

# Environmental Exposure Assessment in Premature Thelarche Cases in the Well-Child Outpatient Clinics

## Sağlam Çocuk Polikliniğinde Prematür Telarş Olgularında Çevresel Maruziyet Değerlendirilmesi

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### ABSTRACT

**Objective:** Breast development, without any signs of sexual maturation, in girls younger than 8 years is almost universally accepted as premature thelarche (PT). Prevalance and etiology are clearly unknown.

We designed a study to follow up girls who had unilateral or bilateral PT and to show regression after stopping care products.

**Material and Methods:** The design of study was retrospective Children and their parents were enrolled into the study from September 2016 to February 2017. All children had one common symptom which was unilateral or bilateral breast development not associated with pubic or axillary hair, vaginal bleeding or other sign of sexual maturation, at the well child visit. In these children with no organic causes, monitoring was taken after stopping of care products.

**Results:** Twenty-eight girls were evaluated, and mean age was 2.3 years ( $\pm 0.3$ ). Noone had a chronic disease. All cases identified as Tanner stage-2 and continued to have early breast development on follow-up. 18 (64.2%) girls had unilateral breast development. After stopping care products, both groups had regression in six months.

**Conclusion:** Currently there are no predictive tests to show the risk of breat development of early or puberty precoccus. Children may be exposed to much more diagnostic tests because of overuse products. Physician must be aware of these products. Families may use a minimum amount of care products for their children.

**Key Words:** Care products, Premature Thelarche

### ÖZ

**Amaç:** Sekiz yaşından küçük kız çocuklarında cinsel olgunlaşma belirtisi olmadan meme gelişimi, neredeyse evrensel olarak prematür telarş (PT) olarak kabul edilir. Prevelans ve etioloji açıkça bilinmemektedir.

Çalışmamızda, unilateral veya bilateral PT olan kız çocuklarını izlemine yapmak ve bakım ürünlerini kullanmayı bıraktıklarındaki gerilemeyi göstermeyi amaçladık.

**Gereç ve Yöntemler:** Çalışma retrospektif planlandı. Eylül 2016 ile Şubat 2017 tarihleri arasında izlemde olan prematür telarş tanısı almış çocuklar ve ebeveynleri çalışmaya dahil edildi. Sağlam çocuk izleminde olan pubik veya aksiller kıllanma, vajinal kanama veya diğer cinsel olgunlaşma bulgusu ile ilişkisi olmayan unilateral veya bilateral meme gelişimi olan tüm çocukların tek semptomu vardı. Organik bir neden saptanmayan bu çocuklarda, bakım ürünleri kesildikten sonra izleme alındı.

**Bulgular:** Yirmisekiz kız çocuğu değerlendirildi ve ortalama yaş 2.3 ( $\pm 0.3$ ) yılı. Çocukların kronik hastalığı yoktu. Tüm vakalar Tanner evre 2 olarak tanımlandı ve erken meme gelişimi nedeniyle takibe alındı. 18 (%64.2) kız çocuğun unilateral meme gelişimi vardı. Bakım ürünleri kullanmayı kestikten sonra, unilateral ve bilateral meme gelişimi olan çocuklarda 6 ay içinde gerileme oldu.



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**Sonuç:** Günümüzde, PT ve Puberte prekoks veya erken meme gelişimi riskini gösteren herhangi bir öngörücü test yoktur. Çocukların, bakım ürün kullanımı nedeniyle birçok teste maruz kalabilir. Klinisyenler bu türlü ürünler yönünden dikkatli olmalıdırlar. Aileler çocukları için bakım ürünlerinin kullanım miktarını asgari düzeyde tutabilirler.

**Anahtar Sözcükler:** Bakım ürünleri, Prematür telarş

## INTRODUCTION

Breast development, without any signs of sexual maturation, in girls younger than 8 years is almost universally accepted as premature thelarche (PT) (1-2). Although available data of prevalence and etiology in different countries are still scarce and unclear, possible mechanism can depend on transient activation of the hypothalamo-pituitary-gonadal (HPG) axis and increased estradiol ( $E_2$ ) secretion (e.g. ovarian cyts), increased  $E_2$  sensivity of breast tissue (3-4). Prevalance of early breast development in school-aged girl is indicated by epidemiologic evidence (5). This may be triggered by in utero and childhood exposure to estrogen-like compounds in the environment (6). This environment includes endocrine disruptors which are presented by pesticides, plastic, shampoo, scented products and other care products (7).

Van winter et al.(8) found in the first year of life the incidence of PT was the highest, falling in the second, third and fourth years, and after fifth year increasing slightly. Although some studies showed that some of these may progress to be puberty precoccus (PP) at a variable rate, some studied girls who had PT, had normal puberty (8-10). The pathophysiology of PT is still unknown (11). In these periods girls may have normal bone age, normal laboratory tests and pelvic USG. Therefore, we designed a study to follow up these girls who had PT and environmental effect, which were care products, shampoos and scented products.

## MATERIALS and METHOD

This study was carried out among the well-child visit groups with ages of 2 and 5 years. The design of study was retrospective. Children and their parents were enrolled into the study from September 2016 to February 2017. All children had one common symptom which was unilateral or bilateral breast development not associated with pubic or axillary hair, vaginal bleeding or other sign of sexual maturation, at the well child visit.

After obtaining informed consent, children and their parents were interviewed by their pediatrician. Same pediatrician examined the children and then obtained information about using care products, shampoos, scented products, number of months breastfeeding. Care products involved powders, lotions, soaps, nail polish, hair products and diaper rash creams.

Pediatrician examined the children first, then breast development was staged according to Tanner criteria (1). This staging was

assessed by visual inspection and palpation. Then parents were informed about this product. Children who had chronic disease and were with true PP at diagnosis were excluded. All children were term-born and their birth weight were between 2500 gr and 4000 gr. Too small and large ones for gestation age were excluded. Bone age (BA) values and calculation of the BA to chronological age (CA) ration (BA/CA ratio) were evaluated using Greulich and Pyle Method (12). Results of hormonal assesment including basal serum luteinizing hormone (LH), follicle-stimulating hormone (FSH) and estrodiol ( $E_2$ ) were recorded. Pelvic ultrasonography (USG) and breast USG evaluations were done using same ultrasound machine by the same experienced pediatric radiologist. Ovarian volume, endometrial thickness and uterine diameter were recorded. Mean ovarian volume was accepted to indicate prepubertal internal female genitalia (13). They were followed up for repeated visual inspection and palpation for breast development during well child visit, minimum of three months after initial evaluation. Height and weight standard deviation score were calculated for all children with Turkish growth charts (14). The laboratory and radiologic finding data were obtained from hospital database. New tests were not needed for these children.

This study was approved by Baskent University Institutional Review Board and Ethics Committee (Project no:KO 16/349). An informed consent to participation in the study was signed by parents at enrolment.

**Data Analysis:** The relationship between demographic, medical and environment factors and PT was examined using Fisher's exact test for binary variables, Student's test for normally distributed continuous variables, and Wilcoxon rank sum test for non-normally distributed continuous variables. Interquartile ranges reflect 25<sup>th</sup> to 75<sup>th</sup> percentile values.

## RESULTS

Twenty-eight girls were evaluated and median age was 2.3 years ( $2.3\pm 0.3$ ). None of them had a chronic disease. All cases identified as Tanner stage 2 and continued to have early breast development on follow-up. 18 girls had unilateral breast development. The number of girls aged 2-5 years who were examined in our clinic during the study period was 402. In this age range, which PT was rare, the incidence was 6.96%.

Thelarche had started in a month of coming well child visit. All of them were born between 38 and 40 weeks of gestation. Birth weight was similar in all cases (mean  $3325\text{ gr}\pm 124$ ). Height and weight were identified in 50-75 percentile. All growth velocities were normal for age. Group didn't have any obese and

malnutrition. Evaluation of breast USG performed 2 of all cases were reported immature breast tissue. Then 24 of all girls had prepubertal pelvic USG findings. All of them had uterin volume  $\leq 2$  ml or lenght  $\leq 34$  mm and prepubertal, tubular-shaped uterus. Bone age was performed for all cases and BA/CA rate was 1.1. Their bone ages were within 1 year of chronologic age. Unilateral and bilateral group had similar BA/CA ratio. None of them had pathologic bone age. The differences in the prevalence of Tanner stages and BA/CA ratio between unilateral and bilateral groups were not statistically significant. Birth weight, weight, height, median age, breastfeeding duration and using a number of products were not statistically significant between two groups. After the use of these products stopped, mean time for regresion was  $4.5 \pm 1.1$  months and median value was 2.9 months. 18 girls had regressive PT at 3 months and 20 of them at 6 months. Hormone levels performed 17 of all were normal. Their estrodiols levels were "not detectable" or close to the detection limit. LH and FSH's datas showed that they were in the prepubertal range.

Number of products were mean 2 (min:1-max:4). These products were asked to families. Most of them used sceented soap, powder, lotion, diaper rash cream and care products. The contents of these products were examined. After the interview, all of them stopped using these products. At the third and sixth-month visits, same pediatrician examined and observed that the breast development stopped for all them.

## DISCUSSION

The retrospective study showed that premature breast development, between 2 and 5 years, might be influenced by the envorinmental exposure to beauty perception and as a result of this, parents overuse these products which causes transient breast development. In the United States since 1994, some cosmetic and hair products contained 1.6 g of estrogen per 100 g. The products containing estrogen appllied to the breast area or used as a topical way for scalp or diaper rash, have resulted in the erarly development of sexual maturation (15,16). Many man-made and natural chemical products have been described and can distrust estrogen signaling. Exposure to phytoestrogens derived from plant sources, such as lignans, isoflavinoids, genisteins, lavender oil and tree tea oil may result in PT seen in children (17).

This study was designed to study the overusage of beauty and care product. As it is known, many external factors affect PT. In this study, no changes were made to the patients' attitude, behavior and lifestyle. Curfman et al.(18) showed that, no statically significant relationship was found between PT and envorinemnt exposure which were prenatal and natal food, care-beauty product and plastics products They had small number of PT cases.

A few data have been reported about prevalance of PT. PT is much more seen in two periods. One is the first years of life and other one is after 6 years old. 10-18 % of children who were after 6 years, may progress to puberty precoccus. First wide data, Van Winter et al. (19) reported that an incidence of PT was less than 0.1/1000 among children 2 to 8 years of age. Curfman et al. (18) showed that PT prevalance was 4.7 %. In Turkish population, at the age of 4 to 8, it was reported % 8.9. (2). In Denmark, PT was seen 3 % among the 8 years (20). The prevalence of PT can be affected by ethnicity. We didn't give a prevalence but we aimed to show PT in age of 2 to 5 years age. The number of girls aged 2-5 years who were examined in our clinic during the study period was 402. In this age range, which PT was rare, the incidence was 6.96 %.

In this study, healty children who had a normal weight, height and body mass index (BMI) were included. Rosenfield et al. (21) showed that non-hispanic girls with normal BMI were performed and PT prevalance was 1.3 %. That study reported the girls with BMI above the 85th percentile and prevalence of PT was 12.3 %. The effect of BMI on thelarche is related (21). On the other hand, the group in this study didn't have SGA, because the same studies linked SGA to the timing of puberty (22,23). Anthropometric and clinical characteristics were similar with previous studies (24,25). In this study, BA/CA ratio was 1,1. Although prematurity and SGA was reported in the PT groups and PT was more prevalent in children born SGA, the group in this study didn't have SGA and premature (11,18,26). Curfmann et al.(18) showed the prenatal exposure (soy products, fish, and beef) and childhood food exposure (fish, beef and organic foods) weren't associated to PT. These exposures were not asked during this study and only the care products were investigated. Number of using products were median 2. Most of them used scented soap, powder, lotion, diaper rash cream and care products. Although De Vries et al. (11) found in almost half of their group had PT at birth, the study group in this study didn't have PT in two years of the life.

Parents concerned about their children's bath, care and diapers. They feel obligated and want for a good looking children. Early breast development and puberty are a concern too. All parents are afraid of PT and concern about puberty precoccus. One clinical importance of PT is the potential relationship with central precocious puberty. More recent studies show a higher percentage of progression, ranging from 14-23 (26,27). Pasquino et al. (24) in a cohort study, found that 100 girls with PT, 14 progressed to central early or PP. In this study, regresion in all girls was found. Between unilateral and bilateral breast development group, regression periods were not statistically significant.

In this study, all children had normal bone age and prepubertal hormone levels. FSH, LH an  $E_2$  were in normal range. None of them had abnormal pelvic USG evaluations, as previously shown by others, and everyone had immatur breast tissue

which was showed by breast USG (11). In this study, after quitting all products or using less if necessary, regression of the breast development was shown. Only 8 of them used less. At first, all of them were evaluated tanner stage 2. After six months, none had breast development. The limitation in this study was the number of group and not asking the food habitus. Ethnicity may influence but parents have care about body habitus and cause transient PT. One of the other limitations is that the length of the follow-up period is relatively short in some of our group.

In conclusion, in this age group which was rare the incidence of PT was found to be 9.45%. After organic reasons have been ruled out, it was thought that the most important reason was the external exposure. Children may be exposed to much more diagnostic tests because of overuse products. Physician must be aware of these products. Families may use a minimum amount of care products for their children.

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