

Serum Estradiol Levels in Infants with and without Labial Adhesions: The Role of Estrogen in the Etiology and Treatment

Musa Kazım Çağlar, M.D.

Department of Pediatrics, Faculty of Medicine, Gaziosmanpaşa University, Tokat, Turkey

Abstract: No strong evidence has been found that estrogen levels in girls with labial adhesions are lower than in girls without. Therefore, this study was based on the determination of estradiol levels in girls with and without labial adhesions in order to show whether a considerable difference exists between these two groups. Serum estradiol levels were measured in 59 infants with labial adhesions and in 60 healthy infants. No significant age difference was seen between affected infants and controls, with a mean age of 12.7 and 12.4 months, respectively. Serum estradiol levels ranged from 6.5 to 14.3 pg/ml (10.27 ± 1.897) in those with labial adhesions and from 6.4 to 15.1 pg/ml (10.47 ± 2.006) in controls, a statistically insignificant difference ($p = 0.5764$). When taking into consideration the effect of estrogen on wound healing and the fact that the difference in estrogen levels between the infants with and without labial adhesion is not significant, it is concluded that hypoestrogenism does not take place in the development of labial adhesions, but that creams containing estrogen might have a beneficial effect on healing after mechanical separation of the adhesion by enhancing wound reepithelialization.

The etiology of labial adhesion is not known, but it has been suggested that it is related to the low levels of estrogens in the prepubertal child. Usage of estrogen creams in the treatment of labial adhesion has been based on the fact that levels of estrogens in prepubertal girls are low (1–4). These creams are expected to lyse the adhesion within a time period of 1–8 weeks (1,2,4,5). Parents have been advised to use or continue estrogen creams after mechanical separation of the adhesion for a while. In a recent study (4), the mean duration of estrogen treatment was 2.4 months (range, 1–3.5 months). However, no

strong evidence exists that estrogen levels in girls with labial adhesion are lower than in those without. Therefore, this study was undertaken to determine estradiol levels in girls with and without labial adhesions in order to show whether a considerable difference can be found between these two groups.

MATERIALS AND METHODS

A total of 59 female infants with labial adhesions were prospectively identified from Efe Alp Medical Center

Address correspondence to Musa Kazım Çağlar, M.D., Abant İzzet Baysal Üniversitesi, İzzet Baysal Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Bolu, Turkey, or e-mail: mkc@ttnet.net.tr.

and Pediatric Ambulatory and Preventive Medicine Services of Gaziosmanpaşa Medical Faculty between January 2000 and May 2005. Their age ranged from 4 to 24 months. Sixty female infants without labial adhesions, whose age ranged from 4 to 24 months, were enrolled in the study as a control group. Informed written consent was obtained from all patients' parents for the performance of estradiol measurement on their infant and the aim of the study was explained.

The diagnosis of labial adhesion was made by visual inspection of the genitalia. Infants with minor degrees of labial adhesion (< 25%) were excluded.

Student's *t*-test was used for statistical analysis of the data. A value of $p < 0.05$ was considered significant.

RESULTS

No significant age difference was found between the affected infants and controls, with a mean age of 12.7 and 12.4 months, respectively. Serum estradiol levels ranged from 6.5 to 14.3 pg/ml (10.27 ± 1.897) in those affected and from 6.4 to 15.1 pg/ml (10.47 ± 2.006) in controls. The difference was statistically insignificant ($p = 0.5764$).

DISCUSSION

Adhesion of the labia is a condition in which the labia minora are fused over the vestibule. It is a common disorder in the female pediatric population and has been estimated to occur in 0.6–3.0% of prepubertal girls (1,6). Labial fusion has only rarely been noted at birth, and most authors regard it as an acquired condition (7). Physiologic fusion is postulated to arise in infants and young children with endogenously low estrogen levels who may or may not have an associated inflammatory condition such as vulvovaginitis (8).

The incidence of labial agglutination is most frequent in younger prepubertal girls (age 3 months to 6 years) with a peak incidence at 13–23 months of age (7,9). Although adhesions occur less commonly after age 6, adhesions beginning at any age may persist or recur until puberty. Most adhesions resolve or do not occur after endogenous estrogen production at puberty. Those adhesions that occur after puberty are customarily the result of surgical procedures (such as episiotomy) or may be associated with vulvar trauma.

Estrogen levels are much higher in infants less than 3 months of age and in children older than 5 years of age than at other times, and this may explain why labial fusion is uncommon at these ages (10).

Reports suggest that over 80% of occurrences spontaneously resolve within 1 year (6). Virtually all lesions

resolve spontaneously with the onset of puberty, and there are only few reports of persistence requiring treatment after the onset of puberty in adolescents (7,11). Once the reproductive years are reached, labial adhesions are extremely unusual (12), even if inciting factors such as active herpes lesions are present, until the postmenopausal period.

All reports summarized above have mentioned the relationship between lower estrogen levels in infants compared with those in pubertal or postpubertal girls and the high incidence among infants and young children. In light of this relationship, estrogen creams have been widely used in the treatment of labial adhesions. However, neither how estrogen lyses the membranous tissue between the labia minora nor whether lower estrogen levels exist in infants and children with labial adhesion than in those without labial adhesion has been shown.

In the current study, the estrogen level of infants with labial adhesion was not lower than the level in those without adhesions. This result indicates that hypoestrogenism is not responsible for the development of labial adhesion. It is obvious that a great difference exists when comparing the estrogen level of infants with the level of pubertal children. The possible reasons why labial adhesions resolve spontaneously with the onset of puberty might support the mechanism of hypoestrogenism in the etiology of labial adhesion, but controversy still exists about the fact that reports also suggest that over 80% of occurrences spontaneously resolve within 1 year. In addition, the combination of isolated premature thelarche and labial adhesions has been recently reported (13). Premature thelarche, a benign condition that affects young girls, has been associated with elevated estrogen levels. To the contrary, labial fusion, a common pediatric gynecologic problem, is believed to be associated with low estrogen status. These two conditions are not known to coexist in the same patient, which suggests the existence of other factors besides hypoestrogenism in the etiology of labial adhesions. Another hypothesis is that different estrogen receptor levels exist in affected and unaffected infants.

Heparin-binding epidermal growth factor-like growth factor (HB-EGF) enhances reepithelialization in wounds. Estrogen is known to promote cutaneous wound repair. Recently, it has been shown that estradiol may enhance wound reepithelialization by promoting HB-EGF production in keratinocytes (14). In another report, the effect of estradiol on the proliferation of neonatal keratinocytes was investigated and it was found that the proliferative effect of estradiol required the availability of functional estrogen receptors and was abrogated by anti-estrogen administration (15).

Episodes of vulvovaginitis may be primary or secondary events leading to vaginal discharge or urinary tract infection, with apposition of the denuded immature labial epithelium resulting in agglutination of the labia minora (1). This situation is most likely to occur in infants and young children in diapers due to the fact that the labia minora lie in close apposition, particularly posteriorly. Episodes of vulvitis may be low grade, easily overlooked, and simply attributed to diaper rash (16). If this mechanism is true for the development of labial adhesion and if hypoestrogenism takes place in the event, it is expected that low estradiol, which is necessary for wound reepithelialization because it promotes HB-EGF production in keratinocytes (14), should cause more adhesion. In such an instance, hypoestrogenism in infants, compared to the pubertal and postpubertal periods, can only explain why most of the infants do not develop labial adhesion. Therefore, relative hypoestrogenism should not be responsible for the development of labial adhesion.

A reverse correlation exists between age and the incidence of labial adhesion, even though no significant change occurs at the level of estrogen among children till puberty (17). It is well known that children progress beyond the use of diapers after the age of 2–3 years, which results in less diaper dermatitis and vulvovaginitis. After that age, they also become more active and frequently sit down and stand up during the day, which causes frequent opening of the labia minora. These events probably prevent the apposition of the denuded immature labial epithelium resulting in agglutination of the labia minora. These events are also valid for adults, even though estrogen level increases after puberty.

Topical estrogen application has been proposed in most reports for first-line treatment of labial adhesion without an explanation of how it works. Generally, the cream is applied with gentle traction to the site by the provider or the patient herself, or a cotton-tipped swab is used to apply the medication against the midline raphe. In a recent study (4) it was reported that the mean duration of estrogen treatment was 2.4 months (range, 1–3.5 months). Both the mechanical effect and the softening effect of substances other than estrogen in cream compositions should be taken into consideration when evaluating the success rate of topical applications. In light of the above evidence, estrogen cream might have no lysis effect on separation of the adhesion, but most probably improves healing after mechanical separation of the adhesion (14,15).

Absence of lab during the neonatal period might be attributed to the transfer of maternal estrogen to newborn infants. However, none of the infants developed intrauterine diaper dermatitis and vulvo-

vaginitis. Furthermore, the development rate of labial fusion is rather low and most authors regard it as an acquired condition (7).

In conclusion, when taking into consideration the effect of estrogen on wound healing and the fact that no significant difference of estrogen level was found between the infants with and without labial adhesion, it is concluded that hypoestrogenism does not take place in the development of labial adhesion, but creams containing estrogen might have a beneficial effect on healing after mechanical separation of the adhesion, by enhancing wound reepithelialization.

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