



Effect of topical estrogen cream compared with observation in prepubertal girls with labial adhesions

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Summary

Background

Topical estrogen treatment has been considered the first-line treatment of labial adhesions in prepubertal girls. However, the effect of topical estrogen cream is different according to studies, and no study compared estrogen cream to observation.

Objective

This study aims to investigate the efficacy of topical estrogen cream treatment compared with observation in prepubertal girls with labial adhesions.

Study design

The medical records of prepubertal girls diagnosed with labial adhesions from April 2005 to June 2019 were retrospectively analyzed. Baseline characteristics such as age at diagnosis and initial symptoms were collected. The primary outcome was the resolution of labial adhesion. Secondary outcomes were recurrence and side effects.

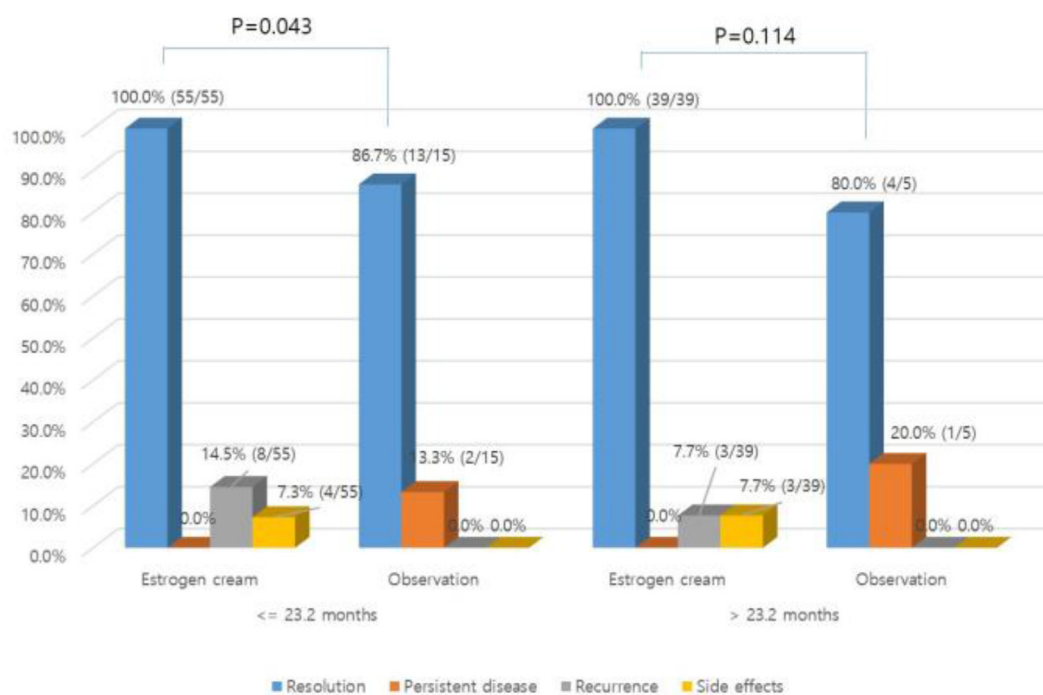
Results

A total of 114 patients were enrolled and divided into two groups, topical estrogen cream ($n = 94$), and observation ($n = 20$). Girls who were treated with estrogen cream had older age (24.6 ± 19.0 vs. 16.7 ± 15.3 months, $p = 0.037$) and higher resolution rate than the observation group (100.0% vs. 85.0%, respectively, $p = 0.005$). Girls younger than 23.3 months showed a significantly higher resolution rate to topical estrogen treatment (100% vs. 86.7%, $p = 0.043$). Side effects and recurrences occurred exclusively in children treated with topical estrogen therapy without significant differences compared to the observation group.

Conclusion

Topical estrogen therapy showed a higher resolution rate than observation for the treatment of prepubertal girls with labial adhesions, especially in younger girls.

¹ Sung Woo Kim and Ji Yeon Han contributed equally as the first authors of this study.



Summary Figure Clinical outcomes of estrogen cream treatment and observation in different age groups.

Introduction

Labial adhesion is an acquired fusion of labia minora or majora, usually located over the clitoris [1]. Labial adhesions occur in 0.6%–3.0% of prepubertal girls and are most common in girls aged 3 months to 6 years [2,3].

Although the cause of labial adhesions is uncertain, it seems to be related to hypoestrogenism and vulvar skin denudation due to irritation or scratching [2]. As labial adhesions usually improve spontaneously, especially when patients reach puberty, observation is one of the treatment options. A previous study reported the resolution of labial adhesions in 40% of girls without treatment during 0.4–20.7 years of follow-up [4].

Topical estrogen treatment has been considered as the first-line treatment of labial adhesions in prepubertal girls [2,5–7]. The success rates of topical estrogen cream are varied from 15.5 to 100%, and recurrence rates are ranged from 11 to 44% [5,7–9]. In a study published previously, after the application of topical estrogen cream for 14 days, the success rate was 66.6% in the third month, and 11% of patients recurred [5]. Among girls with recurrent and persistent diseases, labial adhesions were resolved in 62.5% of patients either partially or completely after topical estrogen treatment [8]. A recent randomized controlled trial reported 36% of complete resolution in the topical estrogen group, and the estrogen cream significantly reduced the severity of adhesion compared with a topical emollient [6]. However, the drawback of this study is that the treatment period varied and the strength of the lateral traction was different between patients.

Until now, numerous studies investigated the outcomes of various treatment options in prepubertal girls with labial adhesions [2,6–8,10–15], but most studies did not describe

the extent of labial adhesion, specific usage of estrogen cream, follow-up period, recurrence, and side effects [2,4–17]. In addition, few studies compared the efficacy of topical estrogen cream with observation. As a result, it is difficult to accurately evaluate the therapeutic effect of estrogen cream compared to the observation through previous studies. Therefore, this study aims to investigate the efficacy of topical estrogen treatment compared with observation only on the resolution, as well as recurrence, and side effects.

Materials and methods

Study subjects

Prepubertal girls with labial adhesions who visited a pediatric and adolescent gynecologic clinic in Seoul National University Children's Hospital from April 2005 to June 2019 were analyzed. Prepubertal girls from 3 months to 8 years old with labial adhesions that covered at least 25% of the vaginal opening were included. The extent of labial adhesions was directly evaluated by physicians who specialized in pediatric and adolescent gynecology by gentle lateral traction with the frog-leg position. Those who visited only once were excluded because it was difficult to assess the effect of treatment.

Patients who received immunosuppressant treatment or had previously undergone surgical separation were excluded. Patients diagnosed with systemic conditions such as Behcet's disease or Crohn's disease were excluded. Additionally, patients with underlying dermatologic diseases such as atopic dermatitis, contact dermatitis, lichen sclerosis, or herpes infection were excluded. This study was

approved by the institutional review board of Seoul National University Hospital (No. H-1905-058-1032).

Data collection

All baseline characteristics including age at diagnosis, and initial symptoms were collected through retrospective medical records review. Outcomes such as the resolution of labial adhesions, recurrence, and side effects were also collected from medical records. Urinary infection was regarded as the presence of WBC and bacteria in urinalysis.

The primary outcome was the resolution of labial adhesions. The secondary outcomes were recurrence and side effects. The resolution was defined as a case in which adhesions were completely resolved. Recurrence was defined as partial or total recurrence of adhesions. Side effects of treatment included vulvar hyperpigmentation, breast development, vulvar irritation, precocious puberty, and vaginal spotting.

Treatment methods

Whether to treat with topical estrogen cream was decided by the physician's preference, taking the parental request or concerns regarding the side effects into consideration. Topical estrogen was applied to the labial adhesion 0.5 g twice daily for 4 weeks without lateral traction. The estrogen cream was applied using cotton swab, and the extent of application was limited to areas with adhesions. Four weeks period of treatment in the present study was based on the recommended length of 2–6 weeks in previous studies [5,8,9]. Two types of estrogen cream, Premarin® (conjugated estrogens 625µg/g, Pfizer Incorporation, New York, USA) and Esgen® (estropipate 1.5 mg/g, Myungmoon Pharmaceutical Company, Seoul, Korea) were used for treatment. Patients returned to the clinic for assessments of resolution within 6 months after the initial evaluation. All patients were evaluated by the physicians whom they had met at the first visit, and the extent of labial adhesions was assessed with gentle lateral traction with the frog-leg position in the same manner as the previous examination. Patients visited the clinic annually for 3 years after resolution to evaluate recurrence. The condition of labial adhesions, treatment compliance and side effects were evaluated by examination and detailed interview at each visit.

Statistical analysis

Statistical analyses were performed using SPSS software (version 22.0; IBM Corporation). Mann–Whitney test and Fisher's exact test were performed to compare baseline characteristics and treatment outcome of topical estrogen cream with close observation. To investigate the effect of age at diagnosis on outcomes, subgroup analysis was performed by dividing patients into two groups according to the mean value of age at diagnosis (23.2 months).

Results

Medical records of 238 patients with labial adhesions were reviewed. Among them, 92 patients were lost to follow-up,

and the medical records of 4 patients showed insufficient information about treatment methods. A total of 28 patients were excluded according to exclusion criteria. 15 patients were treated with other treatments, such as petroleum jelly, steroid lotion, antibiotics cream, etc. 9 patients received estrogen cream treatment with lateral traction, 2 patients underwent manual separation, and 2 patients were diagnosed with atopic dermatitis. Finally, 114 patients were included in the analysis (Fig. 1). Depending on the presence of treatment, patients were divided into two groups, using topical cream containing estrogen ($n = 94$) versus observation only ($n = 20$).

The baseline characteristics of both groups are presented in Table 1. The estrogen cream group was older on average at the time of diagnosis than the observation group (24.6 ± 19.0 vs. 16.7 ± 15.3 , respectively, $p = 0.037$). However, age at follow-up and duration from diagnosis to follow-up were not significantly different between the two groups. Girls from both groups showed comparable initial symptoms; vaginal irritation, urinary dribbling, dysuria, urinary infection, urinary frequency, and residual urine sense.

Table 2 represents the clinical outcomes of estrogen cream treatment and observation. Girls treated with estrogen cream showed a higher resolution rate of labial adhesions than the observation group (100% vs. 85%, respectively, $p = 0.005$). The recurrence rate was 11.7% in the estrogen group and 0% in the observation group, and side effects were 7.4% in the estrogen group and 0% in the observation group. The rate of recurrence and side effects was statistically similar between the two groups. The average time to recurrence was 288.1 days, and it ranged from 129 days to 412 days.

Estrogen cream showed significantly higher resolution rate in younger age group (100.0% [55/55] vs. 86.7% [13/15], $p = 0.043$), but difference did not reach statistical significance in older age group (100.0% [39/39] vs. 80% [4/5], $p = 0.114$) (Fig. 2). The rate of recurrence and side effects did not differ in both younger and older age groups.

The distribution of side effects depending on the use of estrogen cream is shown in Table 3. Seven patients showed vulvar hyperpigmentation, breast development, or precocious puberty. No patient showed vaginal spotting and vulvar irritation in both groups. One patient treated with estrogen cream showed both vulvar hyperpigmentation and breast development. All forms of side effects did not show significant differences between the two groups.

Discussion

To the best of our knowledge, this is the first study investigating the effects of estrogen cream compared with observation in prepubertal girls with labial adhesions. A considerable resolution rate has been reported in patients treated with topical estrogen cream, compared to manual separation or steroid cream [6,7,11,17]. In the present study, prepubertal girls treated with estrogen cream showed a higher resolution rate than the observation group. However, the resolution rate was only 15% higher in the estrogen cream group than in the observation group.

The mean age at diagnosis was 23.2 months in this study. It was comparable to previous studies, ranging from 10 to

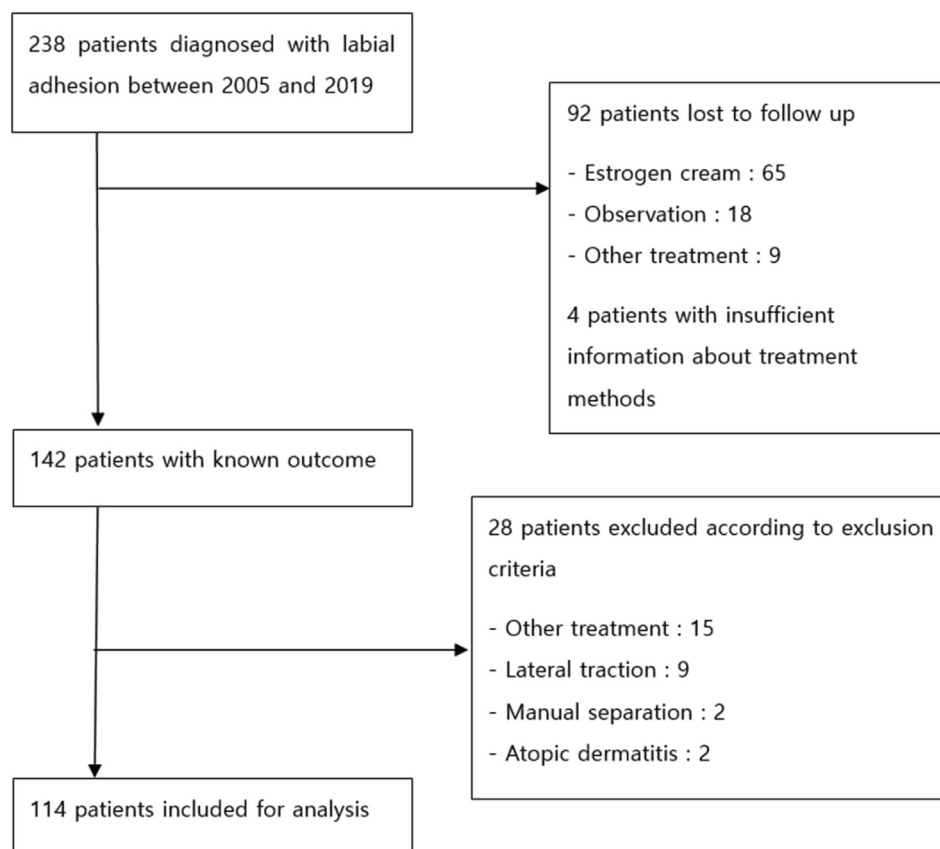


Fig. 1 Flow diagram of patients identified with labial adhesions.

33 months [6,7,15]. According to a demographic study conducted on a Korean population, labial adhesion occurred mainly at 13–24 months of age [18]. Subgroup analysis showed better clinical outcomes of estrogen cream in girls younger than 23.2 months. This implies that girls younger than 23.2 months are more likely to respond to topical estrogen therapy. A possible reason is that the thickness of the skin played an important role in the absorption rate of a topical cream. As reported in previous studies, younger children had thinner skin than older, and the absorption rate of topical steroid cream increased in thinner skin [19,20].

The resolution rates of both groups were higher than in previous reports. Previous retrospective studies reported that the success rate of estrogen cream ranged from 15.4% to 66.6% [5–7,15]. The rate of spontaneous resolution without any treatment was reported as 40% with a follow-up period of 2.6 years [4]. The discrepancy may be attributable to different study cohorts and follow-up periods. Recently, asymptomatic children with minor adhesions are frequently diagnosed due to the generalization of developmental screening tests for infants in South Korea. Thus, it assumed that the present study included a relatively large number of these asymptomatic children. In particular, a

Table 1 Baseline characteristics depending on the use of estrogen cream.

	Estrogen cream (n = 94)	Observation (n = 20)	P value
Age at diagnosis (months)	24.6 ± 19.0	16.7 ± 15.3	0.037
Age at follow-up (months)	27.0 ± 18.9	20.1 ± 15.1	N/S
Duration from diagnosis to follow-up (days)	69.3 ± 126.4	101.5 ± 85.3	N/S
Initial symptoms (total)	21 (22.3%)	3 (15.0%)	N/S
Vaginal irritation	9 (9.6%)	0 (0%)	N/S
Urinary dribbling	5 (5.3%)	0 (0%)	N/S
Dysuria	4 (4.3%)	0 (0%)	N/S
Urinary infection	1 (1.1%)	1 (5.0%)	N/S
Urinary frequency	1 (1.1%)	1 (5.0%)	N/S
Residual urine sense	1 (1.1%)	1 (5.0%)	N/S

Data are presented as mean ± standard deviation or n (%) except where otherwise noted.
N/S not significant.

Table 2 Clinical outcomes of estrogen cream treatment and observation.

	Estrogen cream (n = 94)	Observation (n = 20)	P value
Resolution	94 (100%)	17 (85.0%)	0.005
Recurrence	11 (11.7%)	0 (0%)	N/S
Side effects	7 (7.4%)	0 (0%)	N/S

Data are presented as n (%) except where otherwise noted. N/S not significant.

Table 3 Distribution of side effects depending on the use of estrogen cream.

	Estrogen cream (n = 94)	Observation (n = 20)	P value
Vulvar hyperpigmentation	4 (4.3%)	0 (0%)	N/S
Breast development	2 (2.1%)	0 (0%)	N/S
Vulvar irritation	1 (1.1%)	0 (0%)	N/S
Precocious puberty	1 (1.1%)	0 (0%)	N/S
Vaginal spotting	0 (0%)	0 (0%)	N/S

Data are presented as n (%) except where otherwise noted. N/S not significant.

relatively high percentage of girls improved without any treatment compared to the previous study [4]. It supposes that asymptomatic girls with mild labial adhesions are more likely to require no specific treatment.

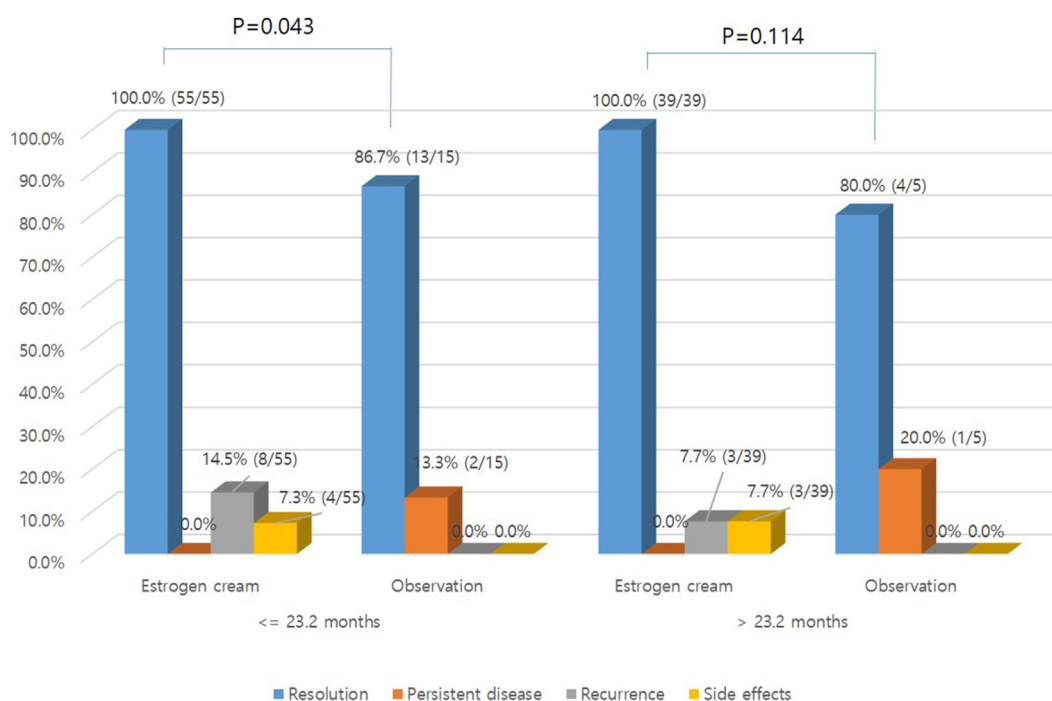
Topical estrogen cream and observation showed 11.7% and 0% of recurrence rates, respectively. The recurrence rate in the present study was lower than that of manual

separation [15]. Unlike manual separation, topical estrogen treatment and observation have no burden of anesthesia. According to previous research, 26 of 138 (19%) girls failed manual separation using topical anesthesia and required surgical separation in the operating room with general anesthesia [2]. Pain is usually not controlled completely with local anesthesia, therefore children can be uncooperative during the procedure. Among girls who failed manual separation, 9 of 26 (34.6%) girls failed due to uncooperativeness [2]. Furthermore, general anesthesia has several complications especially in pediatric patients, from nausea and vomiting to possible harmful effects on the developing brain [21]. Therefore, these complications of general anesthesia in the pediatric population can be burdens for both physicians and parents.

The topical estrogen cream group showed a statistically similar rate of side effects compared to the observation group, but side effects occurred only in children treated with topical estrogen therapy. All side effects of estrogen cream such as vulvar irritation, vulvar hyperpigmentation, breast development, and precocious puberty were resolved after discontinuation [15,16,22,23]. However, parents are usually concerned about side effects, and children sometimes fear and refuse to apply creams to perineum. Therefore, careful prescription is necessary after detailed counseling and patient individualization.

The strength of this study is that the effect of estrogen cream is compared directly with the observation. Most studies compared the effects of estrogen creams with steroid ointments or emollients, manual separation, and surgery [6,7]. Another strength of this study is that accurate evaluation of labial adhesions was possible by a well-trained pediatric and adolescent gynecologist.

The major limitation of this study is the retrospective design and weak statistical power arising from the small sample size of the observation group (n = 20) and its

**Fig. 2** Clinical outcomes of estrogen cream treatment and observation in different age groups.

subgroup (n = 15 or 5). There was the possibility of selection bias in selecting treatment method and loss of follow-up. The possibility of additional treatment at another hospital in observation group could be confounding factor. However, patients who came to the clinic regularly had good compliance. Also, the thickness of labial adhesions was not evaluated because of the absence of corresponding data. It could be bias in evaluating the prognosis of labial adhesions, and further study evaluated the thickness of adhesions is needed. Finally, the follow-up durations after treatment were inconsistent, and short to discriminate between persistence and recurrence of adhesions.

Conclusions

Topical estrogen therapy showed a higher resolution rate than observation in prepubertal girls with labial adhesions, especially in younger patients. However, only children treated with topical estrogen therapy experienced side effects and recurrences without significant difference compared to the observation group. A well-designed prospective randomized controlled trial is needed in the future to discriminate which patients can benefit from treatment with topical estrogen therapy because observations also have shown considerable outcomes in prepubertal girls with labial adhesions.

Ethics approval and consent

This study was approved by the institutional review board of Seoul National University Hospital (No. H-1905-058-1032).

Conflicts of interest

The authors declare that there is no conflict of interest.

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