⁸ Despite the lack of statistical significance in complete resolution of labial adhesions between the 2 treatment groups, this study provides valuable data, which can be used to better estimate effect size for future studies. Prospective studies with rigorous methodology

including a larger sample size, use of a composite severity score accounting for size and thickness of labial adhesions, correlation of severity of labial adhesions and associated symptoms, and longitudinal follow-up to assess the risk of recurrence are needed to effectively determine the comparative results of various options for the treatment of prepubertal labial adhesions.

Clinically, no guidelines have clearly outlined limits on the duration of topical therapy for the treatment of labial adhesions, amount of lateral traction to apply, and methods to decrease the recurrence.⁷ Although our preliminary data suggest that lateral traction with the application of a topical emollient might be effective in the treatment of prepubertal labial adhesions, further investigation is needed.

Acknowledgments

This study was funded by the Children's Mercy Hospitals Clinical Fellowship Research Award and the University of Missouri-Kansas City School of Graduate Studies Research Award.

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