Research Article

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The Impact of Antibiotic Use on Puberty.

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ABSTRACT

Introduction: Antibiotic exposures in early life may affect weight by altering the gut microbiota, potentially increasing the likelihood of early pubertal maturation.
Objective: To examine whether repeated antibiotic exposure by age eight is associated with early pubertal maturation.
Design, Setting, and Participants: This research is a retrospective study involving 122 children. There were sixty-nine cases with early pubertal development (pubertal group), in which fourteen cases (20%) were started with leuprolide acetate. There were fifty-three cases without pubertal development (control group). The antibiotics prescriptions were evaluated retrospectively in both groups using electronic health records. The first age antibiotic prescription, the type of antibiotics, and the total number of antibiotic prescriptions were recorded.
Results: There were no significant differences between the groups regarding the first-age antibiotic prescription, the type of antibiotics, and the total number of antibiotic prescriptions.
There was no correlation between the number of antibiotics prescriptions, the first-age antibiotic prescription, and levels of LH, FSH, E2, and the difference between bone age and chronological age.
Conclusion: Although environmental antibiotic exposure may trigger precocious. puberty, the use of antibiotics prescribed for treatment may not affect precocious puberty.

Keywords: *Antibiotics, Early Puberty, Bone Age, Bone Age-Chronological Age Difference (ΔKY-TY).*

INTRODUCTION

Antibiotics are the most commonly prescribed drugs in the pediatric age group, reducing morbidity and mortality associated with bacterial infections. Antibiotic use has increased, and bacterial resistance and microbiota dysbiosis have become substantial concerns [1].
Precocious puberty in girls is characterized by breast development and pubic hair growth before the age of eight, with idiopathic central precocious puberty being the most common type. In these cases, the hypothalamic-pituitary-gonadal (HPG) axis has activated prematurely [2].
Although the exact reason for the early activation of the HPG axis is not clearly understood, a complex interaction of metabolic, nutritional, and hormonal factors resulted [3].
The human microbiota is impressed by diet and antibiotics. The metabolites of gut microbiota can impact the secretion of sex hormones through pathways involving the immune system, chronic inflammation, and the gut-brain axis, which are some neuroendocrine axis [4]. The girls with precocious puberty have an overproduction of bacterial species in their gut microbiota that produce metabolites capable of activating the HPG axis [5].

Antibiotic therapy reduces the diversity of gut microbiota species, leading to a condition known as dysbiosis, which causes antibiotic resistance and diarrhoea in the short term and obesity, asthma, and inflammatory bowel disease in the long term. However, there were no studies suggesting that antibiotic use triggers precocious puberty. In our country, the use of antibiotics and antibiotic prescriptions is frequent. The incidence of precocious puberty is also increasing [6].
While the role of genetic and environmental factors is partially known, the impact of antibiotics used for treatment purposes is not clear in pubertal maturation. This study aimed to evaluate the contribution of antibiotic use to the development of early pubertal symptoms. Additionally, we sought to answer a common question asked by parents in pediatric endocrinology practice: Is there a relationship between the early onset of pubertal symptoms and the use of multiple antibiotics at an early age?

METHODS

A total of 122 girls aged 6 to 8 years attended the Pediatric Endocrinology Clinic at Kayseri City Hospital. These girls underwent an examination by a pediatric endocrinologist. Among them, 69 girls exhibited Tanner stage ≥ 2 breast

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development (the pubertal group), while 53 girls had no breast development (the control group). Medical records were retrospectively reviewed. The study protocol was approved by the Kayseri City Hospital Clinical Research Ethics Committee under reference number 949 and conducted by the Helsinki Declaration.

Exclusion criteria encompassed malnutrition (defined as a body mass index below -2 SD), chronic illnesses necessitating regular medication, organic etiologies of precocious puberty, and male gender.

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Anthropometric measurements (weight, height, body mass index, and standard deviation scores [SD]) and pubertal stages were analyzed using medical records [7]. Additionally, factors such as birth weight, gestational age, duration of breastfeeding, maternal height, paternal height, age at first maternal menarche, and maternal BMI were evaluated.

In patients with breast development, bone age, the difference between bone age and chronological age, pelvic ultrasound findings, and levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol (E2) were recorded. For both groups, the age at first antibiotic prescription, the number and types of antibiotics prescribed, and confirmation of their use were also recorded.

Anthropometric measurements were conducted in the morning under fasting conditions, with the child barefoot and without outer garments. Stature was assessed using a Harpenden stadiometer (Holstein Limited, Crymych, Dyfed, U.K.), which offers a precision of 0.1 cm. Concurrently, body mass was determined using a SECA scale (GmbH & Co. KG, Hamburg, Germany) with an accuracy of 0.1 kg."

The pubertal staging was meticulously conducted by the pediatric endocrinologist employing the Marshall and Tanner method [8].

Bone age was determined through left wrist radiography by the Greulich and Pyle atlas [9].

In patients presenting with breast development, those exhibiting an estradiol level exceeding 9 pg/ml, bone age surpassing chronological age, and a GnRH stimulation response (1h LH ICMA ≥ 5 mIU/ml) were diagnosed with central precocious puberty. Gonadotropin-releasing hormone therapy was initiated if pelvic ultrasonography revealed a uterine height exceeding 35 mm and an ovarian long diameter greater than 20 mm [10] [11].

Statistical Analysis

Data were analyzed utilizing IBM SPSS Statistics version 24.0. Descriptive statistics encompass mean values, standard deviations, frequencies, and percentages. Parametric data comparisons between groups were performed using Student's t-test. Non-parametric data were analyzed using the Mann-Whitney U test. The Pearson Chi-Square test was employed for the assessment of categorical variables. Relationships between variables were examined through Pearson or Spearman correlation analyses. Statistical significance was set at a p-value of <0.05. A power analysis conducted with G*Power software established that, with a confidence level of 95% (1-α), a test power of 81% (1-β), and an effect size of 0.50 (medium effect size according to Cohen's criteria), a sample size of 52 per group was required for independent sample t-tests."

RESULTS

The clinical, laboratory and radiological characteristics of the cases are delineated in Table 1. Amoxicillin-clavulanic acid emerged as the most frequently prescribed antibiotic. Antibiotics were administered to all cases, with a mean prescription rate of 20.4 ± 12.9 per case. The pubertal group exhibited significantly higher values in terms of weight, weight standard deviation (SD), body mass index (BMI), BMI SD, the difference between bone age and chronological age (ΔKY-TY), and luteinizing hormone (LH) levels ($p < 0.05$). There were no discernible differences between the groups concerning the age at first antibiotic prescription, the total number of antibiotics prescribed, or the number of cases receiving antibiotics within the first six months, first year, or two years of life. Furthermore, the types and quantities of antibiotics prescribed were no significant differences between the groups (Table 2).

Adjustments for age at first antibiotic prescription, the number of antibiotics prescribed, and BMI revealed no statistically significant correlations (Table 3).

Fourteen cases (11%) were diagnosed with idiopathic central precocious puberty and were initiated on leuprolide acetate treatment. No significant differences in antibiotic prescription data were observed between those who received leuprolide acetate and those who did not (Table 4).

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Table 1. Clinical Laboratory and Radiological Data of Subjects.

	Pubertal (n=69)	Control (n=53)	p
Age, Years *	7.44 (6-7.99)	7.39 (6-7.99)	0.395
Duration of Breastfeeding, Months *	18 (0-36)	12.5 (0-30)	0.718
Age at Mother's First Menstruation, Years *	13 (10-140)	12 (9-16)	0.167
Maternal BMI, kg/m²	27.8 ±5.5	29.2 ±5.94	0.358
Target Height, cm	160.3 ±5.52	161.2 ±5.43	0.549
Target Height, SD	-0.46 ±0.94	-0.30 ±0.91	0.562
Weight, kg *	30 (15.4-44.8)	25 (15.1-51.15)	0.015
Weight, SD *	1.40 (-2.15-3.79)	0.44 (-2.54-4.90)	0.032
Height, cm	126.1 ±6.9	124.2±7.9	0.162
Height, SD	0.59 ±1.12	0.34 ±1.28	0.250
BMI, kg/m² *	18.56 (13.2-26.3)	16 (13.17-30.27)	0.030
BMI, SD	0.9 ±1.27	0.41 ±1.31	0.039
Basal FSH, mIU/L *	1.53 (0.33-6.57)	1.22 (0.1-4.38)	0.158
Basal LH, mIU/L	0.3 (0.1-3.4)	0.3 (0-0.5)	0.031
Bazal E2, pg/ml*	5 (5-42)	5 (0-26.3)	0.911
Bone Age, years*	8 (5.8-11)	7.8 (4-8.8)	0.053
ΔBA-CA, years*	0.61 (-1.55-3.07)	0.4 (-2.62-1.27)	0.021

* Non-parametric Test

Abbreviations:BMI: Body Mass Index; SD: Standard Deviation; FSH: Follicle Stimulating Hormone; LH: Luteinizing Hormone; E2: Estradiol; BA: Bone Age; CA: Calendar Age

Table 2. Antibiotic Usage Data of Groups.

	Pubertal (n=69)	Kontrol (n=53)	p
Timing of Exposure to Any Antibiotics			
Age at Start of Antibiotic Use, Years *	0.73 (0.08-5.64)	0.72 (0.2-6.15)	0.943
Number of Antibiotic Courses per Case *	17 (2-53)	17 (3-78)	0.896
% Starting Antibiotics Before 6 Months **	21 (30)	13 (24)	0.471
% Starting Antibiotics Before 1 Year **	29 (42)	23 (43)	0.880
% Starting Antibiotics Before 2 Years **	59 (85)	45 (84)	0.926
Type of Antibiotics			
Penicillins (%)**			
None	-	-	0,740
1-3	7 (10.3)	7 (13)	
4-6	12 (17.3)	11 (20.7)	
>6	50 (72.4)	35 (66)	
Macrolides(%)**			
None	10 (14.4)	10 (18.9)	0.876
1-3	37 (53.6)	25 (47.1)	
4-6	13 (18.8)	10 (18.9)	

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>6	9 (13.2)	8 (15.1)	
Cephalosporins (%)**			
None	11 (16)	6 (11.3)	0.162
1-3	27 (39)	21(39.7)	
4-6	14 (20.4)	19 (35.8)	
>6	17 (24.6)	7 (13.2)	
Metronidazole (%)**			
None	32 (46.3)	29 (54.7)	0.580
1-3	31(44.9)	19 (35.9)	
4-6	5 (7.3)	5 (9.4)	
>6	1 (1.5)	-	
Trimethoprim sulfometakszaol (%)**			
None	54 (78.3)	46 (86.8)	0.304
1-3	13 (18.8)	7 (13.2	
4-6	2 (2.9)	-	
>6	-	-	

*Non-parametric test

** Chi-square test

Tablo 3. Correlation between the age at first antibiotic prescription and the number of antibiotics prescribed

	Age at first antibiotic prescription, years	**Number of antibiotics prescribed, n**
LH, mIU /L	r=0.013 p=0.946	r=-0,177 p=0.544
FSH, mIU /L	r=0.146 p=0.451	r=-0.138 p=0.475
E2, pg/ml	r=0.08 p=0.968	r=0.040 p=0.835
ΔBA-CA, years*	r=0.137 p=0.479	r=-0.307 p=0.105
Number of antibiotics prescribed, n	r=-0.170 p=0.378	-

* Adjusted for BMI and age

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Table 4. Antibiotic data of patients started on leuprolide acetate

	Leuprolide acetate initiated (n=14)	Leuprolide acetate not initiated (n=55)	p
Number of antibiotic prescriptions, n	16.5 (5-53)	18 (2-50)	0.858
Age at first antibiotic prescription, years	0.79 (0.12-3.97)	0.72 (0.08-5.64)	0.654
Percentage of cases prescribed antibiotics before the age of one, %	9 (64)	31 (56)	0.592
Percentage of cases prescribed antibiotics before the age of two, %	12 (85)	47 (85)	0.980

DISCUSSION

This study evaluates the impact of antibiotic use for treating upper respiratory infections, urinary tract infections, and similar conditions on the early development of pubertal signs. We assessed the age of the first antibiotic prescription, the total number of antibiotics prescribed, and the types of antibiotics used in girls with and without breast development before the age of eight. No statistically significant differences were found between these two groups.

The prevalence of early puberty in children is showing a marked and rapid increase [12]. Genetic factors, rising obesity rates, and endocrine disruptors are contributing to the early onset of pubertal signs. The effects of antibiotics on early pubertal development remain contentious [13] [14] [15] [16].

Between 2014 and 2017, a program was implemented in Turkey that banned over-the-counter antibiotic use in 2015 and initiated public awareness campaigns to reduce outpatient antibiotic use. Consequently, daily antibiotic usage decreased from 42.2 daily doses per 1,000 patients in 2011, to 40.4 daily doses per 1,000 patients in 2014, and further to 35.25 daily doses per 1,000 patients in 2017 [17].

In our study, an average of 2.8 antibiotic prescriptions per patient per year was recorded (2.7 prescriptions/year for the pubertal group and 2.9 prescriptions/year for the non-pubertal group).

Early puberty is a complex process influenced by obesity and endocrine disruptors. Antibiotic use before the age of four and during pregnancy has been reported to increase the risk of obesity[18]. Li et al.'s study did not associate antibiotic use with obesity but argued that infections during infancy contribute to increased obesity risk [19].

Despite the pubertal group being more obese, no differences in antibiotic use or types of antibiotics were found compared to the non-pubertal group.

The microbiota-gut-brain axis regulates intestinal neuronal, endocrine, and immunological pathways, affecting the central nervous system. Huang et al. demonstrated higher levels of Bifidobacterium, Balutia, and Streptococcus species, as well as tetracycline biosynthesis pathway activation, in girls with precocious puberty, suggesting that antibiotic exposure could be a factor [14].

Recent studies have shown that gut microbiota influences sex hormones and affects the initiation of the HPG axis. In rat models of obesity-related early puberty, decreased production of short-chain fatty acids in the gut microbiota was observed, which could be mitigated by supplementing with short-chain fatty acids, thus delaying the development of the HPG axis [20].

Antibiotics are widely used in medical treatment as well as in agriculture [21].

Residual antibiotics are commonly found in environmental and animal-derived foods, accumulating in humans through the food chain. Elevated levels of fluoroquinolones and tetracyclines have been detected in the urine of children with precocious puberty, indicating exposure through water and food. However, no patients in our study were found to use tetracyclines or fluoroquinolones [13].

In our study, after adjusting for age and BMI data, no statistically significant correlations were found between the number of antibiotics prescribed, the age at first antibiotic prescription, and the onset age of pubertal signs.

For true precocious puberty cases, treatment with gonadotropin agonists is administered. In our patient cohort, the rate of initiating treatment at the first examination was 25%, which is consistent with similar studies. Pubertal disorders are assessed within a spectrum, categorized as true precocious puberty or telarche variants. Telarche variants are characterized by ΔKY-TY of less than one year, with no Tanner stage progression within six months [22].

In our cohort, no treatment was administered to this group at the time of presentation. Follow-up is ongoing, and prospective evaluation could be the subject of future research. No significant differences in the number of antibiotic prescriptions, age at first antibiotic prescription, or the number of cases receiving antibiotics before one year or two years of age were found between the leuprolide acetate-treated group and those who did not receive this treatment.

The most significant confounding factor in this study is

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infections, which are known to impair the immune system and contribute to conditions such as asthma, type 1 diabetes mellitus, and obesity [23].

The impact of infections on the early onset of pubertal signs was not detected in this study.
Limitations of the study include its retrospective and cross-sectional nature, which precludes knowledge of the duration of antibiotic use. While cohort studies on antibiotic exposure and obesity are being conducted, similar studies for puberty are challenging. The limited number of cases is due to the need for concurrent antibiotic use information and pubertal examination. Although it was considered to analyze antibiotic levels in urine samples, budget constraints prevented this.
Another limitation is that only cases from the Pediatric Endocrinology Clinic were assessed. The control group may also experience the onset of pubertal signs during follow-up. This study is cross-sectional.

CONCLUSION

Various genetic and environmental factors influence the onset of pubertal signs. Given its association with hormone secretion and obesity, gut microbiota could trigger precocious puberty. Although larger-scale studies have noted antibiotic exposure in cases of precocious puberty, the role of antibiotics prescribed for treatment purposes in triggering pubertal signs remains unclear. Our study found no effect of treatment-related antibiotic use on the early onset of pubertal signs.

REFERENCES

1. Karakan T, Ozkul C, Küpeli Akkol E, Bilici S, Sobarzo-Sánchez E, Capasso R. Gut-Brain-Microbiota Axis: Antibiotics and Functional Gastrointestinal Disorders. Nutrients. 2021 Jan 27;13(2):389.

2. Carel JC, Léger J. Precocious puberty. N Engl J Med. 2008;358(22):2366-77.

3. Sorensen K, Mouritsen A, Aksglaede L, Hagen CP, Mogensen SS, Juul A. Recent secular trends in pubertal timing: implications for evaluation and diagnosis of precocious puberty. Horm Res Paediatr. 2012;77(3):137-45.

4. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: Interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol (2015) 28:203–9.

5. Li Y, Shen L, Huang C, Li X, Chen J, Li SC, et al.. Altered nitric oxide induced by gut microbiota reveals the connection between central precocious puberty and obesity. Clin Transl Med (2021) 11:e299.

6. Eklioğlu BS, Atabek ME, Akyürek N, Sarıkaya E. The Etiologic Distribution and Clinical Features of Cases Presenting with the Findings of Puberty to the Pediatric Endocrinology Clinic. Türkiye Çocuk Hast Derg. 2016;10(4):233-6.

7. Neyzi O, Gunoz H, Furman A, et al. Weight, height, head circumference and body mass index references for Turkish children. Cocuk Sağlığı ve Hastalıkları Dergisi 2008;51:1-14.

8. Marshall WA, Tanner JM. Variations in pattern of pubertalchanges in girls. Arch Dis Childh 1969;44:291-303.

9. Greulich WW PS. Radiologic atlas of skeletal development of the hand and wrist. . 2 ed. Standford(CA): Stanford University Press 1959.

10. Rosenfeld RL. Puberty in the female and it's disorders. In: Sperling MA eds.Pediatric Endocrinology 5th ed. Philedelphia Saunders Company 2020: 528-626.

11. Carel JC, Eugster EA, Rogol A, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics 2009;123:752-762.

12. Bräuner EV, Busch AS, Eckert-Lind C, Koch T, Hickey M, Juul A. Trends in the Incidence of Central Precocious Puberty and Normal Variant Puberty Among Children in Denmark, 1998 to 2017. JAMA Netw Open. 2020 Oct 1;3(10):e2015665.

13. Hu Y, Li J, Yuan T, Yu T, Chen Y, Kong H, Lin C, Shen Z, Tian Y, Tong S, Yu X, Liu S. Exposure to antibiotics and precocious puberty in children: A school-based cross-sectional study in China. Environ Res. 2022 Sep;212(Pt C):113365.

14. Huang X, et al. Gut microbiome combined with metabolomics reveals biomarkers and pathways in central precocious puberty. J Transl Med. 2023 May 11;21(1):316.

15. Vidal AC, et al. Associations between antibiotic exposure during pregnancy, birth weight and aberrant methylation at imprinted genes among offspring. Int J Obes (Lond). 2013 Jul;37(7):907-13.

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16. Gaml-Sørensen A, Brix N, Ernst A, Lunddorf LLH, Sand SA, Ramlau-Hansen CH. Prenatal exposure to antibiotics and timing of puberty in sons and daughters: A population-based cohort study. Eur J Obstet Gynecol Reprod Biol. 2020 Jul;250:1-8.

17. Isler B, Keske Ş, Aksoy M, Azap ÖK, Yilmaz M, Yavuz SŞ, Aygün G, Tigen E, Akalın H, Azap A, Ergönül Ö. Antibiotic overcosumption and resistance in Turkey. Clin Microbiol Infect 2019;25:651-53.

18. Chelimo C, Camargo CA Jr, Morton SMB, Grant CC. Association of Repeated Antibiotic Exposure Up to Age 4 Years With Body Mass at Age 4.5 Years. JAMA Netw Open. 2020 Jan 3;3(1):e1917577.

19. Li DK, Chen H, Ferber J, Odouli R. Infection and antibiotic use in infancy and risk of childhood obesity: a longitudinal birth cohort study. Lancet Diabetes Endocrinol. 2017 Jan;5(1):18-25.

20. Wang L, et al. Gut microbiota and its derived SCFAs regulate the HPGA to reverse obesity-induced precocious puberty in female rats. Front Endocrinol (Lausanne). 2022 Dec 9;13:1051797.

21. Gaskins HR, Collier CT, Anderson DB. Antibiotics as growth promotants: mode of action. Anim Biotechnol. 2002 May;13(1):29-42.

22. Burlo F, et al. Prevalence and characteristics of thelarche variant. Front Endocrinol (Lausanne). 2023 Dec 1;14:1303989.

23. Cox LM, Yamanishi S, Sohn J, Alekseyenko AV, Leung JM, Cho I, et al. Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. Cell. 2014; 158: 705–21.