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Precocious puberty: An overview and management

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Abstract

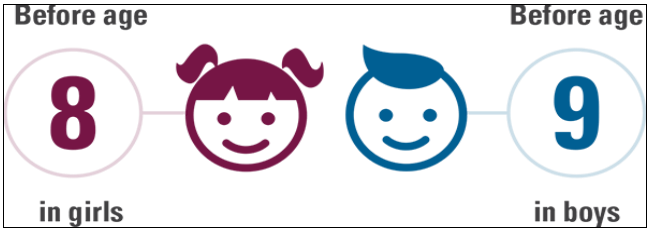
Precocious puberty (PP) is defined by means of the inception of secondary sexual traits earlier the age of eight years in girls and nine years in boys. Precocious puberty may be particularly categorized as central precocious puberty (CPP) and peripheral precocious puberty (PPP) as per the activation of hypothalamic-pituitary-gonadal (HPG) axis. CPP is 5 to 10 times more recurrent in girls. The early maturation of the hypothalamic-pituitary-gonadal axis is specifically due to diet-related factors and endocrine disruptors. Excessive consumption of processed, high-energy and high-fat food can lead to obesity and PP. Nutritional status is considered as one of the most important factors modulating pubertal development. In later life, precocious puberty increases the risk of several diseases such as breast cancer, CVD, diabetes, PCOD etc. PP is diagnosed through physical examination and several biochemical tests. A healthy diet and lifestyle can be proposed as preventive measures for PP. Maintaining physical and mental health, as well as a safe environment is not only beneficial for children not only at adolescence, but also for whole life health.

Keywords: Substituted Li ferrite, magnetostatic and spin waves, microstrip array antenna, X-band frequency range

1. Introduction

Puberty is a distinct transition period when the body reaches mature size and reproductive capacity. Sexual development, growth spurts, and behavioural changes result from the activation of the hypothalamic-pituitary-gonadal axis (HPG). The HPG axis comprises of a complex central nervous system (CNS) that includes several neuronal populations in the hypothalamus, pituitary gonadotroph cells, and gonads. Neurons leading to the activation of the HPG axis are sent to the pituitary portal vein through the pulsatile neurosecretion of hypothalamic GnRH decapeptide. Gonadotropic activation of the pituitary gland, the synthesis and release of gonadotropins, and the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) into the peripheral circulation.

Puberty is usually defined as the beginning of secondary sexual characteristics by the age of eight in girls and nine in boys. This range was chosen as 2 to 2.5 standard deviations (SD) from the mean age of adolescents. The average age at puberty is approximately 10.5 years for females and 11.5 years for males, with an SD of almost one year (Boepple and Crowley, 1996) [10].



In most populations, the onset of puberty follows a normal distribution, with the average age of puberty being about 10.5 years, 11.5 years for girls, and about one year of elementary school for boys (Harrington and Palmert, 2022) [24].

History of Precocious Puberty

1) The 1920s was a period of rapid scientific development based on the finding and synthesis of several gonadal steroid hormones.
2) In 1923-1924, at Washington University in St. Louis,

Edgar Allen and Edward Dois (who were neighbours and continued to work together) exhibited that the follicular fluid extracted from the uterine tube induced cornification of the mucous epithelium in oviparous mice along with sexual maturity in young rats.

Taken together, when follicular fluid from the ovaries of sows (sows) was injected into ovariectomized mice, it was said to have two potent effects.

1. Changes in the vaginal skin: The liquid causes the skin layer of the mouse to change, making it firmer and more protective.
2. Early reproductive development: In addition, when young mice are given the same fluid, it accelerates their sexual development and undergoes reproductive changes earlier than their natural state.

In fact, this study shows that certain components of pig ovarian follicular fluid can affect the reproductive development of mice. This type of research is important to understand the role of various hormones and factors in the reproductive process in different species, and this can have implications for animal science and human medicine (Allen and Doisy, 1923) [3].

The hypothalamus and pituitary gland's role in regulating ovulation was not completely realized until the 1920s. In 1926, Philip Smith published research on the effects of pituitary removal in mice, showing that it causes uterine atrophy. Kisspeptin, KNDy neurons, and adolescent neuroendocrinology.

Precocious puberty→ Identification of the mechanisms and hormonal products of the H-P-G axis has provided remarkable insight into the normal physiology of adolescence. However, until the introduction of Tanner stages by Dr. James Tanner in the 1960s, there was no standard approach for assessing pubertal clinical status and development. James M. Tanner is a British paediatric endocrinologist and Professor Emeritus at the Institute of Child Health, University of London.

Marshall and Tanner identified the normal stage of teenage development in children known as the stage of sexual maturity or "Tanner stage". This study stated that the primary sign of adolescence in girls is breast growth at an average age of 11 years, followed by hair growth and then menarche. In boys, the first sign is testicular expansion at an average age of 11.5 years, shadowed by penile enlargement and hair growth. The stage system is used to describe physical changes during puberty. Tanner stages define secondary sex traits such as breast development in females, hair growth in both sexes, and genital development in males (Marshall and Tanner, 1969, 1970). In general, puberty has been defined as the beginning of breast development in adolescent girls before the age of 8 and sexual development before the age of 9 (Bajpai *et al*., 2007) [6].

In 2007, Goodman and co-workers discovered that kisspeptin neurons in the nucleus express the excitatory neurotransmitter neurokinin B and the inhibitory neurotransmitter dynorphin A, and named them KNDy neurons.

Over the years, various terms have been widely used to indicate the onset of central puberty. Initial reports called "constitutional sexual orientation" or "constitutional isosexual youth." The "true" or "complete" option is used to distinguish this setting from more common changes such as premature warming and premature adrenarche. "Gonadotropin-dependent puberty" was and still is used to differentiate the state from peripheral (gonadotropin-independent) puberty.

Table 1: Tanner stages in Female

Tanner Stage	Breasts	Pubic Hair	Growth	Other
1.	Elevation of papilla only	Villus hair only	2-2.4 inches per year	Adrenarche and ovarian growth
2.	Breast bud under the areola, areola enlargement	Sparse hair along the labia	2.8-3.2 inches per year	Clitoral enlargement, labia pigmentation, growth of uterus
3.	Breast tissue grows but has no contour or separation	Coarser hair curled pigmented covers the pubes	3.2 inches per year	Axillary hair, acne
4.	Projection of areola and papilla, secondary mound formation	Adult hair, does not spread to the thigh	2.8 inches per year	Menarche and development of menses
5.	Adult-type contour, projection of papilla only	Adult hair, spreads to the medial thigh	Cessation of linear growth	Adult genitalia

Table 2: Tanner stages in Male

Tanner Stage	Genitalia	Pubic Hair	Growth	Other
1.	Testes <2.5 cm	Villus hair only	2.0-2.4 inches per year	Adrenarche
2.	Testes 2.5-3.2 cm Thinning and reddening of the scrotum	Sparse hair at penis base	2.0-2.4 inches per year	Decreases in body fat
3.	Testes 3.3-4.0 cm Increase of penis length	Thicker curly hair spreads to the pubis	2.8-3.2 inches per year	Gynecomastia, voice break, increased muscle mass
4.	Testes 4.1-4.5 cm, penis growth darkening of scrotum	Adult hair does not spread to thighs	4.0 inches per year	Axillary hair, voice change, acne
5.	Testes >4.5cm, adult genitalia	Adult hair spreads to medial thigh	Deceleration, cessation	Facial hair, muscle mass increases

Youngest case of Precocious Puberty

The youngest recognized case of central puberty (CPP) was Lina Marcela Medina de Jurado, a Peruvian girl who gave birth to a healthy baby in 1939 at the age of 5 ½. Lina's parents were taken to the hospital because of a large stomach mass, which was thought to be a tumour (Fig 1). There she was more than 7 months pregnant and had a caesarean section 6 weeks later. She reportedly went through menopause at 8 months and was said to have matured reproductive organs at the time of the caesarean section. The case was presented with interest and surprise at the yearly conference of *Academia Nacional de Medicina del Peru*. At that period, there was an emerging consideration of normal reproductive physiology, unaware of the potential disruption of the initiation of the hypothalamic-pituitary-gonadal (H-P-G) axis that happens in CPP (Escomel, 1939) [19].

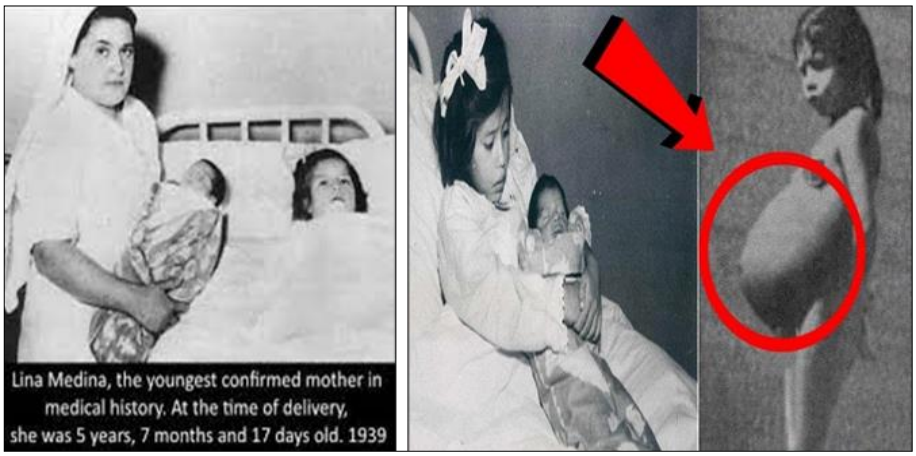


Fig 1: Youngest case of Precocious Puberty

Prevalence of Precocious Puberty

Precocious puberty (PP) is the second most public childhood hormone disorder after childhood obesity. The timing of puberty in girls is decreasing worldwide (Gu *et al*., 2022) [23]. This temporal trend, was first documented in developed countries, is also renowned in developing countries. The accurate epidemiology of PP is unknown. An US study assessed the prevalence of PP in the overall population to be between 1: 5,000 and 1: 10,000. It is more common in women than in women: the male ratio is 3/1 to 23/1 (Mucaria *et al*., 2021) [35].

PP disease in northwest India

Retrospectively analyzed the medical records of adolescent children from a tertiary care clinic in North-West India from 2004 to 2018. Out of a total of 80 children, 55 children (36 girls and 19 boys) were identified in their medical records as adolescents at the time of the study (Dayal *et al*., 2020) [17].

PP disease in South India

In Chennai, the Department of Pediatric Endocrinology, Mehta Multispeciality Hospital recorded data on approximately 100 adolescent girls who were treated and followed up from October 2016 to October 2020. Throughout the study period, 39 girls were diagnosed with CPP (Selvaraj *et al*., 2021) [41].

In Kerala, a case study was conducted between July and September 2014, enrolling 250 school girls in one school each from an urban and a rural area. The occurrence of menopause was found to be 10.4%. Urban (12.35%) and rural (8.43%) (Binu and Thomas, 2017) [8].

Out of 77 adolescent children in Department of Endocrinology, Chennai, Egmore, 76.6% (n = 59) were girls and 23.4% (n = 18) were boys. The mean age for girls and boys in the study was 5.8 ± 2.1 and 7.43 ± 1.4, respectively (Fig 2) (Srinivasan, 2012) [43].

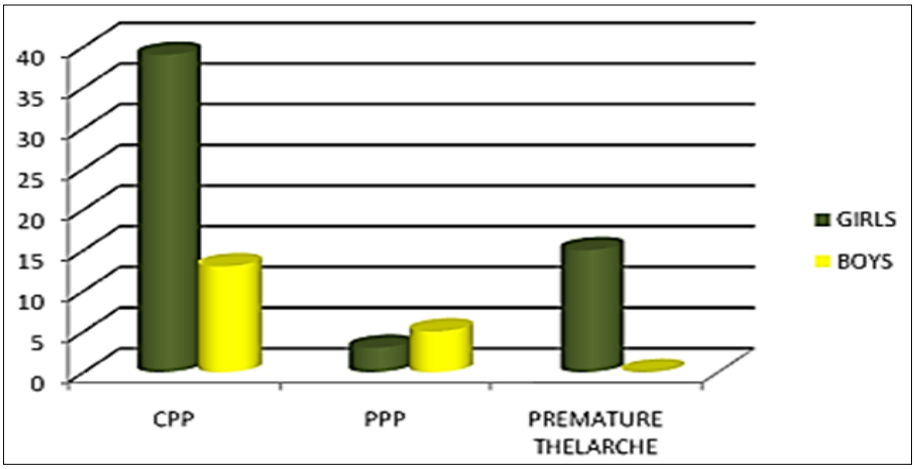


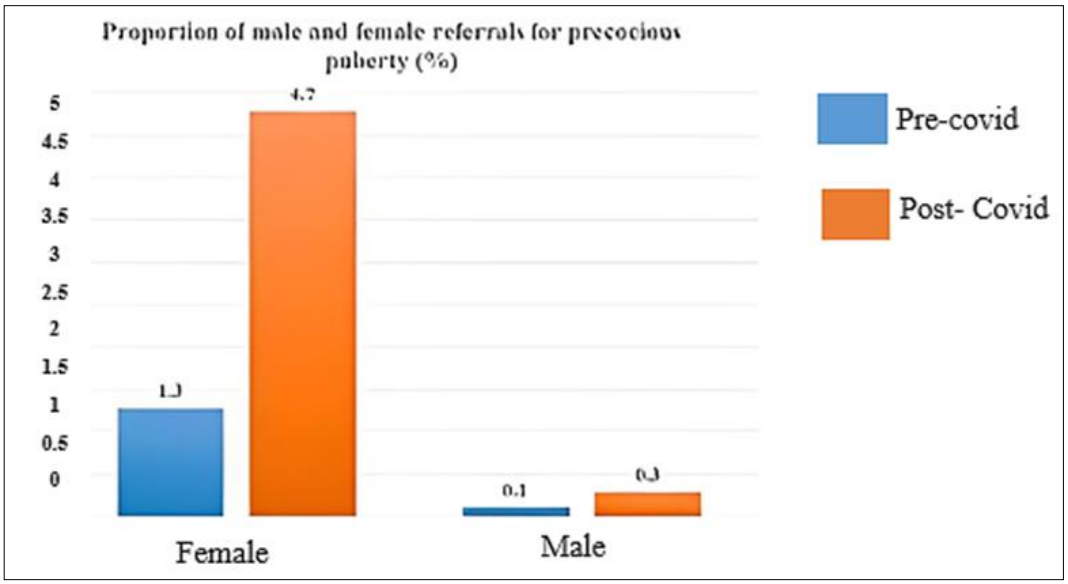
Fig 2: Prevalence of Precocious puberty in Girls and Boys

Incidence of PP during Covid-19

In a new study available in the Journal of Pediatric Endocrinology and Metabolism, scientists found that 155 (5.1 percent) of 3,053 hospital admissions were associated with hospitalization, compared to 59 (1.4 percent) of 4,208 before the pandemic. Anuradha Hadilkar, deputy director of developmental and pediatric endocrinology and consultant, said: "Excessive use of mobile phones, late sleep, stress, anxiety, depression, all these factors contribute to adolescence and these factors dominate." Ward at Jehangir Hospital.

"Due to the widespread use of sanitizers during pregnancy, it is possible that increased exposure to triclosan may cause early puberty in children. However, more research is needed to confirm this association," Hadilkar and co-author described triclosan is an antibacterial and antifungal agent present in products such as toothpaste, soap, detergents, sanitizers, toys and surgical cleaning treatments. It is recognized as an endocrine-disrupting chemical (EDC) that is identified to modify the timing and development of obesity and early puberty.

India was locked down in March 2020. Like the rest of Maharashtra, schools have started opening gradually from October to December 2021. The study investigated two groups: the pre-covid lockdown group from September 1, 2018, to February 29, 2020, and the other post-covid from 1 March 2020, until September 30, 2021. Among these, there is a significant increase in referrals among girls (Fig 3).



(Mondkar *et al*., 2022)

Fig 3: Precocious puberty cases during pre-covid and post-covid phases

Classification of precocious puberty based upon the fundamental pathologic process

Central precocious puberty (CPP)

CPP (also known as gonadotropin-dependent precocious puberty or true precocious puberty) is triggered by pre-maturation of the hypothalamic-pituitary-gonadal axis. CPP is characterized by progressive development of the breast and genital hair in girls, testicular enlargement and pubic hair in men. The gender characteristics of this patient correspond to the gender of the child (isosexual).

Peripheral puberty (also known as peripheral puberty, gonadotropin-independent puberty)

Extreme release of sex hormones (estrogens or androgens) from the gonads or adrenal glands caused by exogenic causes of sex steroids or ectopic production of gonadotropins (eg, human chorionic gonadotropin [hCG]) from germ cell tumors. Peripheral accuracy can be suitable for the child's gender (isosexual) or appropriate, virilizing girls and feminizing boys (contrasexual).

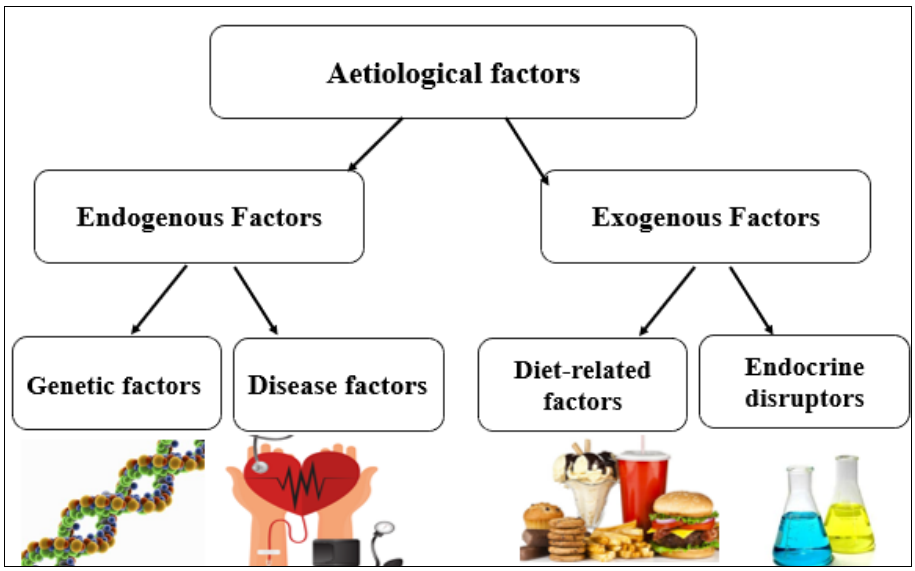
Pubertal benign or immature forms

The best medical teenage possibilities comprise isolated breast development (premature pubescence) in girls or isolated androgenic-intersex characteristics (pubic and/or axillary hair, pubic and apocrine hair) in boys or girls (early adrenarche) resulting from the early activation) of. hypothalamic-pituitary-adrenal axis, as evidenced by mild age-dependent dehydroepiandrosterone sulfate [DHEAS] levels).

In girls, gondarche includes breast development, changes in body position, uterine enlargement, and finally menstruation. In boys, gonadarchy includes enlargement of the testicles; phallic development; primitive presence of pubic, facial, and axillary hair; adult body odor; and oily skin or acne. For girls and boys, adrenarche includes body hair growth, body odor, and acne. Incomplete or unstable pubertal development, often isolated precocious or adrenocortical, is common. Precocious girls show breast development in the first 2 years of life, but these changes are not related to puberty hormone levels, menstruation, bone age on X-rays, or growth spurts.

Isolated premature adrenarche is also not related with the development of puberty. Adrenergic premature infants may have signs of slow adrenal androgen production without a linear growth spurt (eg hair, acne, body odor). Premature adrenocorticism during adolescence may be related with the future development of polycystic ovary syndrome.

Aetiology of Precocious Puberty



Endogenous Factors

Genetic factors	Disease factors
• Genes such as • KISS1 • GPR54 • FGFR1 • FGF8 • Prokineticin 2 • Prokineticin receptor 2 • TAC3 and • TACR3 is related to the abnormal HPG axis activity that induces precocious puberty accompanied by some diseases	• CNS Lesions • Hypothalamic hamartoma • Tumors (Astrocytoma, glioma) • McCune Albright Syndrome • Acquired-CNS Irradiation • Follicular Ovarian Cysts • Hypothyroidism • Spinabifida • Epilepsy

(Leka *et al*., 2017)

Exogenous-Diet related factors

Early-Life Nutrition→ Increased Risk of Precocious Puberty		
Dietary Source	**Mechanism of Action**	**BMI dependent/ Independent Action**
Formula Feeding & Complementary feeding	Formula Feeding instead of breast milk causes overweight development and predisposition to obesity through increased IGF-1 and consequent Sex hormones production.	BMI dependent
Soy-based Formulas & Foods	Soy contains phytoestrogens (genistein and daidzein) that can have estrogen-like effects on the body. These compounds can bind to estrogen receptors in the body and potentially influence hormonal processes.	BMI independent

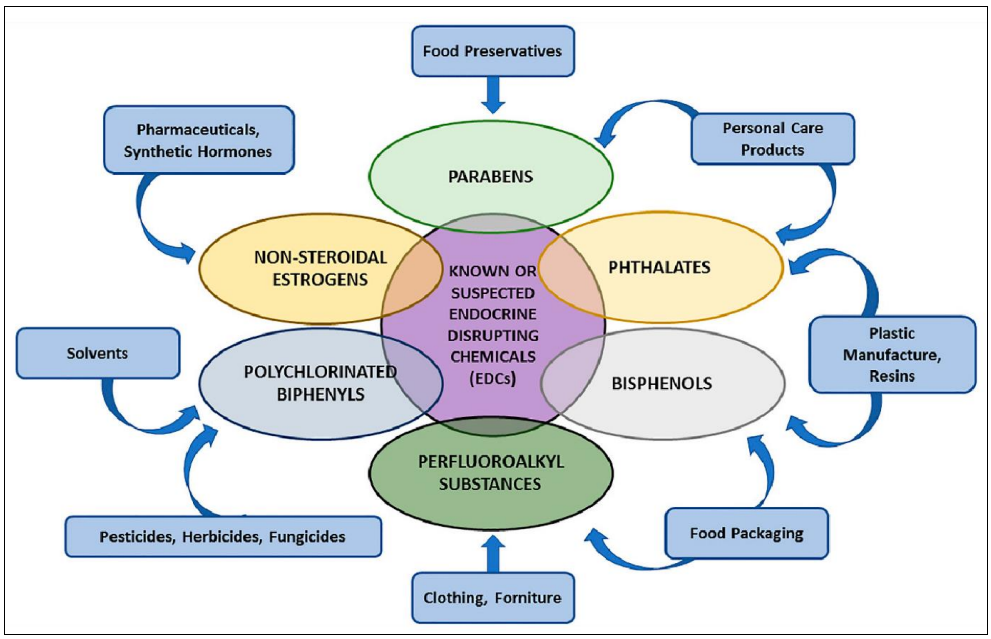
Childhood Nutrition → Increased Risk of Precocious Puberty		
Dietary Source	**Mechanism of Action**	**BMI dependent/ Independent Action**
High Energy Intake	Higher levels of Leptin and IGF-1 activation leads to overproduction of adrenal androgen overproduction and increased conversion of androgens→ estrogens.	BMI dependent
High Protein intake	Adiposity rebounds before pubertal onset and high protein intake leads to increased levels of IGF-1.	Both
High Fat intake (saturated fats and trans fats)	Direct effect on steroidogenesis and mammary glands development, indirect effect through induction of hypothalamic inflammation	BMI independent
High Carbohydrate intake	Rapid increase in insulin concentration in high GI can influence sex hormone levels, primarily by affecting the production of sex hormone-binding globulin (SHBG)and also increases IGF-1	BMI independent
Vitamin D deficiency (VDD)	Vitamin D receptors (VDR) are present in various tissues, including the hypothalamus, pituitary gland, and gonads (testes and ovaries). VDD has been associated with disruptions in the balance of sex hormones.	Both

(Calcaterra *et al*., 2021)

Endocrine Disruptors (EDs)

Exogenic substances that disrupt the endocrine system are defined as endocrine disruptors. Several EDs that disturb teenage development in humans have been recognized, including phytoestrogens, topical and natural estrogens, pesticides, industrial chemicals, and phthalates. As a result, many studies have been conducted in animals and humans on the effects of certain chemicals on the maturation and inhibition of EDs (Fig 4).

Endocrine disorders can disturb the synthesis, metabolism, and action of endogenous hormones, which can contribute to the regulation of usual biological processes and development during adolescence (Veiga *et al*., 2018) [45].



(Buoso *et al*., 2020)

Fig 4: Suspected Endocrine disrupting chemicals that may cause precocious puberty

Hormones with disrupting potential can affect the action at multiple stages, including the hypothalamic-pituitary neuroendocrine axis, the sex glands, and peripheral organs such as the breast, hair follicles, and genitalia. In the brain, EDs can act by stimulating estrogen-sensitive nuclei, including hypothalamic neurons, releasing kisspeptin and encouraging hypothalamic development leading to precocious puberty. Nevertheless, other substances can act

through gonadotropin inhibition via negative feedback. It is also possible that EDs directly affect body weight and the HPG axis in the endocrine system.

These compounds apply estrogenic effects by directly attaching to estrogen receptors, increasing endogenous estrogenic production by the GnRH system, which can lead to precocious puberty. The antiestrogenic and androgenic effects of these substances are frequently mediated by the suppression of aromatase enzyme activity and steroidogenic enzyme production. Finally, they exhibit their antiandrogenic effects by blocking androgen receptors by suppressing testicular steroidogenesis. Finally, depending on the type of exposure to the endocrine disruptors can cause precocious puberty, delayed puberty and sexual differentiation (Ozen *et al*., 2014) [36].

Other causes of precocious puberty are as follows:

Chronic hypothyroidism & precocious puberty

Persistent hypothyroidism is usually categorized by delayed puberty, puberty, and premature menarche in hypothyroid children. Some women with primary hypothyroidism may develop large recurrent ovarian cysts. (Rivkees *et al*., 1988) [39]. Bone age is significantly hindered in both sexes. An increase in serum TSH is constant with the Van Wyk-Grumbach syndrome, in which elevated TSH might act directly on FSH receptors to facilitate puberty (Van Wyk and Grumbach, 1960) [49].

Vitamin-D & precocious puberty

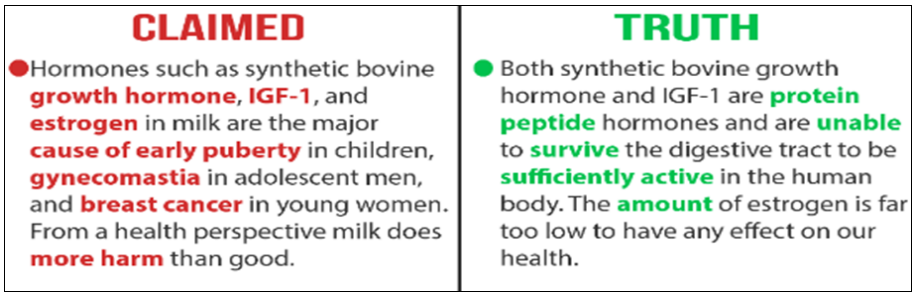
An organized meta-analysis differentiating the serum vitamin D levels between patients with central precocious puberty (CPP) and controls were vitamin D-deficient subjects which were more likely to develop Central PP, signifying that Central PP might be related to vitamin D deficiency (Liu *et al*., 2020) [31].

Sleep & precocious puberty

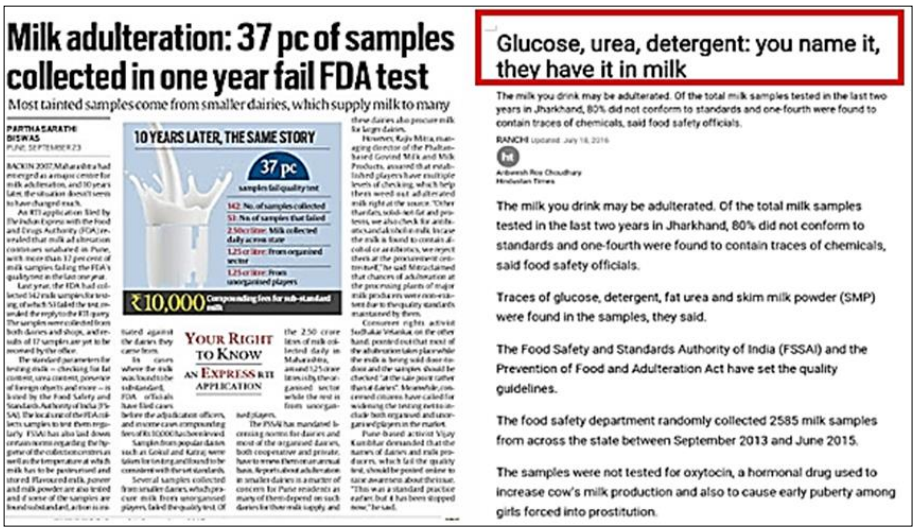
Assuring the time and quality of children's sleep is correspondingly significant in hindering obesity and precocious puberty. The biological rhythm controls various physiological processes, including metabolism, hormones, immune, and reproductive functions. The time and quality of sleep regulate the release of melatonin, which affects the transcription of GnRH and kisspeptin. In addition, sleep promotes the release of growth hormones and prevents ADHD. In addition, the psychological status of children should also be taken into account, and refraining from negative emotions is one of the effective strategies to manage a healthy regime for children (Imamura *et al*., 2022) [27].

Relationship between Milk-Hormones-Precocious puberty

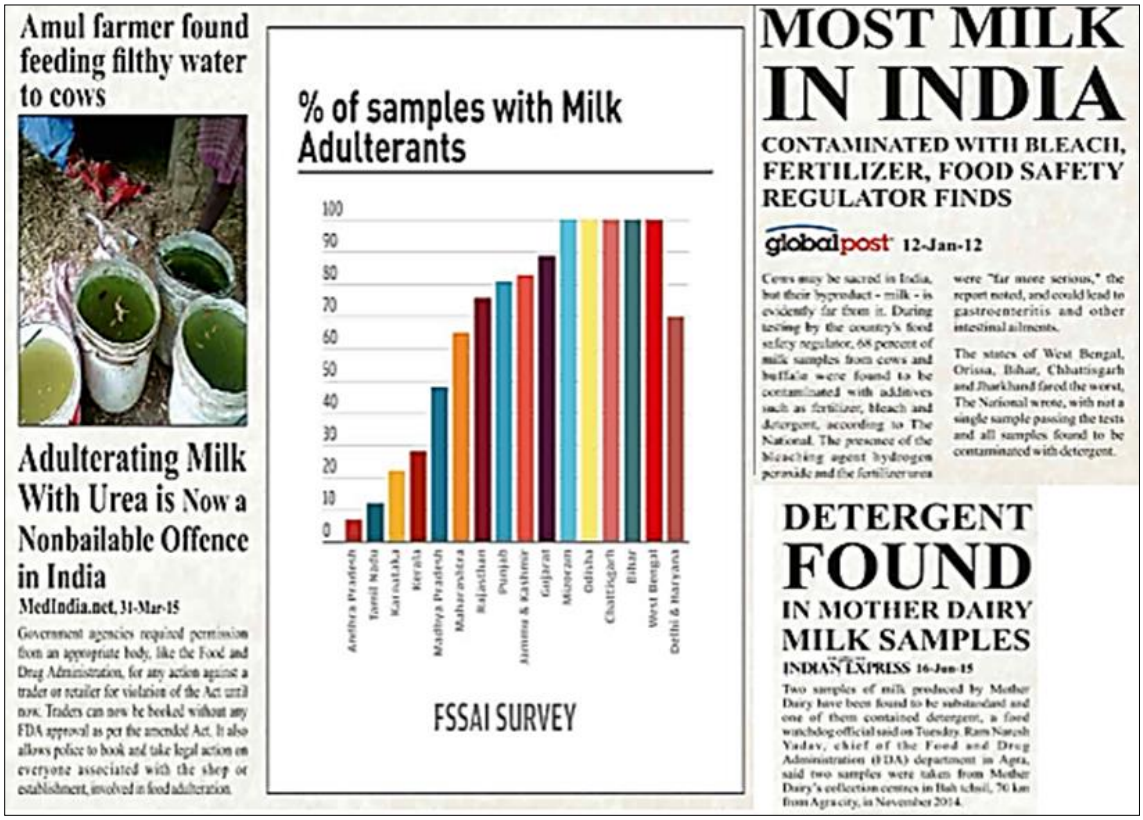
The reason people think milk can cause precocious puberty is because milk contains IGF-I in the human body. Many studies have been done over the last 20 years, but there is no clear connection. The FDA also concluded that IGF-I is metabolized and not directly absorbed by the body, so it has no direct effect on the body.



Following are the new paper articles related to adulteration of milk with urea, pesticides, ammonium sulphate, detergents etc., which are endocrine disrupters and cause precocious puberty.

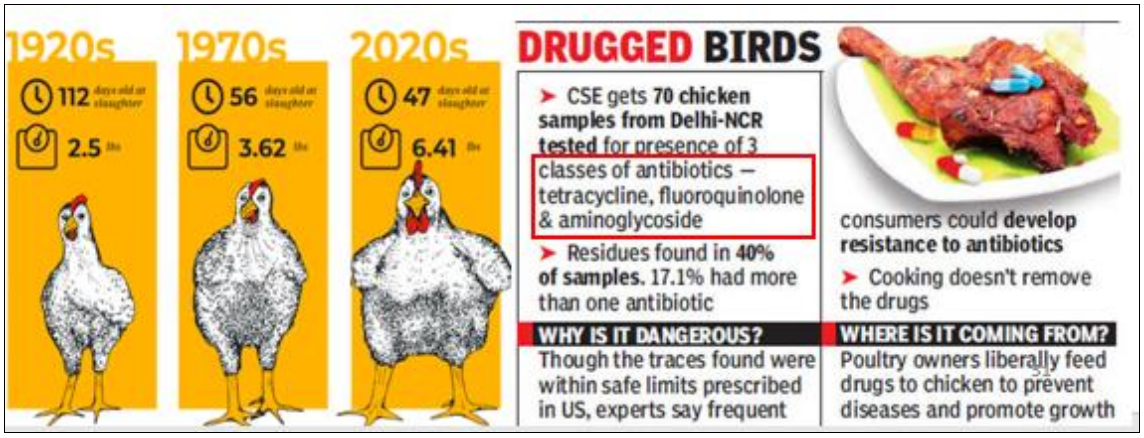


North Indian states are more prone to adulteration in milk compared to southern states of India→



Relation between broiler chicken and precocious puberty→

Injecting hormones into chicken is banned by FDA since 1951. Injecting hormones into a chicken is too expensive. Now-a-days chicken weight is more compared to the olden days. It is due to "Selective breeding". And these chickens have more body weight but are easily susceptible to diseases. So, they have been injected with antibiotics. Acquaintance to antibiotics, particularly fluoroquinolones and tetracyclines was positively correlated with precocious puberty (Hu *et al*., 2022) [25].



Diet-related pathophysiology of precocious puberty

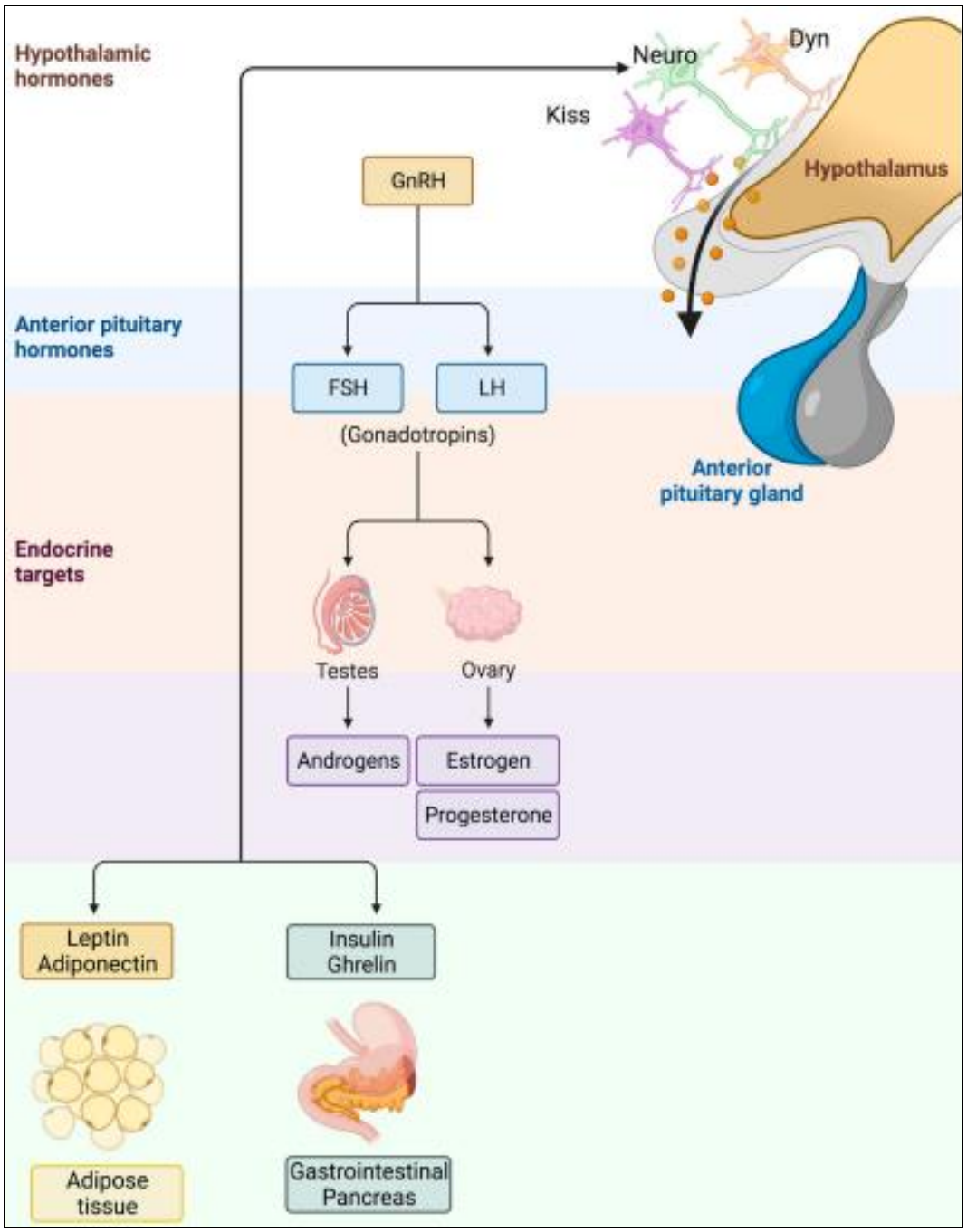


Fig 5: Association within activation of the hypothalamic-pituitary-gonadal (HPG) axis and obesity (Calcaterra *et al*., 2023).

Fluctuations in body mass and protein metabolism during puberty are controlled by several endocrine mechanisms. The hastening of puberty development is mostly because of the synergistic consequences of high amounts of gonadal sex steroids, growth hormone (GH), IGF-I, and insulin. Concentrations of free insulin, IGF-I, and IGF-binding protein 3 (IGFBP-3) during puberty are positively related to leukocyte retention (protein accretion). IGF-I and GH reduce leukocyte oxidation and control protein utilization efficiency during puberty. IGF-I also slows energy expenditure and may cause indirect effects of protein degradation through its effect on energy metabolism during feeding. Plasma insulin levels increase significantly throughout adolescence, with a positive correlation with IGF-I (Fig 5 & 6).

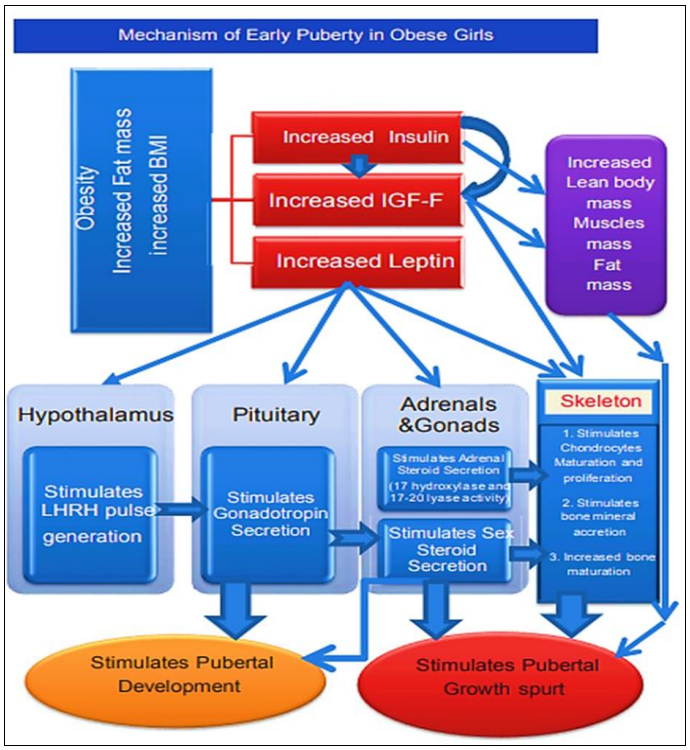


Fig 6: Mechanism of early puberty in obese girls (Soliman *et al*., 2014)

Leptin deficiency causes delay of puberty in rats and humans, which can be treated by leptin administration. In rodents, leptin activates gonadotropic hormone secretion at the level of the hypothalamus and pituitary. Finally, LHRH trigger the pituitary to release LH and FSH, and sequentially promote the sex glands to release testosterone and estrogen. Leptin with low concentrations regarding lack of food may elucidate hunger-induced hindering of the hypothalamic-pituitary-gonadal axis and dysfunction of several other neuroendocrine functions. It is distinct that leptin can be a connection between adipose tissue, the hypothalamic axis that controls energy metabolism, and sexual endocrine glands (Fig 7).

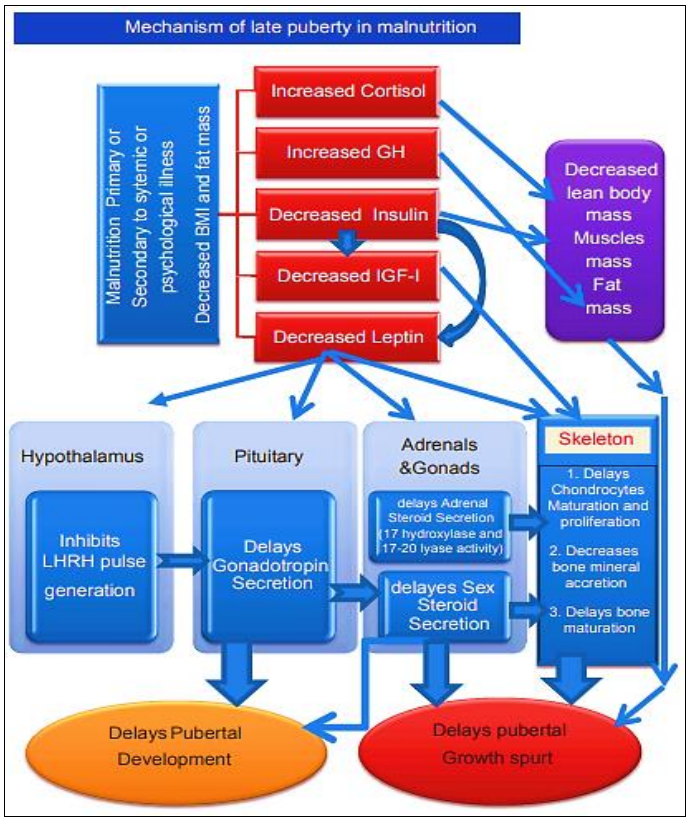
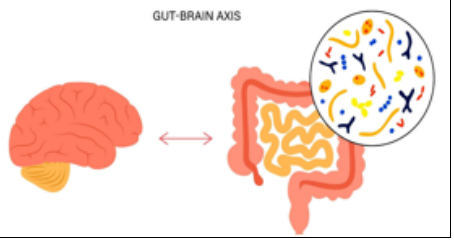


Fig 7: Mechanism of delayed puberty in malnutrition (Soliman *et al*., 2014)

Key communication pathways of the microbiota-gut-brain axis

Dysregulation of the gut microbiota subsequently leads to alterations in all of these central processes. The consumption of junk foods causes gut microbiota imbalances which trigger the hypothalamus to release sex hormones and cause precocious puberty.



Adverse outcomes of precocious puberty

Precocious puberty may cause fast bone expansion, obesity, and dwarf personality. Moreover, precocious puberty is also correlated with higher disease risk in adulthood, such as

- Increased blood sugar levels may cause diabetes.
- Increased weight can cause cardiovascular diseases.
- Increase in BMI and weight may increase blood pressure and metabolic syndrome.
- Endocrine disruptors which cause precocious puberty may increase the risk of breast cancer, PCOD (Polycystic ovarian disease) and Infertility.
- Increased vulnerability to mental and behavioral disorders and also decrease the life expectancy.

Precocious puberty and infertility

Girls with precocious puberty usually have menstrual problems; precocious puberty can lead to sterility for both men and women. Research has found that kisspeptin, a hormone produced in the brain's hypothalamus, as the principal regulator of puberty.

Puberty occurs instantaneously when kisspeptin is released, and puberty is delayed or absent when its release is stopped. Research shows that kisspeptin and the menstrual cycle are disturbed due to obesity and contribute to the development of PCOD and infertility (Jillian, 2020).

Precocious puberty and breast cancer

For the study, researchers analyzed data on 180 girls from the Cincinnati area who entered the Developing Women's Study at ages 6 and 7 in 2004 and remained in the study for 14 years. During the investigation, the girls gave several blood samples.

The results of the study revealed that there are hormonal factors correlated with a greater risk of breast cancer in older women with early puberty. One factor is the high concentration of insulin-like growth factor (IGF-1), a potent growth stimulator, associated with breast density and breast cancer in older women. Second, there is a greater ratio of the hormone estrogen and the hormone androstenedione, leading to a greater effect of estrogen, another risk factor for breast cancer (Alicia, 2020) [2].

Precocious puberty and diabetes

The prevalence of diabetes (type 2) in Korean women (aged 20-50 years) was 3.61 times more in women with first menstrual period before the age of 12 years compared to the women with first menstrual period above the age of 12 years. Central obesity and insulin resistance were 1.83-fold, 2.02-fold, and 1.80-fold, respectively, in women who had first menstrual period before age 12 years.

The prevalence of dysglycemia, prediabetes, and diabetes was 1.85 times, 1.80 times, and 2.43 times higher in Korean women who had first menstrual period before the age of 13 years than women who had first menstrual period at the average age (Fig 6) (Baek *et al*., 2015) [4].

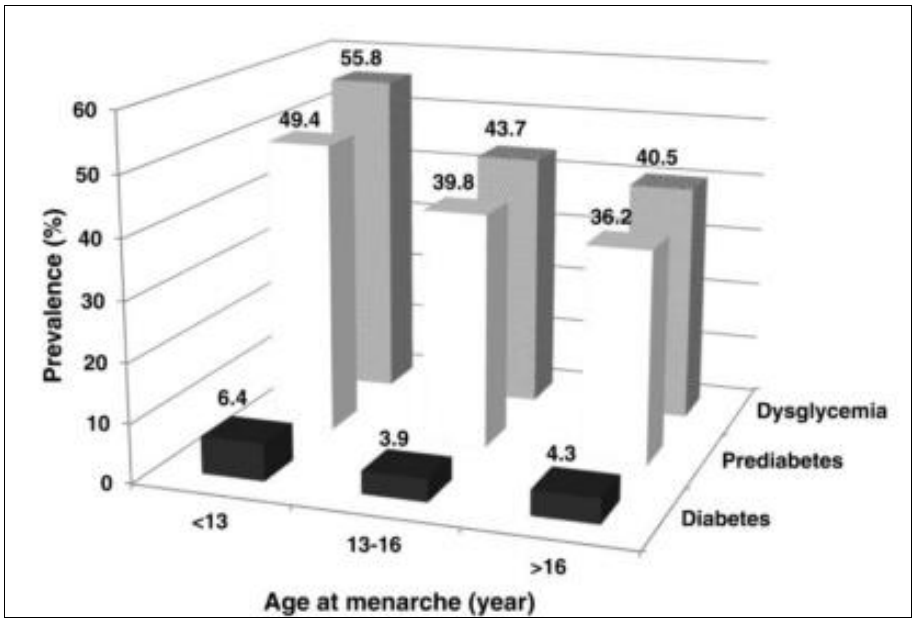


Fig 8: Incidence of diabetes, prediabetes, and dysglycemia conferring to age at their first menstrual period (Baek *et al*., 2015) [4].

Precocious puberty and cardiovascular diseases

The possibility of cardiovascular disease is lowest in the 13-month menstrual period and gradually increases with lower or higher menstrual periods. This possibility is higher in the first menstrual period age groups ≤10 and ≥17 years, with relative possible risk 1.27 and 1.23, respectively (Fig 9). The association between cerebrovascular disease risk and menstrual period is similar to that of coronary heart disease, although weaker (Fig 9). Compared with the group aged <13 months at menarche, the risk was highest in the age groups ≤10 and ≥17, with risk ratios of 1.16 and 1.13 respectively.

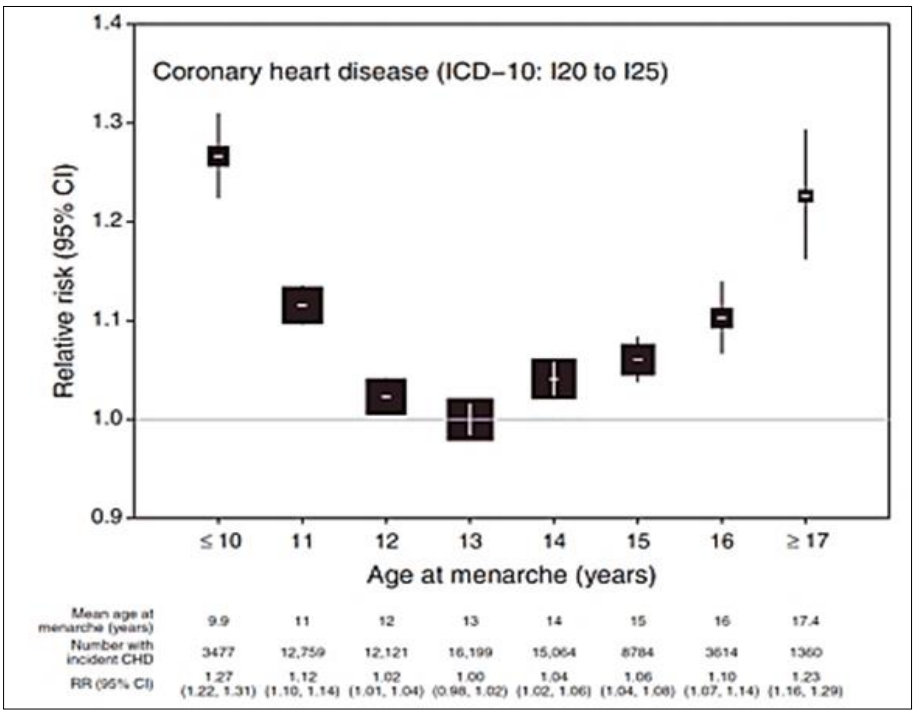
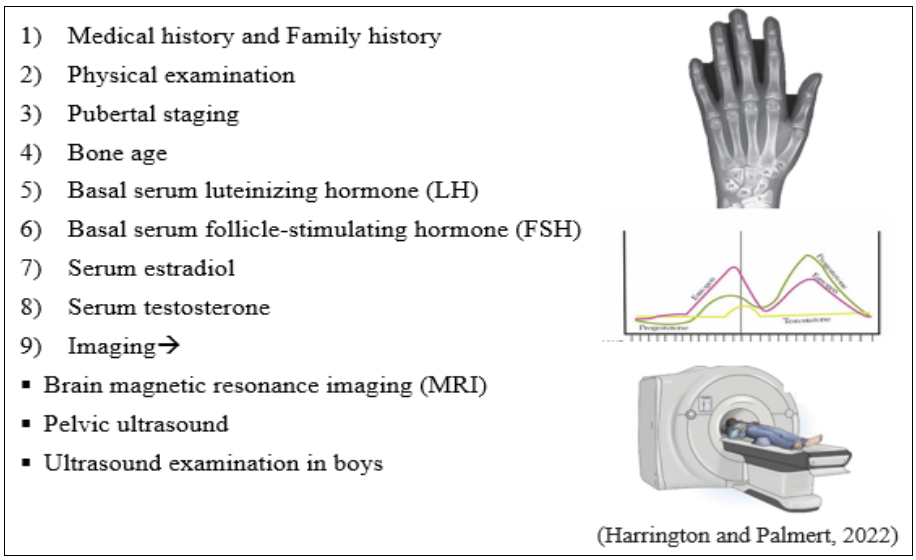


Fig 9: Relative risk (RR) and 95% confidence interval (CI) of occurrence coronary heart disease (CHD) conferring to age at menarche.

Risk of psychosocial problems in precocious puberty

Consumption of tobacco, alcohol, and drugs are more common among teenagers experiencing early adolescence than during middle or late adolescence, although there are insignificant variances in national and social characteristics. Mental and emotional problems such as misery, stress, anxiety, anorexia nervosa, bulimia etc. are more common in tennage girls experiencing precocious puberty. Reportedly, crime and aggressiveness in teenage girls was more who experience precocious puberty. Teenagers of this age may be vulnerable to peer pressure because it is closely correlated to the deviant behavior of their close friends. Therefore, prevention and intensive management of primary school girls is necessary, that is, 2-3 years before their first menstruation, is the most delicate period for teenage girls exposed to adolescent risk behavior (Yoo, 2016) [46].

Diagnosis of Precocious Puberty



Precocious puberty is difficult to diagnose in children with negligible symptoms. Particularly in girls, the diagnosis of PP should be established by demonstrating increased gonadotropins and/or sex steroids, increased somatic growth, and increased bone age. It is also necessary to track the early signs of sexual development. If these symptoms do not persist, early breast development can be considered a normal option.

Initial evaluation

Evaluation of patients suspected of pregnancy typically commences with a thorough history-taking and physical examination. In many instances, bone age is assessed through radiographic measurements to ascertain the progression of epiphyseal maturation. Should there be indications of advancing development of secondary sexual characteristics, further investigation is warranted to identify the underlying cause, determine the necessity for treatment, and decide on appropriate interventions. The initial step involves measuring basal levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), and estradiol and/or testosterone concentrations. These results aid in distinguishing between central precocious puberty (CPP) and peripheral precocity, guiding subsequent diagnostic tests.

Medical history

The patient's history delves into the timing of initial pubertal changes and the onset of puberty in family members. Additionally, inquiries are made regarding episodes of rapid linear growth, headaches, alterations in behavior or vision, seizures, or abdominal pain, which may suggest central nervous system or maternal involvement. Any previous history of CNS disease or focal injury is also explored. Furthermore, potential exposure to exogenous sex steroids from pharmaceutical or cosmetic sources, as well as substances with sex steroid-like properties such as endocrine-disrupting chemicals, is investigated.

Physical examination

This involves assessing height, weight, and growth rate (measured in centimeters per year). Unlike adults, children with benign preadolescent forms do not usually experience early growth spurts. During physical examination, it is important to conduct visual field assessment, as defects may indicate a potential CNS mass. Additionally, cafe-au-lait staining should be examined, as it could be indicative of conditions such as neurofibromatosis or McCune-Albright syndrome.

Pubertal staging

Assessment of secondary sexual development is essential to determine the Tanner stage of pubertal development. This includes evaluating breast growth in girls, penis growth in boys, and hair growth in both sexes. In girls, the diameter of breast tissue and the nipple-areola complex should be palpated, with compression applied to differentiate it from adipose tissue when necessary. Testicular volume is measured in boys. Penis size, specifically the length from the shaft to the tip of the glans, is rarely used to monitor fetal growth due to its late onset during puberty, difficulty in accurate measurement, and potential discomfort for teenage boys. Unlike brain volume, the "pubertal" threshold for penile elongation is not as clearly defined. Accurate measurement of testicular volume is crucial to determine the need for further radiological or laboratory tests.

Bone age

In patients exhibiting confirmed secondary gender precocity upon physical examination, assessing skeletal maturation through radiographic evaluation of bone age can aid in differential diagnosis and determining its potential impact on final height. However, bone age assessment may not be necessary for patients with isolated prematurity or characteristic features indicative of adrenarche, as initial clinical observations may suffice for evaluating pubertal development. A significant advancement in bone age, typically around 2 standard deviations (SD) greater than chronological age, suggests central precocious puberty (CPP) or peripheral precocity rather than benign pubertal variations. Notably, substantial bone growth does not rule out the diagnosis of benign pubertal variations. For instance, up to 30 percent of children with adrenarche may have a bone age that is over two years younger than their chronological age.

Basal serum luteinizing hormone (LH)

An initial test to detect activation of the hypothalamic-pituitary-gonadal axis is measuring the basal LH concentration, ideally in the morning. This is done using a sensitive immune chemiluminescence test with a lower limit of detection of 0.1 mIU/mL (where mIU = milli-international units). The interpretation of results is as follows:

- LH concentrations within the premenopausal range (or <0.2 mIU/mL) typically indicate benign pubertal patterns, such as peripheral spotting or precocious puberty.
- LH concentrations greater than 0.2 to 0.3 mIU/mL (depending on the specific threshold test used) can effectively identify children with progressive CPP with high sensitivity and specificity.
- Basal LH concentration provides limited information in the assessment of adolescent children who are not experiencing growth or are growing steadily. While such children generally have a basal LH concentration of <0.2-0.3 mIU/mL, some may fall within the early pubertal range.
- In cases where there is a lack of development of secondary sex characteristics or a low LH:FSH ratio, a post-gonadotropin stimulation test can help differentiate these children from those with progressive CPP.

Basal serum follicle-stimulating hormone (FSH)

Basal FSH concentrations are not sufficiently useful for distinguishing children with central precocious puberty (CPP) from those with benign pubertal variations. While children with CPP tend to have higher FSH levels compared to those with normal pubertal variations, there is considerable variability within these groups. Similar to LH, FSH concentrations are typically suppressed in children with peripheral precocity.

Serum estradiol

Elevated estradiol concentrations along with suppressed gonadotropin levels often suggest a peripheral diagnosis such as an ovarian tumor or cyst. Many estradiol immunoassays cannot effectively differentiate between prepubertal and early pubertal concentrations at the lower limit of detection. Utilizing more sensitive methods like tandem mass spectrometry for estimating estradiol concentrations can provide better discrimination between prepubertal and pubertal levels, and should be requested separately. However, further research is required to establish the threshold concentration.

Serum testosterone

Elevated testosterone concentrations suggest exogenous exposure, either from testicular testosterone production in boys or adrenal testosterone production in both sexes. When testosterone levels are very high and gonadotropin levels are suppressed, it often indicates peripheral precocity. Measurement of other adrenal steroids, such as dehydroepiandrosterone sulfate (DHEAS), may be necessary to differentiate between adrenal and testicular sources of androgens. In children with central precocious puberty (CPP), testosterone immunoassays cannot distinguish between prepubertal and early pubertal testosterone concentrations accurately. However, the tandem mass spectrometry method is more discriminative, similar to the estradiol assays mentioned earlier.

Other biochemical tests

For boys, assessing human chorionic gonadotropin (hCG) levels is important to evaluate the possibility of hCG-secreting tumors in cases of peripheral precocity. If a tumor is detected in the anterior mediastinum, conducting a karyotype analysis is recommended to evaluate for Klinefelter's syndrome, which is associated with mediastinal germinoma. Thyroid stimulating hormone (TSH) levels should be measured if chronic primary hypothyroidism is suspected as the underlying cause of gender dysphoria.

Imaging

Central precocious puberty (CPP)

Brain magnetic resonance imaging (MRI): It is advised to conduct a contrast-enhanced brain MRI for all boys with central precocious puberty (CPP) and girls who exhibit secondary sexual characteristics before the age of six. This is due to the elevated occurrence of central nervous system (CNS) abnormalities in this patient cohort.

Pelvic ultrasound

Pelvic ultrasound can serve as a valuable diagnostic tool in distinguishing between central precocious puberty (CPP) and benign pubertal variations, particularly when the assessment remains inconclusive. In girls with CPP, larger uterine and ovarian volumes are often observed compared to those with normal pubertal development. While diagnostic criteria for ovarian size have been proposed, there is variability among studies, and significant overlap may exist between CPP patients.

Peripheral precocity

In cases of progressive peripheral precocity in girls, a pelvic ultrasound may be conducted to exclude the presence of ovarian cysts or tumors. However, it's important to note that routine ovarian ultrasound examination may not definitively rule out the diagnosis of ovarian cysts, as cysts can recur during the examination, as mentioned earlier. Adrenal ultrasonography should be strongly considered for suspected adrenal pathology, particularly in cases of rapid virilization.

For boys with peripheral lesions, an ultrasound scan of the testicles can be performed to assess for potential Leydig cell tumors. Additionally, abdominal ultrasound and/or computed tomography (CT) of the abdomen should be considered in children suspected of having adrenal tumors, characterized by progressive virilization and increased serum adrenal androgens, such as DHEAS (Harrington and Palmert, 2022) [24].

Treatment and prevention strategies of precocious puberty

Treatment→ GnRH analog (GnRHa)

Since the mid-1980s, GnRH agonists (GnRHa) have been widely regarded as the primary treatment for precocious puberty. GnRHa function by competing with GnRH for binding to GnRH receptors in the anterior pituitary gland, thereby reducing pituitary stimulation and inhibiting the secretion of LH and FSH. The suppression is most pronounced for LH, making basal LH levels the most reliable biochemical marker for predicting the onset of puberty (Carel *et al*., 2009) [48].

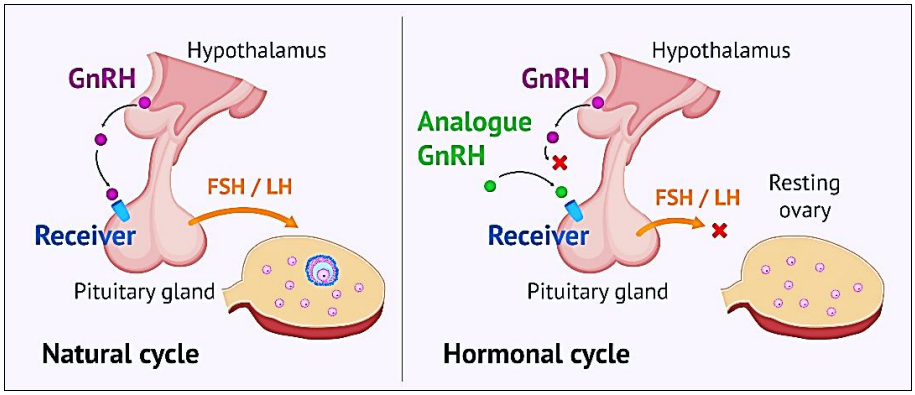


Fig 10: Natural and Hormonal menstrual cycle

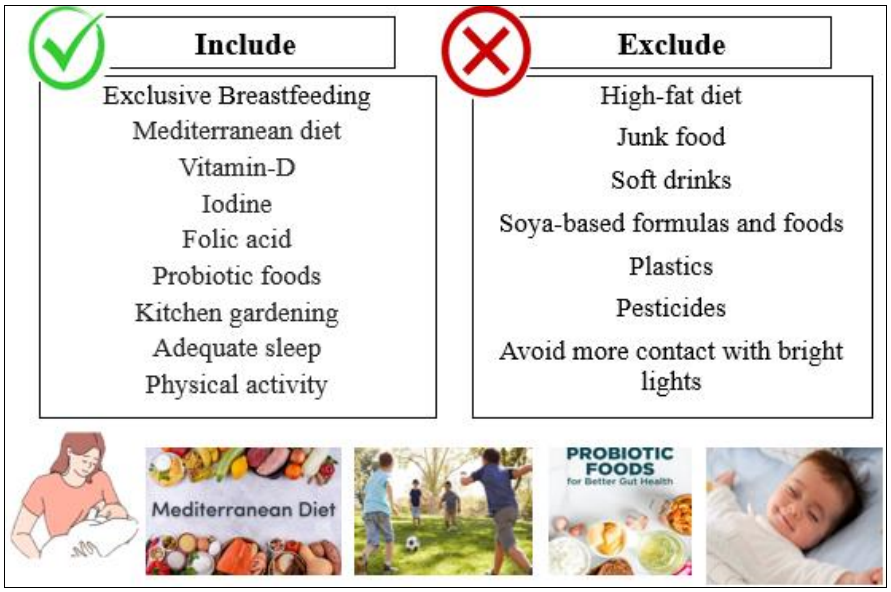
Adverse effects of GnRH analog treatment

GnRH analog therapy has generally been deemed safe for most individuals. However, treatment is associated with decreased growth rates, which may occasionally decline to abnormally low levels. Additionally, GnRH analog therapy can lead to reduced bone mineral density due to decreased estradiol levels. Although this adverse effect was not consistently observed across all studies, calcium supplementation (1 g of calcium carbonate daily) is recommended for all girls receiving GnRH analogs (Bajpai and Menon, 2011) [7]. Several reports have highlighted that short-term GnRHa therapy may entail side effects and limitations, including allergic reactions, vaginal bleeding, hot flashes, and joint pain (Vincenzo *et al*., 2020) [16].

Discontinuation of treatment

GnRH analog therapy should be maintained until the age of 10 for girls and 12 years for boys. Ceasing treatment results in the gradual appearance of secondary sexual characteristics. Typically, menarche occurs around 12-18 months following the discontinuation of treatment (Bajpai and Menon, 2011) [7].

Prevention strategies of precocious puberty



Summary

Puberty (PP) is characterized by the onset of secondary sexual characteristics typically occurring by age eight in girls and nine in boys. Precocious puberty is broadly categorized into central precocious puberty (CPP) and peripheral precocious puberty (PPP), depending on whether the hypothalamic-pituitary-gonadal (HPG) axis is activated. CPP is significantly more prevalent in girls, occurring 5-10 times more often than in boys. Premature activation of the hypothalamic-pituitary-gonadal axis is primarily attributed to dietary factors and exposure to endocrine disruptors. Overconsumption of processed foods, high-energy, and high-fat diets can contribute to obesity and precocious puberty. Nutritional status is recognized as a key factor influencing puberty development. Additionally, early puberty increases the risk of various diseases later in life, including breast cancer, cardiovascular disease (CWD), diabetes, and polycystic ovary syndrome (PCOS). Diagnosis of precocious puberty involves physical examination and several biochemical tests. Encouraging a healthy diet and lifestyle serves as a preventive measure for precocious puberty. Maintaining both physical and mental well-being, along with fostering a safe environment, is beneficial not only during adolescence but also for long-term health.

Conclusion

The incidence of precocious puberty is on the rise globally, driven by changes in lifestyle, dietary habits, and exposure to harmful chemicals across society. The timing of puberty is a significant public health concern with both clinical and social ramifications. Ensuring adequate nutrition during pregnancy, promoting exclusive breastfeeding over formula feeding, maintaining a balanced diet rich in probiotics, fostering exposure to sunlight, prioritizing sufficient sleep, minimizing consumption of soy-based and junk foods, reducing exposure to toxins, limiting contact with bright lights, and encouraging regular physical activity all have the potential to mitigate the risk of precocious puberty.

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