BRITISH MEDICAL JOURNAL

British Medical Journal
Volume 2, No 4., 2022
Internet address: http://ejournals.id/index.php/bmj
E-mail: info@ejournals.id
Published by British Medical Journal
Issued Bimonthly
3 knoll drive. London. N14 5LU United Kingdom
+44 7542 987055
Chief Editor
Dr. Fiona Egea

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British Medical Journal Volume-2, No 4
10.5281/zenodo.7231814

SEXUAL DEVELOPMENT OF CHILDREN IN NORMAL AND PATHOLOGICAL CONDITIONS

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Abstract:

In the article, the authors show the features of sexual development and the state of the pituitary-gonadal system in children and adolescents in normal and pathological conditions. The pathophysiological mechanisms of delayed sexual development were disclosed based on the analysis of the literature. The authors emphasize the breadth and importance of the problem of sexual development in children with chronic lung diseases. An analysis of the data available in the literature on the factors influencing the violation of sexual development in chronic lung diseases in children shows that there is no consensus on this issue. Thus, the prevalence of disorders of sexual development in this pathology has not been sufficiently studied. A detailed study of the role of chronic respiratory diseases in the development of sexual disorders allows us to make the correct diagnosis and the right choice of treatment tactics.

Keywords: sexual development, pituitary-gonadal system, chronic lung disease

Sexual differences are significantly expressed only with the onset of puberty. The period of life when a growing organism reaches biological sexual maturity is called puberty and is characterized by the appearance of secondary sexual characteristics. The time of appearance of the latter depends on the state of health, nutrition, climatic conditions and genetic characteristics [2,22,14,32,46].

Adolescence is a period of rapid development of feelings and emotional experiences. At this age, the process of forming life plans and self-awareness is most active, the need for interpersonal communication increases, interest in the opposite sex grows, first love comes, and elements of reproductive behaviour are formed. A teenager finally realizes his gender and develops an appropriate psychosexual orientation [63,64].

Timely sexual development is the result of accurate integration and harmonious regulation of endocrine structures at all levels: the hypothecalamus, adenohypophysis and gonads [8,14].

All somatic changes in boys referred to as puberty, begin at 10 and end at 18. However, the main part of this process in most adolescents takes 3-4 years [46,63].

The appearance of secondary sexual characteristics lags behind the initial enlargement of the external genital organs by approximately 1 year. So, if the first significant increase in the testicles occurs at 11.5 years, then the diameter of the penis increases at 12 years, the length - at 13 years, then its size increases gradually, and mainly due to the diameter [63]. Hair at the base of the penis or on the pubis appears

10.5281/zenodo.7231814
on average by 12.8 years (with an interval of 11 years to 14 years 11 months). Then other signs of puberty appear sequentially - a voice mutation, an increase in the cartilage of the larynx, acne, hair growth on the face, in the axillary cavities. By the age of 15.5, in most adolescents, pubic hair becomes masculine [63].

Adequate erections occur in boys on average at 13 years old, and the first ejaculations - at 14 years old. However, since the second half of the twentieth century, every 10 years there has been a significantly earlier onset of puberty in adolescents [63].

The development of puberty in boys does not vary widely depending on race, ethnicity, geographic location, nutritional and environmental factors and is considered normal when it occurs from 9 to 13.5 years [21,55].

An increase in testicles of more than 3 ml (G2 stage according to Tanner) is a marker of the onset of puberty in boys [55]. On the basis of visual examination without palpation of the testicles and measurement of their volume, the age of onset of puberty was most often determined abroad [16]. However, according to modern requirements, as previously mentioned in the editorial comment of Reiter and Leah [49], measurement is important, since the slightest increase in the volume or size of the testicles can be critical for setting the G2 stage according to Tanner. Measuring the size of the penis is also of great importance, since the development of the penis is androgen-dependent and even a slight decrease can be a marker of genetic pathology [30].

Studies of a large population of schoolboys living in central Russia made it possible to establish standards for puberty in this region. So, the testicles reach a volume of 4 cm3 (which is considered the beginning of their pubertal development), on average, by 11 years 10.5 months. The maximum rate of testicular growth is noted at the age of 13-14.5 years, which corresponds to the maximum rate of puberty. The first significant enlargement of the penis occurs at 12-13 years of age, or 1 year after the onset of testicular enlargement. The maximum growth of the penis in length and thickness was registered at 13-14 years [24,63]. In 1987, the Research Institute of Endocrinology and the Department of Endocrinology of the Tashkent Medical Institute developed standards for puberty for boys in our region by examining 304 schoolchildren in Tashkent 7-13 years old. The first testicular enlargement (length ≥ 2.5 cm, volume ≥ 4 cm3 according to the Prader orchidometer) appears on average between 10 years and 10 months. and 11 years 4 months. [51].

G.D. Mamedova [40] examined 1835 schoolchildren-boys in Tashkent at the age of 7-17 years. The first significant testicular enlargement in this population was noted between 11.5-12 years of age. A delay in the appearance of signs of puberty by more than 2 years can be considered as a delay in sexual development. Consequently, the absence of testicular enlargement in boys older than 13.5 years and pubic hair growth in adolescents older than 14.5 years can serve as a reason for diagnosing delayed sexual development [62]. An extremely important and responsible stage in the life of girls is the period of puberty [8]. The maturation of the reproductive system is a complex and lengthy developmental process that begins

10.5281/zenodo.7231814
in the early perinatal period and ends with the achievement of the parameters of an adult organism at the end of the pubertal period [58].

As for the period of puberty in girls, its turn comes approximately from the age of 8-9 years. The puberty of a girl takes place in several stages and takes a time interval equal to 9-10 years, that is, from 8-9 to 17-18 years. The initiation of sexual development in 99.6% of healthy girls occurs at the age of 8-13 years [58,62]. Due to the fact that the mechanism of regulation of the reproductive system in this age period is not completely formed, most organs and systems are on the verge of normal and pathological and are characterized by increased sensitivity to the action of adverse environmental factors [58]. Therefore, it is a period of increased risk of dysfunction of the reproductive, endocrine and nervous systems of the female body. Early detection of these disorders and timely correction is a manageable factor in maintaining the health of adolescents [10].

The period of puberty in all girls is not the same: both psychologically and physically, sexual development can be individual [26,39].

The period of puberty of a girl begins, as a rule, with a sharp "jump" in growth - up to 10 cm per year. Due to the fact that girls begin puberty earlier than boys, at its beginning, girls often overtake their peers in growth and development. Boys and girls “level out”, as a rule, only by the last grades of the school, while a boy of 17-18 years old is still growing, and a girl of the same age has long stopped growing [22,32,39].

Most authors consider the first recorded sign of puberty in girls to be thelarche - maturation and growth of the mammary glands, which begins at the age of 10, along with growth acceleration [9]. The mammary glands reach the penultimate stage of development by the age of 16, and the last stage - during the feeding of the child. Breast growth begins with the growth of the nipple and areola. The color of the nipple can be anything from light pink to dark brown, it depends only on the total amount of pigment in the body (color of the skin, hair, eyes) and nothing else, does not affect the function or sensitivity of the gland. Pubarche - pubic hair. Starts at 10-11 years old. The last stage is reached by the age of 15-16. Hair color, stiffness, curl depend only on genetic characteristics and do not affect sexual function. Approximately from the age of 13, hair growth of the armpits and the front surface of the lower leg begins [11,37,63].

The timing of the arrival of menarche for girls of the middle zone is 12.5-13 years, for the developed countries of Europe and the USA, the average age of menarche is 13 years [63]. For girls in the Uzbek population, the average age of menarche according to F. M. Ayupova [5] is 12 years 10 months. Late menarche (after 15 years) indicates a delay in puberty. Amenorrhea is the absence of menses for 6 months or more. There are primary (not the onset of menarche by the age of 15) and secondary (absence of menstruation for 6 months) amenorrhea [6].

The results obtained by R. T. Kamilova [29] on the study of the sexual development of girls indicate that girls living in Uzbekistan are characterized by general patterns of sexual development.

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Some authors suggest that the leading position of the appearance of menarche is occupied by the hypothesis of achieving "critical body mass". According to a number of authors, menarche occurs after a weight gain of 44–47 kg [22,32,37].

Conventionally, it is considered that adolescence ends with the cessation of rapid growth. Physiologically, adolescence is due to an increase in the production of a number of hormones, the main of which are growth hormone, sex hormones, thyroid hormones, and insulin. Only their simultaneous and interconnected action ensures the timely correct development of the child.

Three tropic hormones of the pituitary gland are directly involved in the regulation of the reproductive system: luteinizing hormone (LH), follicle-stimulating hormone (FSH) and prolactin. Undoubtedly, other pituitary hormones - thyroid-stimulating (TSH), somatotropic (STH), adenocorticotropic (ACTH) are also partially involved in the regulation of sexual function. The action of gonadotropins on the reproductive system is complex and multidirectional [7,14,28].

In the female body, follicle-stimulating hormone during puberty causes the growth and maturation of follicles. The specific effect of follicle-stimulating hormone on the ovaries is to stimulate follicular cell mitosis and DNA synthesis in cell nuclei. In addition, FSH induces the sensitivity of the gonads to the effects of luteinizing hormone, ensures the normal secretion of estrogens. In a sexually mature organism, LH serves as the main ovulation stimulator, providing rupture of the follicle, release of the egg and its implantation in the endometrium [62].

Estrogens are the main hormones that ensure the formation of the female phenotype (female skeletal structure, typical distribution of the subcutaneous fat layer, development of the mammary glands). The target organs of estrogen are all tissues and organs. First of all, there is growth and development of external and internal genital organs [63]. In addition to the well-established organizational influence and activation effect on the reproductive neuroendocrine function, estrogens exhibit a variety of effects on cognitive functions, pain mechanisms, fine motor functions, creation of good mood, regulation of temperature and sleep [6].

Androgens in the female body cause secondary hair growth, and at puberty, together with estrogens, lead to a significant acceleration of growth, maturation of bone tissue [63].

The main androgen in the male body is testosterone. In puberty, under the influence of androgens, the growth and development of the genital organs are enhanced, secondary male-type hair is formed. In adulthood, testosterone stimulates spermatogenesis, determines the male type of sexual behavior [31,55,63].

Thus, the process of puberty in girls can be divided into two stages. The first stage, early puberty, is characterized by an increase in the concentration of FSH and LH in the blood and a change in the sensitivity of the negative feedback mechanism of the interaction of gonadotropins and sex steroids. The second stage (from the middle to the end of puberty) is associated with the formation of a positive feedback, reflecting the completion of the sexual differentiation of the hypothalamus and the formation of the central mechanisms of regulation of the reproductive function, the final fixation of the sexual cycle [62].

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In the male body during puberty, FSH stimulates the growth and development of hormone-producing interstitial Leydig cells. In adolescence and adulthood, FSH stimulates spermatogenesis. Under the action of LH in the interstitial Leydig cells, the synthesis of testosterone is stimulated. Female and male sex hormones - estrogens and androgens are a regulator of the secretion of gonadotropins, interaction with receptors at the level of the hypothalamus and pituitary gland according to the principle of negative and positive feedback [44,63].

According to a number of authors [7,14,15] in boys of 8-10 years of age, before the onset of puberty, there is an increase in testosterone production, which closely correlates with an increase in the concentration of LH in the blood, while the concentration of FSH in boys of this age is lower than in girls. And circadian rhythms of sex hormones in children of prepubertal age are not observed. Therefore, the authors indicate that in the prepubertal period, PH - the function of the pituitary gland in boys plays a more important role in the development of the reproductive system than in girls. The onset of puberty is characterized by a rapid decrease in the sensitivity of the hypothalamus to sex hormones, which leads to an increase in the concentration of LH and FSH. Studying the age dynamics of changes in the levels of gonadotropic hormones in boys [15,46] note a significant increase in the concentration of FSH at the age of 11, while an increase in the level of LH was found only at the age of 14 years. At the same time, the authors note that if the level of LH, having reached the values characteristic of an adult organism at the age of 14, does not change further, then the concentration of FSH continues to gradually increase up to 13-16 years.

The most telling hormonal sign of sexual development is an increase in testosterone production by the gonads. Thus, the correlation of testosterone levels with the level of lutropin was established. The first significant increase in testosterone levels is observed in boys aged 12-13, by the age of 14 it increases 2.5 times and continues to grow until the age of 17-18. The definitive level of testosterone is established after 18 years [45].

When diagnosing disorders of somatosexual development, it is necessary to take into account not only pathogenetically caused disorders in the hypothalamus-pituitary-gonadal system, but also the functional state of other endocrine glands. It is also impossible to ignore the circumstance when the failure of any endocrine gland can lead to disruption of the synchronization of all parts of the endocrine system, especially during puberty [40].

There is evidence of a change in the somatotropic function of the pituitary gland during puberty [35], indicating an increase in the concentration of the hormone during puberty and its low content in men who have reached puberty [14].

The importance of thyroid hormones during puberty is indicated by an increase in cases of violation of its function, as well as an increase in the size of the gland without clinical signs of damage. In the same period, according to the content of thyroid hormones and thyroid-stimulating hormone, the authors [39,46] noted an increase in the activity of the "pituitary-thyroid gland" system. It has been established that physiological concentrations of thyroid hormones stimulate the

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formation of sex hormones and spermatogenesis, while higher concentrations inhibit these processes [4,31].

Thyroid hormones affect the functional activity of not only thyrotropin-producing pituitary cells, but also cells that produce gonadotropins [1,50], and are also necessary to maintain the biochemical homeostasis of the testes and the manifestation of the action of gonadotropins on steroidogenesis [43].

In turn, sex hormones also affect the hypothalamic-pituitary-thyroid system, so estrogens increase the sensitivity of thyrotrophs to thyroliberin [25], and testosterone and its metabolites are able to enhance thyroid function, bypassing the hypothalamic-pituitary system [4].

Glucocorticoids also have an effect on the reproductive system. So, hypercorticism or the introduction of synthetic corticosteroids for therapeutic purposes reduce the activity of the testes, lead to a drop in the level of testosterone in the blood [17], suppress the production of adrenal androgens [38]. There are direct and feedback connections between the thymus gland and the hypothalamic-pituitary system [41].

A decrease in thymosin production by 2.5 leads to blocking of the function of the gonadotropic releasing factor and the synthesis of sex hormones, as a result, gonadal hypoplasia [16]. The functional activity of the thymus gland is controlled by somatotropic and thyroid-stimulating hormones of the pituitary gland, which, in turn, are considered thymotropic and increase the secretion of thymus polypeptides [16].

The most vulnerable reproductive system during its formation. And only timely diagnosis of sexual development disorders with subsequent correction can lead to a complete or partial recovery, to the social and psychological rehabilitation of the patient [40].

The body of children and adolescents reacts sensitively to various environmental factors. The quality of the environment has a pronounced effect on the formation of indicators of the health status of the child's body [29]. Industrial plants that pollute the air and water with harmful emissions disrupt the sexual development of children living nearby. This conclusion was reached by Belgian scientists who compared the development of adolescents from large cities and rural areas. The scientists found that boys from the polluted areas had smaller testicles, while girls lagged behind in size mammary glands. According to researchers, the delay in sexual development is explained by the substances found in the organisms of the examined: polychlorinated biphenyls and dioins [29].

Observations made by Sh. Zh. Teshaev [56] in the Republic of Uzbekistan also show that boys living in ecologically unfavorable areas lag behind in sexual development. Studies have shown that the closer and longer contact with chemical factors, the greater the difference in volume between the right and left testicles. All this indicates that chemical factors that have a negative impact on the body as a whole lead to testicular hypotrophy with subsequent hypoplasia [30]. When studying the degree of sexual development of adolescent boys on the Marshall-Tanner scale in the iodine-deficient region of the Republic of Dagestan, there was a pronounced tendency to lag behind in sexual development, this is especially pronounced in the

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comparison of residents of the city, plain and mountain climatic and geographical zones [55].

Numerous observations have shown that often various somatic diseases, especially protracted, chronic ones, can often affect the timing of sexual development [12,18,23,59] as well as diseases of the endocrine system [20,26,57]. The influence of this pathology can have different consequences on the development of children of different sexes. There are numerous publications showing the negative impact of diabetes on the normal course of puberty [11,59]. The researchers also noted that disorders of sexual development are much more common in boys. In another study, delayed sexual development occurred in 14.3% of patients. These deviations were more often recorded at puberty with the same frequency in both boys and girls. In other works, it is noted that dysfunctions of the reproductive system were more common in girls and delayed sexual development occurs in 2.5-9.8%, and in recent decades there has been an increase in its frequency. [8].

S. U. Irgasheva [26], examining a group of adolescents with delayed puberty, revealed the highest frequency of thyroid disorders: 88.5% had diffuse goiter I-II degree, of which accompanied by hypothyroidism of varying degrees of activity - in 8,9%. E. N. Grak and others [19] noted that the rate of development of secondary sexual characteristics in girls with autoimmune thyroiditis is higher and this is often accompanied by gonadal dysfunction, anovulatory nature of the menstrual cycle, diffuse mastopathy and cystic ovarian degeneration.

General somatic diseases in some cases have a significant impact on the course of the pubertal period. Frequent childhood infectious diseases, chronic pathology, intoxication lead to late puberty in children [2,3,25].

A study conducted by A. Kh. Akhmedova [2] showed that in children with chronic viral hepatitis, sexual development delays occurred in 60.4% of boys and 52.7% of girls. Parallelism between the delay in physical and sexual development was established in 78.3% of cases. The authors have shown that the delay in sexual development is influenced by the duration of the disease and the activity of the pathological process in the liver [25].

In adult patients with CLD, there are significant changes in the functioning of the endocrine system. M. Van Vliet et all [60] noted changes in the concentration of growth hormone, thyroid hormones, anabolic hormones and testosterone. Much attention was paid to the study of androgenic status. The authors found that the androgenic status was reduced in more than 70% of patients with CLD [60]. According to M. V. Kuandykova [36], it was noted that in men with severe BA, there is an increase in luteinizing hormone by 2.4 times, and follicle-stimulating hormone by 2 times. And the observations of E. G. Kolosova et al. [33] in children with bronchial asthma indicated, on the contrary, a decrease in the concentration of LH and FSH in both sexes. V. V. Shamraeva [52] shows that the formation of the pituitary-gonadal system of adolescents suffering from bronchial asthma is accompanied by hormonal abnormalities, which increase in severe asthma and during the transition to puberty. In girls, blood concentrations of LH, FSH decrease and prolactin levels increase. The lag of adolescent girls in sexual development,

menstrual dysfunction are noted by many scientists in chronic lung diseases, bronchiectasis and tuberculosis [12,23,53].

According to E. A. Rechkina [47,54], boys with severe bronchial asthma lag behind in sexual development, they enter puberty about a year later. For girls with bronchial asthma, an imbalance characteristic of the premenstrual period, which is caused by a violation of the estrogen / progesterone ratio, acts as an additional trigger for exacerbation of the disease, since estrogens have a stimulating effect not only on the synthesis of antibodies, but also on other immunological parameters. Unlike boys, girls with severe bronchial asthma have early onset of secondary sexual characteristics and menarche, although the process of developing menstrual function and cyclicity is longer in them than in healthy ones. Also, according to V. V. Shamraeva [52,53], adolescents with bronchial asthma have various disorders of menstrual function and mastopathy. The author points out that sexual disorders in

BA asthma are caused not only by oxygen imbalance, but also by the negative effects of systemic glucocorticoids used to treat BA.

There are few works devoted to the violation of sexual development in children with chronic lung diseases (CLD), and the results obtained are contradictory. The authors unanimously admit only one thing: the problem of impaired puberty in CLD really exists. Much more research is devoted to the problem of sexual dysfunction in adult patients with CLD. The role of sex hormones in the regulation of metabolic processes in children with chronic lung disease has not been studied enough.

Thus, the literature review shows the breadth and importance of the problem of sexual development in children with chronic lung diseases. Against the background of puberty, which in itself is a critical and most vulnerable stage in terms of metabolic changes. In turn, it is in the pubertal period that chronic lung diseases often form initial deviations in the functioning of the gonads, which, progressing in the future, lead to a persistent violation of sexual function.

Despite the relevance of the problem, the analysis of the data available in the literature on the factors influencing the violation of sexual development in children with chronic lung disease showed that there is no consensus on this issue. Thus, the prevalence of sexual development disorders in this disease, its relationship with physical development, as well as the state of bone mineral density, the gonadotropic function of the pituitary gland and gonads, depending on prescription, clinical forms of CLD and the severity of the disease in children, have not been sufficiently studied.

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