ZKTB

REVIEW *(Derleme)*

Precocious Puberty and Role of Pediatric Nurse

Puberte Prekoks ve Pediatri Hemşiresinin Rolü

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ABSTRACT

Precocious puberty (PP) is the physical and hormonal manifestations of early pubertal development occurring at an earlier age than the normally accepted limit. With this present article it is aimed to increase the awareness of pediatric nurses about PP. In this literatüre review, the definition of PP pathophysiology, etiology, epidemiology, clinic, diagnosis, treatment, nursing initiatives and definitive diagnosis. The early onset of puberty can lead to early growth of the mammals, premature menstruation, growth in the penis and testes in boys, early onset of sperm production and increased libido, due to early closure of the epiphyses in children and short stature in the adult years. Emotional stress or behavioral problems cause psychosocial problems due to incompatibility of physical, hormonal and psychological development. Pediatric nurses have important responsibilities in the early diagnosis of PP children, in the orientation to appropriate centers, in the implementation of school-family cooperation as well as of the application of nursing approaches to the necessary precautions.

Keywords: child, pediatric nurse, precocious puberty

ÖZET

Puberte Prekoks (PP) ergenliğin fiziksel ve hormonel belirtilerinin, normal kabul edilen sınırlardan daha erken ortaya çıkmasıdır. Bu yazıda, pediatri hemşirelerinin PP ile ilgili farkındalıklarının artırılması amaçlanmıştır. Bu literatür derlemesinde, PP'nin patofizyolojisi, etiyolojisi, epidemiyolojisi, kliniği, tanısı, tedavisi, hemşirelik girişimleri ve ayırıcı yanları tanımlanmıştır. Ergenliğin erken başlaması kızlarda memelerin erken büyümesine, erken menarşa, erkeklerde penis ve testislerin büyümesine, erken sperm üretimine ve libido artışına, epifiz kapaklarının erken kapanması sonucu yetişkin yaşta boy kısalıklarına sebep olabilmektedir. Fiziksel, hormonal ve psikolojik gelişimin uyumsuzluğu nedeniyle duygusal stres ve davranışsal problemler, psikososyal sorunlara sebep olmaktadır. Pediatri hemşirelerinin, PP'li çocukların erken tanılanmasında, uygun merkezlere yönlendirilmesinde, okul-aile işbirliğinin sağlanmasında ve hemşirelik yaklaşımlarının uygulanmasında önemli sorumlulukları vardır.

Anahtar Kelimeler: çocuk, pediatri hemşiresi, puberte prekoks

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INTRODUCTION

Physical, hormonal, psychological and social transition process from childhood to adulthood is defined as adolescence period. Puberty refers to the neuroendocrine changes and their accompanying somatic and sexual functions as well as the developmental period in which reproductive ability is gained. Acceleration in somatic growth, change in body fat distribution, gonads, maturation in internal and external genital system, sexuality of the secondary sexuality become evident in this period. Puberty results in menstrual cyclic ovulation in females and completely mature spermatogenesis in males. Although age at onset of puberty varies racially, many factors such as genetic and environmental factors, stress, metabolic rate, skeletal maturation and body fat ratio are thought to affect the age of onset of puberty (1, 2).

Precocious Puberty (PP), physical and hormonal manifestations of early pubertal development which occurs at an earlier age than the normally accepted limit (3). PP is defined as the development of breast growth (thelarche) in girls before the age of 8, which is the initial limit and the initiation of testis growth before 9 years of age in males (4).

PP is classified as central (true-gonadotropin dependent) and peripheral (pseudo-gonadotropin independent) (5). While the central PP hypothalamus-pituitary-gonad axis (HPG axis) work is effected by releasing sex steroids, the pseudo-PP is not axillary and the source of sex steroids is different (6). Early onset of puberty causes many problems in children (3). These are as follows; early growth of breasts, premature menarche, pubic or axillary hair growth, changes in the vaginal mucosa due to estrogen increase and the shortness of the stature with the closure of the epiphyses resulting from rapid bone growth with rapid growth. (7). In boys, growth in the penis and testes, axillary and pubic hair, early onset of sperm production and increased libido can be seen. The psychosocial development of the resulting child is usually normal according to age, but some children experience emotional distress (3). Due to the inconsistency of physical, hormonal and psychological development, emotional stress or behavioral problems cause psychosocial problems (8). Early identification of children with PP, the direction to appropriate centers and the realization of their treatment will help to prevent many problems that may be caused by PP. The key person in fulfilling

these tasks and responsibilities are the child nurses. Pediatric nurses should be involved in a multidisciplinary approach for the maintenance and improvement of these children's health. Pediatric nurses have important responsibilities in the implementation of nursing approaches to these precautions (9), as well as early detection of PP children and directing them to appropriate centers (10). When the role and importance of the child nurses is taken into consideration; this study aimed to increase the awareness of pediatric nurses about PP.

Epidemiology

The frequency of central PP, which is seen very rare in childhood, is 1: 5000-10000 for the general population. In females it is more frequent than males. It is reported to be 10-20 times more in females than males (9). Central PP is five times more common than peripheral PP (10).

In the National Health and Nutrition Examination Survey III study conducted in the United States between 1988 and 1994, thelarche age was reported to be 10.3, 9.8, 9.5 in white people with Mexican and American roots, respectively, while pubic hair initiation age was found to be 10.5, 9.5, 10.3 respectively (11). In Herman-Giddens et al. (1997) study where 17077 girls aged between 3-12 years have been assessed in the Pediatric Research in Office Setting; 6.7% of whites aged 7 years and 27.2% of African Americans were reported to have breast development or pubic hair growth; thelarche age of African Americans and whites was 8.87±1.93 and 9.96±1.82, respectively; Whereas the pubic hair growth age was 8.78±2.00 and 10.51±1.67, respectively; the menarche age was 12.16±1.21 and 12.88±1.20, respectively (12). During the 19th and 20th centuries, studies in Europe and the United States have shown that the age of menarche is gradually decreasing and this is called the trend of the century (13). While today the trend of the century is continuing in developing countries, it has stopped in many developed countries. The authors of the opinion that the tendency of the century is continuing show this as a result of an increase in obesity frequency (14).

Pathophysiology

The onset and continuation of puberty, the onset of sexual maturation and the acquisition of fertility depend on the healthy functioning of HPG axis. The measurement of the onset of pulsatile release of gonadotropin releasing hormone (GnRH) from the hypothalamus in normal pubertal development results in secretion of the hormone/ testis cells upon release of pituitary luteinizan hormone (LH) and follicle stimulating hormone (FSH) (15).

In females LH stimulates estrogen synthesis from over follicular cells and corpus luteum production after ovulation begins, while FSH stimulates estrogen conversion of testosterone in granulosa cells. Estrogen is responsible for the development and progression of breast development, the maturation of genital organs and vaginal mucosa, the growth of the uterus, and the development of female type of body fat distribution. In males, LH testosterone stimulates testosterone synthesis from leydig cells, stimulating FSH sertoli cells to provide spermatogenesis (16). The testosterone is responsible for the secondary sex characters, such as the growth of external genitalia, the development of the male body structure and the appearance of beard (3).

Central PP is caused by premature activation of HPG axis for any reason. In peripheral PP, the early development of secondary sex characters results in secretion of sex steroids from gonads or non-gonads, independent of gonadotropin release without activation of HPG axis (6).

Etiology

The most common cause of central PP is idiopathic. Central nervous system (CNS) can also lead to abnormalities (tumors, abscesses, encephalitis etc.). In addition, sex steroid-secreting tumors may develop in the second-line central PP due to early maturation of the CNS, such as congenital adrenal hyperplasia and luteinizing hormone receptor activation mutation. In the etiology of peripheral PP there are gonadal causes (McCune Albright syndrome (MAS), familial testotoxicosis, ovarian tumors, leydig cell tumors etc.), adrenal tumors (congenital adrenal hyperplasia, functioning adenomas/ carcinomas etc.), human chorionic gonadotropin (hCG)-secreting tumors (disgerminomas, teratomas, hepatomas etc.), primer hypothyroidism and iatrogenic causes (1, 9).

Whereas PP in females is 90-95% idiopathic, it is more depending on pathological reasons in males (17). Especially in girls and those older than six years, there are more cases of central PP without an organic cause. However, there is a high probability of finding an underlying pathology in male cases of PP that begin under four years of age. Pathology in the CNS has been determined of more than 90% of boys (18). Hypothalamic hamartomas, arachnoid cysts, gliomas, astrocytomas and neurofibromatosis are among the most common causes of central pathologies (19). This tumor is a small, non-massive tumor that generally does not tend to grow. There is a GnRH pulse generator in the tumor, which prematurely releases GnRH, activating HPG axis and initiating the effects of sex steroids (20).

Congenital adrenal hyperplasia, which plays an important role in the etiology of peripheral PP, leads to the development of isosexually in males and heterosexual puberty in girls. Although MAS is seen mostly in girls, sexual steroids are secreted when there are no gonadotropins in the activating mutation-ending medium, and secondary sex hormones specific to these hormones are seen. Apart from PP, cafe au lait spots on the skin and fibrous dysplasia on the bones form a typical triad (6).

Endocrine disruptors are also thought to play an important role in the shift of puberty to earlier ages (21). It has been suggested that endocrine disruptors may change puberty timing in children due to their estrogenic and antiandrogenic effects (22). Agricultural chemicals, cosmetic products, chemi-

cal substances used to soften plastics are shown as factors in puberty erection. It has been reported that estrogen used especially in shampoos, creams and lotions cause early breast development in girls and gynecomastia in boys (23).

Clinic

Central pubic PP usually follows the sequence seen in normal pubertal development and is always isosexual. In girls, first of all, breast development, pubic hair growth, acceleration in somatic development, vaginal bleeding which shows periodicity over time and sweat odor are remarkable. Sometimes there may be changes in the sequence, the mestrual cycles are more irregular than the normal puberty and are usually anovulatory. In men, bilateral testis growth, penis growth, pubic hair growth, thickening of the voice, acne, frequent erections, night ejaculation, initiation of sweat smell, axillary hair growth and acceleration in somatic development are the main findings (6, 24). Findings according to the etiological cause can be added to the clinical picture in organic PP. The length, weight and bone age of the patients are based on chronological age advanced. The progression of the bone age of these children, who are looking older than their age, results in premature closure of the epiphyses and leads to shorter stature than the adult genetic potential of adult patients (25).

Diagnosis

PP are diagnosed by history, clinical findings, hormonal and radiological evaluation.

Medical history; It is very important to have a detailed story of a child applying with PP findings. The history should include information like birth weight, growth pattern from birth, age at onset of pubertal findings and rate of progression, increase in length, undergone diseases, medications used, exogenous hormone exposure, central nervous system diseases or findings that suggest these diseases (headache, head circumference growth, visual disturbances, convulsion story) should be questioned. A complete medical history must be taken from the mother, father, and siblings, including the age of puberty onset and their length (18).

Physical examination; Typical findings in PP are that secondary sex characteristics are showing theirself earlier than it should be, rapid increase in length and bone aging (25). Secondary sex characteristics identification and classification of a patient with PP suspicion (breast growth in girls, testis measurement in boys and pubic hair growth evaluation for both genders) should be done according to Marshall criteria (26, 27). Evaluation of the vaginal mucosa may provide information on estrogen exposure. While the vaginal mucosa under the estrogen effect is bright red, the pale pink color develops in the presence of estrogen, edema is built and vaginal secretion begins (2). In men, testicular volume typically grows in central PP, but does not reach pubertal size in peripheral PP. Growth in the penis may not be expected in early puberty growth, as the penis growth is usually at a time when the testosterone level is increasing noticeable (18, 25). Also acne, oily skin and hair structure, axillary hair, sweat, muscle development should be evaluated. Physical examination may reveal evidence of puberty etiology in the presence of pelvic mass, skin lesions such as cafe au lait, neurological or dysmorphic findings, galactore, hypothyroidism compatible symptoms, especially long bones and skull palpation in terms of bone deformities (25).

Laboratory findings: Hormonal assessment in PP should absolutely be done early in the morning. Gonadotropins (FSH, LH) measured in serum provide good information about oestradiol in girls and testosterone puberty in men (25). The high level of LH is significant in the central PP diagnosis (8). Due to the pulsatile release of gonadotropins, the diagnostic value of baseline measurements is limited and the GnRH stimulation test is accepted as the golden standard (29).

Knowing that gonadotropin levels may be physiologically high in children under two to three years of age is also very important in terms of diagnosis. Apart from that, care should be taken in the hormonal evaluation of children in this age group (25). Estrodiol levels above 12 pg/ mL are accepted as pubertal, but low estradiol levels do not exclude pubertal precocious diagnosis. The presence of low or suppressed gonadotropin levels together with high estrodiol levels supports peripheral PP diagnosis (30). Serum testosterone is an excellent marker for early puberty in men. In pubertal men, morning testosterone values are usually 20 ng/ dl and above (25). In addition, when serum hCG levels or congenital adrenal hyperplasia are considered to elucidate the etiology of peripheral PP, the levels of 17 hydroxyprogesterone, 11 deoxycortisol, and cortical hormones in adrenocortical tumor have diagnostic value (6).

Radiological evaluation: Anterior-posterior left wrist bone graphy is evaluated to determine bone age. In addition to being mandatory for the diagnosis and treatment, Bayley-Pinneau method is used to estimate the adult size in order to obtain the information if the targeted length will be reached or not (5). Regardless of the etiology of PP, bone age is expected to be later than chronological age except hypothyroidism. Exposure to sex steroids, especially estrogen, accelerates bone maturation (25). Assessment of internal genital organs and gonads by pelvic ultrasonography (USG) in girls is important in the follow-up of PP diagnosis, etiology and treatment initiation. Bullous formation from the tubular structure of the uterus, growth in volume, increase in corpus/ cervix ratio, prominent endometrium thickening are signs of estrogen exposure. The finding of uterine volume >2 ml or >34 mm in length supports PP diagnosis. Menarch begins with an endometrium thickness of 5 mm (31). With pelvic USG, ovarian size can be determined, ovarian follicular structure can be seen, ovarian cysts and tumors can be detected. The bilateral enlargement of the ovarian suggests a PP. Ovaries showing homogeneous or microcystic features before puberty gain a multikistic or follicular structure with puberty (32).

Multicystic ovaries that have grown in the MAS bilateral are USG findings that support the diagnosis (25). When male peripheral PP is considered or if asymmetric testis is palpated, scrotal USG should be taken in terms of testicular masses (6). The ideal method for visualization the pituitary region in central PP is magnetic resonance imaging (MRI). In MRI, the expected physiological growth of the pituitary gland in normal puberty can be detected, and organic pathologies that may lead to central PP can be determined. In all male and female patients with complaints starting before 6 years of age with rapid breast development, serum estradiol level above 30 pg/ ml or neurological findings, CNS organic pathologies are highly likely to be detected and cranial and pituitary MRI should be performed in these patients (33).

Treatment

The purpose of central PP treatment are as follows; suppression of the intentional release of pulsatile gonadotropin, controlled sexual maturation until normal pubertal age, restraint or cessation of sexual characteristics, prevention of premature closure of epiphyses and achievement of adult target length, psychosocial abuse of the child and avoidance from late complications that high estrogen from early ages can create (34).

Furthermore, it is also aimed to reduce parental anxiety, delay the onset of sexual activity, prevent gestation and reduce the risk of sexual abuse through PP treatment (5). In untreated central PP patients, the average adult height has been reported as 151-156 cm for males and 150-154 cm for females. According to that information the final height loss is 20 cm in males and 12 cm in females (35). In treatment indication; the age at onset of the disease, the pubertal stage, the rate of progression of the findings, the predicted negativity in adult height using bone age, and rapid somatic development have to be taken into account. All male patients who have had pubertal findings before 9 years of age and girls who have been diagnosed before 7 years of age with rapid progression have a definite indication for treatment (6).

Long-acting GnRH analogues (GnRH) have been used in the standard treatment of central PP since 1980s. These are synthetic analogs of native GnRH decapeptide. A pulsatile stimulation with GnRH is required to release gonadotropins from the pituitary gland. A more potent and long-acting GnRHa than the native GnRH provides a continuous stimulation of GnRH receptors. This continuous stimulus causes the down regulation of GnRH receptors, desensitization of the pituitary gland and suppression of gonadotropin levels over time after a short period of stimulation. After all; it is also possible to maintain the genetic height potential and to prevent the loss of the final length, preventing the regression or stabilizing the secondary sex characters, restoring normal growth rate and decreasing the progression in bone maturation (18).

There are many different GnRHa used. Although these medicines differ in their route of administration, doses and intervals of administration, they are all effective in treatment. Subcutaneous implants, intramuscular reservoirs, short acting injection forms and nasal spray form are available for administration. The selection of GnRHa and route of administration will take into account the characteristics of the patient, the experience of the physician and the products available in the market approved in that country. In the treatment of central PP, slow dissolving storage forms, which are made intramuscularly once a month or every 3 months, are frequently preferred in terms of efficacy and compliance (36, 37).

Patients with central PP treated with GnRHa are followed clinically by assessment of growth rate, sexual maturation and bone age (5). Patient puberty grades and growths should be evaluated every 3-6 months, bone age should be monitored periodically (38). Pause or regression in the development of secondary sex characters, a decrease in the prepubertal level of the increased growth rate, slowing of the rapid progression in the bone age are indicators of a clinical response to treatment. Continuation of breast development while using GnRHa indicates that the treatment was unsuccessful (37). However, GnRHa therapy is ineffective on adrenal androgen secretion, so increased pubic hair during treatment does not indicate failure of treatment (2). If pre-menstrual GnRHa treatment is initiated, withdrawal bleeding due to decreased estrogen level may be seen. In the first months of treatment, continuation of the bleeding is not a sign of ineffectiveness of the treatment (38).

At the end of treatment, patient's and family's wishes are considered in addition to criteria such as synchronizing puberty with the patient's peers, adequate growth potential and psychosocial readiness (38). Retrospective studies have shown that treatment after 11 years adversely affects the adult height and that cutting the chronological age of the treatment to ~11,0 and bone age to ~12,0 will lead to the best results in terms of adult final height (39). In males, the best results have been reported to be obtained when the treatment has been finished with a bone age between 13-13.5 years (28). The HPG axis is activated again within weeks or months after GnRHa therapy is discontinued. After the end of treatment, the majority of the patients show (2-61 months) menarch during the 16-18 months (40). No negative data on the effect of GnRHa treatment on fertility have been reported (41). Information on the safety of GnRHa treatment in boys with central PP is very limited. It was reported that serum testosterone level reached to pretreatment level after 3 months of GnRHa treatment termination, testis volume increased, testosterone level reached normal adult level after 1 year and testicle volume reached pre-treatment level. USG evaluation of testicular structures of patients is recommended because testicular microcalcifications in males treated with GnRHa are four times more common in normal young adult males (42).

GnRHa treatment is generally well tolerated by patients. Rarely, complaints like headaches or hot flashes occur. These complaints are usually short-

term. Local side effects such as redness, temperature increase, swelling or granuloma formation at the injection site occur in 10-15% of patients. The most serious local effects are sterile abscess formation. Treatment is thought to be leading to body weight gain and osteoporosis, but studies have reported that these children are not obese and bone mineral densities are normal (25). Peripheral PP is not a standard and effective treatment, such as central PP. Treatment methods differ according to etiological cause (43).

Nursing Initiatives In PP

Purpose in nursing care are as follows; to inform the child and the family about the PP, to prevent the complications that may arise by monitoring the growth and development and to prevent the psychosocial problems that may occur in the child (44). In PP, the time when the growth accelerates and the symptoms occur is very important and should be observed very well. Pediatric nurses should observe physical and behavioral changes associated with puberty, as well as observe testicular growth, breast development, pubic and axillary hair during physical examination and compare it with normal pubertal developmental ages (9, 10).

The fact that both the somatic and the sexual development are advanced compared to their peers, lead to vaginal bleedings in girls as well as social and psychological problems. For this reason, they are far from social activities such as swimming and sports, and they feel better when they are beside older people than their peers (9). The pediatric nurse should tell parents, the child's teachers and the people around them that they should behave according to the chronological age of the child (24). The situation in which the patient is present should be clearly explained in accordance with the age, and counseling services should be provided where necessary (2).

As PP children are exposed to sexual abuse, parents should also be alerted in terms of child abuse. In PP the fear of family and child is usually about sexual problems. Families are often afraid of the progress of children's psychosexual development and of increasing sexual interest. Pediatric nurses should tell parents that their sexual interests and activities can not go beyond the chronological age (9). One of the most important roles of the pediatric nurse is to educate children and families about adolescence. The disclosures should be adjusted according to the level of intellectual development and age of the child and the family. The nurse should explain to the family that puberty is a normal process, but that it occurs at an early age (24).

When it is planned to start the treatment, PP patients as well as the families should be informed about the indications, contraindications, complications, side effects by pediatric nurse. The nurse should also explain how often and how to use the medicine (9).

Definitive Diagnosis

If PP is evident by a single pubertal finding, progress is absent and a new pubertal finding is added, the progress in somatic development is mild and the findings show spontaneous regression over time, this condition is interpreted as incomplete PP. These non-pathological and non-treatment-related conditions are more common than the central and peripheral PP (6).

Premature telarche; is a self-regressing, benign, single or bilateral, isolated breast development without the presence of any other puberty in girls before the age of eight. It is usually seen in girls under 2 years of age (45).

Premature adrenarche; is the beginning of pubic or axillary hair growth in the age of eight for girls and before the age of nine for boys. It is characterized by a moderate increase in the production of adrenal androgens. Classical and nonclassical congenital adrenal hyperplasia, surrenal tumors should be considered in differential diagnosis (23). Children with premature adrenal insufficiency have a higher risk of developing adult metabolic syndrome and policystic over syndrome (46).

Premature menarch; is the formation of menstrual blood without any other findings of puberty, and retention within a few years. In etiology transient overactivity is emphasized. It is known that during their follow-up they enter puberty on time and their fertility is normal. Endogenous and exogenous estrogen exposure, vulvovaginitis, foreign body, tumors, trauma and abuse probabilities should be considered in differential diagnosis (23).

REFERENCES

1. Kliegman RM, Stanton BF, Geme JW St, Schor NF. Disorder of pubertal development. In: Behrman RE, editors. Nelson textbook of pediatrics. 20th ed. C.V.Mosby. 2016. pp 2656-2660. ISBN 978-0-323-35307-6

2. Lifshitz F. Pediatric endocrinology: growth, adrenal, sexual, thyroid, calcium, and fluid balance disorders. İnforma Healthcare. 5th ed. CRC Press. 2006. ISBN 9781420042702 - CAT# H4270

3. Kaplowitz PB. Precocious puberty. In: Hillard PJA, editors. Practical pediatric and adolescent gynecology. 2013. pp 87-90. doi: 10.1002/9781118538555.ch15

4. Park J, Kim JH. Change in body mass index and insulin resistance after 1-year treatment with gonadotropin-releasing hormone agonists in girls with central precocious puberty. Annals of Pediatric Endocrinology & Metabolism. 2017; 22(1): 27-35.

5. Brito VN, Latronico AC, Arnhold IJ, Mendonça BB. Update on the etiology, diagnosis and therapeutic management of sexual precocity. Arquivos Brasileiros de Endocrinologia & Metabologia. 2008; 52(1):18-31.

6. Berberoglu M. Precocious puberty and normal variant puberty: definition, etiology, diagnosis and current management. Journal of Clinical Research in Pediatric Endocrinology. 2009; 1(4):164–74.

7. Kim EY, Lee MI. Psychosocial aspects in girls with idiopathic precocious puberty. Psychiatry İnvestigation. 2012; 9(1): 25-8.

8. Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics. 2009; 123(4), 752-62.

9. McKinney ES, James SR, Murray SS, Nelson K, Ashwill J. Precocious puberty. Maternal-child nursing. 5th ed. Canada: Elsevier Health Sciences; 2017. pp 1256-1257. ISBN9780323478342

10. Ricci SS, Kyle T. Precocious puberty. Maternity and pediatric nursing. China: Wolters Kluwer Healty; 2009. pp 1599-1600. ISBN 0781780551, 9780781780551

11. CDC-Centers for Disease Control and Prevention . National health and nutrition examination survey III, 1988-1994. 2018 Mar; Available from http://www.icpsr.umich.edu/icpsrweb/NACDA/studies/2231.

12. Herman-Giddens ME, Slora EJ, Wasserman RC, Bourdony CJ, Bhapkar MV, Koch GG, Hasemeier CM. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the pediatric research in office settings network. Pediatrics. 1997; 99(4): 505-12.

13. Karlberg J. Secular trends in pubertal development. Hormone Research in Paediatrics. 2002; 57(Suppl 2): 19-30.

14. Parent AS, Teilmann G, Juul A, Skakkebaek NE, Toppari J, Bourguignon, JP. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. Endocrine Reviews. 2003; 24(5), 668-93.

15. Aycan Z. Delayed puberty. Turkish Archives of Pediatrics. 2011; 46(11): 88-91.

16. Hockenberry MJ, Wilson D. Precocious puberty. Clinical companion for Wong's essentials of pediatric nursing. 8th ed. USA: Elsevier Health Sciences; 2008. Pp 299-301. ISBN 978-0323053549

17. Hockenberry MJ, Wilson D. Precocious puberty. Wong's nursing care of infants and children. 10th ed. Canada: Elsevier Health Sciences; 2014. pp 1501-1502. ISBN 0323293395

18. Partsch CJ, Heger S, Sippell, WG. Management and outcome of central precocious puberty. Clinical Endocrinology. 2002; 56(2): 129-48.

19. Faizah M Z, Zuhanis AH, Rahmah R, Raja AA, Wu LL, Dayang AA, Zulfiqar MA. Precocious puberty in children: a review of imaging findings. Biomedical İmaging and İntervention Journal. 2012; 8(1): e6.

20. Chan YM, Fenoglio-Simeone KA, Paraschos S, Muhammad L, Troester MM, Ng Yu-tze, Johnsonbaugh RE, Coons SW, Prenger EC, Kerrigan Jr JF, Seminara SB. Central precocious puberty due to hypothalamic hamartomas correlates with anatomic features but not with expression of GnRH, TGFα, or KISS1. Hormone Research in Paediatrics. 2010; 73(5): 312-9.

21. James SR, Nelson KA, Ashwill JW. The child with an endocrine or metabolic alteration. Nursing care of children: Principles and practice. 4th ed. Saunders; 2013. pp 700-730. ISBN 9781455703661

22. Euling SY, Selevan SG, Pescovitz OH, Skakkebaek N. Role of environmental factors in the timing of puberty. Pediatrics. 2008; 121(Suppl.3): 167-71.

23. Nebesio TD, Eugster EA. Current concepts in normal and abnormal puberty. Current Problems in Pediatr Adolescent Health Care. 2007; 37(2): 50-72.

24. Synovitz LB, Chopak-Foss J. Precocious puberty: Pathology, related risks, and support strategies. Open Journal of Preventive Medicine. 2013; 3(9): 504-9.

25. Carel JC, Leger J. Precocious puberty. The New England Journal of Medicine. 2008; 358(22): 2366-77.

26. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Archives of Disease in Childhood. 1969; 44(235): 291-303.

27. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Archives of Disease in Childhood. 1970; 45(239): 13-23.

28. Carel JC, Lahlou N, Jaramillo O, Montauban V, Teinturier C, Colle M, Lucas C, Chaussain JL. Treatment of central precocious puberty by subcutaneous injections of leuprorelin 3-month depot (11.25 mg). The Journal of Clinical Endocrinology & Metabolism. 2002 Sep; 87(9): 4111-6.

29. Lee PA. Laboratory monitoring of children with precocious puberty. Archives of Pediatrics and Adolescent Medicine, 1994; 148(4), 369-76.

30. Sloboda DM, Hart R, Doherty DA, Pennell CE, Hickey M. Age at menarche: influences of prenatal and postnatal growth. The Journal of Clinical Endocrinology and Metabolism. 2007; 92(1): 46-50.

31. de Vries L, Horev G, Schwartz M, Phillip M. Ultrasonographic and clinical parameters for early differentiation between precocious puberty and premature thelarche. European Journal of Endocrinology. 2006; 154(6), 891-8.

32. Battaglia C, Mancini F, Regnani G, Persico N, Iughetti L, De Aloysio D. Pelvic ultrasound and color doppler findings in different isosexual precocities. Ultrasound Obstet Gynecol, 2003; 22(3): 277-83.

33. Chalumeau M, Chemaitilly W, Trivin C, Adan L, Bréart G, Brauner R. Central precocious puberty in girls: an evidence-based diagnosis tree to predict central nervous system abnormalities. Pediatrics. 2002; 109(1): 61-7.

34. Chemaitilly W, Trivin C, Adan L, Gall V, Sainte-Rose C, Brauner R. Central precocious puberty: clinical and laboratory features. Clinical Endocrinology. 2001; 54(3): 289–94.

35. Ojeda SR, Lomniczi A, Mastronardi C, Heger S, Roth C, Parent AS, Matagne V, Mungenast AE. The neuroendocrine regulation of puberty: is the time ripe for a systems biology approach? Endocrinolgy. 2006; 147(3): 1166-74.

36. Kaplowitz PB. Treatment of central precocious puberty. Current Opinion in Endocrinology, Diabetes and Obesity. 2009; 16(1): 31-6.

37. Tuvemo T, Gustafsson J, Proos LA. Swedish Growth Hormone Group. Suppression of puberty in girls with short-acting intranasal versus subcutaneous depot GnRH agonist. Hormone Research in Paediatrics. 2002; 57(1-2): 27-31.

38. Neely EK, Wilson DM, Lee PA, Stene M, Hintz RL. Spontaneous serum gonadotropin concentrations in the evaluation of precocious puberty. Journal of Pediatrics. 1995; 127(1): 47–52.

39. Antoniazzi F, Arrigo T, Cisternino M, Galluzzi F, Bertelloni S, Pasquino AM, Borrelli P, Osio D, Mengarda F, De Luca F, Tatò L. End results in central precocious puberty with GnRH analog treatment: the data of the Italian study group for physiopathology of puberty. Journal of Pediatric Endocrinology and Metabolism. 2000; 13(Suppl.): 773-80.

40. Paterson WF, McNeill E, Young D, Donaldson MD. Auxological outcome and time to menarche following long-acting goserelin therapy in girls with central precocious or early puberty. Clinical Endocrinology. 2004; 61(5): 626-34.

41. Arrigo T, De Luca F, Antoniazzi F, Galluzzi F, Iughetti L, Pasquino AM, Salerno MC, Marseglia L, Crisafulli G. Menstrual cycle pattern during the first gynaecological years in girls with precocious puberty following gonadotropin-releasing hormone analogue treatment. European Journal of Pediatrics. 2007; 166(1): 73-4.

42. Bertelloni S, Mul D. Treatment of central precocious puberty by GnRH analogs: long-term outcome in men. Asian Journal of Andrology. 2008; 10(4): 525-34.

43. Schoelwer M, Eugster EA. Treatment of peripheral precocious puberty. Endocrine Development. 2016; 29: 230–9.

44. Datta P. Endocrine disorders in children. Pediatric nursing. 3th ed. India: Jaypee Brothers Medical Publishers; 2014. pp 424-425. ISBN 978-9351521488

45. Blondell RD, Foster MB, Dave KC. Disorders of puberty. American Family Physician. 1999; 60(1): 209-18.

46. Rastogi MV, Boston BA. Precocious puberty. The Global Library Of Women's Medicine. 2008; doi: 10.3843/GLOWM.10292.