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Association of Exclusive Breastfeeding to the Prevention of Precocious Puberty

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Abstract

Introduction: *Exclusive breastfeeding is breast milk given without other foods to children up to 6 months of age. Breast milk has many uses, including helping children's growth and development, preventing infections, reducing the risk of obesity, and helping children's mental and psychomotor development. Exclusive breastfeeding was found to have a protective effect against the incidence of precocious puberty. Precocious puberty is defined as the onset of puberty that occurs before age 8 in girls and age 9 in boys.* ***Objective:*** *Based on these findings, the authors want to make a study to compile the latest research results on the association of exclusive breastfeeding as one of the prevention of precocious puberty.* ***Method:*** *The author searches, selects, and selects journals related to exclusive breastfeeding with the prevention of precocious puberty through several research databases including ScienceDirect, Google Scholar, PubMed, and Wiley. The keywords used are "exclusive breastfeeding", "precocious puberty", and "prevention".* ***Results and discussion:*** *Various studies have shown that exclusive breastfeeding has a protective effect against the incidence of precocious puberty. Exclusive breastfeeding alone can reduce the risk of obesity in children. Obesity in this child, based on several studies, is a risk factor for precocious puberty.* ***Conclusion:*** *Exclusive breastfeeding of children can prevent the incidence of precocious puberty.*

Keywords: Exclusive Breastfeeding; Precocious Puberty; Prevention;

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Introduction

Breastfeeding is called exclusive if only breastfed and not given other foods other than vitamin and drug supplementation (Couto et al., 2020). Breast milk has an ideal composition consisting of water, proteins, fats, carbohydrates, fatty acids, vitamins, and minerals. The composition of breast milk is important in the healthy growth and development of the child. Breast milk also protects children from various infections, reduces the risk of obesity, endocrine diseases, and helps children's mental and psychomotor development (Couto et al., 2020).

In Indonesia itself, based on recommendations from the Indonesian Pediatric Association (IDAI) which are adjusted to WHO guidelines, exclusive breastfeeding is given to children up to 6 months of age, and breastfeeding is continued until children are 2 years old along with complementary foods (MPASI). As much as 65% of the energy needs of children aged 6-8 months are still met by breast milk, and as children grow older, the energy needs of breast milk needed are getting less and less up to 20% at the age of 1-2 years. According to research conducted by IDAI, the number of mothers who breastfeed newborn children amounts to 90%, this figure is high. However, the number of mothers who breastfeed exclusively for 6 months is still low, which is around 20% (Sembiring, 2022). Exclusive breastfeeding as already mentioned can prevent endocrine problems, one of which is obesity. Based on research, it is stated that children with obesity have a high risk for puberty disruption to be earlier (Hegar, 2013; Sembiring, 2022).

Puberty is a complex biological process that includes physical and psychological changes in the pediatric population (Fadila &; Nugroho, 2018). This period is one of the crucial phases where there are changes in physical, mental, and maturity of sexual organs. Biological development during puberty can be seen from physical changes that can be observed easily such as changes in the voice to become heavier and the appearance of Adam's apple in men, as well as breast size that is getting bigger in girls. Emotional and social development in children who are going through puberty is often overlooked, this development is the result of the interaction between biological development with individual cognitive and environment.

In most children, the onset of puberty occurs in the age range of 10 – 14 years. The early onset of puberty is influenced by various factors such as genetics, gestation, nutrition, and lifestyle. Some studies reveal that there is a tendency for the early onset of puberty to be earlier. Individuals who experience puberty earlier than normal are called precocious puberty. In individuals with precocious puberty, there has not been maturation in psychosocial aspects, but there has been maturation of physical characteristics sexually (Fadila &; Nugroho, 2018).

Precocious puberty is defined as the onset of puberty that occurs before age 8 in girls and age 9 in boys. Precocious puberty causes earlier progression of secondary sexual growth, rapid bone maturation, reduced final height, inappropriate body appearance, and psychological abnormalities (Felício et al., 2021). Based on several studies conducted, exclusive breastfeeding during infancy was found to have a protective effect on the incidence of precocious puberty, especially central precocious puberty (Felício et al.,

2021). Based on these findings, the authors want to make a study to compile the results of the latest research on the association of exclusive breastfeeding as one of the prevention of precocious puberty.

Method

The authors searched, selected, and selected journals related to exclusive breastfeeding with the prevention of precocious puberty through several research *databases* including *ScienceDirect*, Google Scholar, PubMed, *and* Wiley. The keywords used are "exclusive breastfeeding", "Puberty", and "Prevention". The results of the literature search amounted to 4750 journals with 28 journals meeting the selection criteria through titles and abstracts. We prioritize research published within the last five years. Writing begins with literature selection through titles and abstracts, followed by a review of the content of each literature that meets the criteria and followed by discussion between authors.

Results and Discussion

Overview of Exclusive Breastfeeding

Breast milk is a food needed to meet the nutrition of newborns. WHO recommends breastfeeding without food or other beverages in infants who are newborns up to 6 months of age, or called exclusive breastfeeding. Based on recommendations from WHO and IDAI, exclusive breastfeeding is carried out for 6 months and then continued until the child is 2 years old (*Breastfeeding*, 2023; Sembiring, 2022).

Breast milk has a unique composition containing antimicrobial, anti-inflammatory, immune-regulating agents and leukocytes. This unique composition helps the growth of the body's immune system in children (Meek &; Noble, 2022). The nutrients in breast milk are diverse and specific to each mother. The composition of breast milk changes according to the needs of the baby according to his age. Based on the time, breast milk can be divided into 3 stages, namely colostrum (breast milk days 1 – 7), breast milk transition period (breast milk days 7 – 14), and mature breast milk. Colostrum is the first milk to come out with a yellowish tint. Colostrum has high protein and few carbohydrates, fats, mineral salts, water, and fat-soluble vitamins. Colostrum contains high Immunoglobulin A (IgA), lactoferrin, leukocytes, and growth factors. Colostrum also has a function as a laxative that can clean the gastrointestinal tract of newborns. Transitional breast milk is a change in breast milk from colostrum to mature breast milk. At this stage, the protein composition decreases and the composition of fats, lactose, vitamins increases. After 14 days of breast milk, this transition period will be replaced by mature breast milk. In this phase the composition of breast milk becomes relatively constant. Mature breast milk is divided into 2 parts, namely early milk and late milk. Early milk is milk that comes out at the beginning of each feeding. Early milk contains a lot of water, while late milk has more fat which is one of the sources of energy for babies (Boix-Amorós et al., 2019; Lind et al., 2018; Sembiring, 2022).

Breast milk has many benefits for babies, including providing ideal nutrition for babies compared to formula milk which is more difficult for babies to digest. Breast milk also contains colostrum which has many antibodies and can form local protection by SigA on the surface of the gastrointestinal tract which makes a reduced risk of gastrointestinal infections. Exclusive breastfeeding for 6 months can also guarantee the achievement of children's intelligence more optimally. Breastfeeding the baby also helps the child have an inner bond with the mother and also helps the baby get the ideal weight. Babies who are exclusively breastfed have a reduced risk of *sudden infant death syndrome (*SIDS) besides that it can also reduce the risk of respiratory tract infections, gastrointestinal infections, diabetes, obesity, and certain cancers (Kwok et al., 2012; Meek &; Noble, 2022; Sembiring, 2022).

Based on studies and meta-analyses that have been conducted, it was found that in addition to being beneficial for children, breastfeeding is also beneficial for mothers who provide breast milk. In the study, it was stated that there was a significant relationship in mothers who breastfed for more than 1 year with a reduced risk of type 2 diabetes mellitus, hypertension, breast cancer, and ovarian cancer (Meek &; Noble, 2022).

Puberty and its Physiology

Puberty is a major stage in a person's growth, this stage is a complex biological process in adolescence. In puberty there are two main events, namely, activation of the gonads by *follicle stimulating hormone (*FSH) and *luteinizing hormone* (LH) by the pituitary, this is called gonadarche. In addition to gonadarche, there is also adrenarche which is an increase in androgen production by the adrenal cortex (Fadila &; Nugroho, 2018; Wood et al., 2019).

Puberty is a complex process, this process starts from the earliest stages of development. In the first week of life, when the mother's steroid hormones suddenly drop, a phenomenon called "mini puberty" occurs. This process is preceded by early activation of the *Hypothalamic Pituitary Gonadal (*HPG) axis, which increases the synthesis of steroid hormones. An increase in LH and FSH triggers the release of testosterone from the testes in men and the release of estradiol from the ovaries in women. Hormone levels during mini puberty impact genital organ development, fertility, somatic growth, and body composition during the first 12 months of life, as well as cognitive development. This phenomenon lasts approximately during the first six months of life, after which the HPG axis undergoes inactivation until the age of five, and finally reactivates during adolescence.

When *gonadotropin-releasing hormone* (GnRH) induces the secretion of FSH and LH from the adenohypophysis. FSH and LH will promote spermatogenesis and oogenesis as well as the release of testosterone in males and estradiol in females. GnRH stimulation is strictly regulated by excitatory and inhibitory control. Therefore, at the beginning of puberty, there will be an increase in stimulation, while the inhibitory signal will decrease. Some of the stimuli associated with puberty are leptin, kisspeptin, neurokinin B (NKB), and glutamate (Calcaterra et al., 2021).

In particular, a key role in the timing of early puberty is played by leptin and kisspeptin. The action of these two metabolic hormones, in addition to depending on the specific genetic background of the individual, is also influenced by epigenetics. The kisspeptin system is affected by excessive and impaired early malnutrition. There are studies that show that lack of nutrients in the fetus affects the production of this kisspeptin hormone, and directly impacts puberty. Furthermore, puberty is characterized by the presence of chronic central injection of kisspeptin. Circulating leptin levels were found to correlate with birth weight and increased significantly just before the onset of puberty. It is considered a good important factor at the onset of puberty, as well as being a major factor in fertility. Recently, it was reported that leptin can also be considered a positive regulator of the kisspeptin system, although the relationship is not yet fully understood (Calcaterra et al., 2021).

The most noticeable in the physical and biological changes of puberty are postural growth and the growth of secondary sex characteristics. These secondary sex characteristics can be assessed by a sex maturity assessment modality, the Tanner *Stages,* proposed by Marshall and Tanner. This assessment describes systematically secondary sex growth such as breast growth (telarche) in *women,* genital growth in males, and *pubarche hair growth (*pubarche) in both. Changes in these three things are described in 5 stages, the first stage describes the prepubertal phase, while the fifth stage describes adult growth (Calcaterra et al., 2021; Wood et al., 2019).

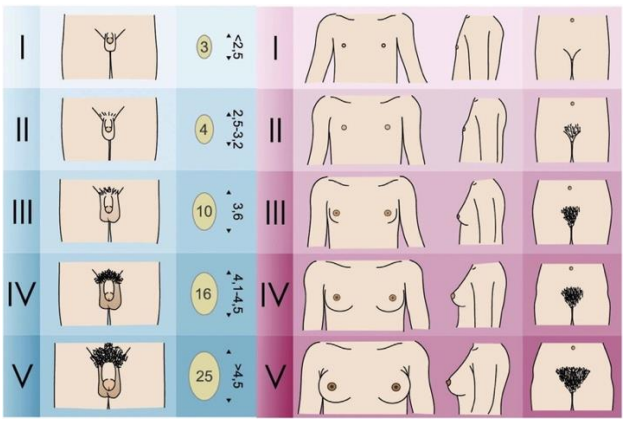

Figure 1. Marshall and Tanner classification (Wood et al., 2019)

Precocious Puberty

Precocious puberty is defined as the occurrence of puberty before the age of 8 years in girls and 9 years of age in males. Precocious puberty is divided into two types, namely central precocious puberty (CPP) and peripheral precocious puberty *(*PPP) (Felício et al., 2021).

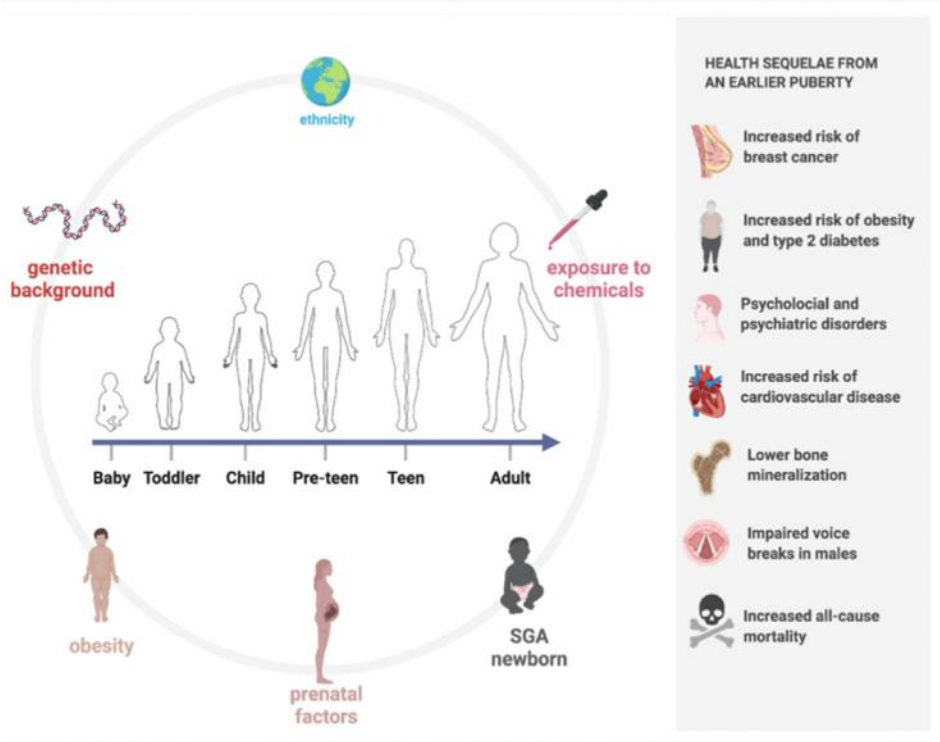

Figure 2. Puberty Time and Sequels to Precox Puberty (Wood et al., 2019)

Epidemiology-wise, CPP was found to be more common in women than men with a ratio of 3 to 1. The cause of CPP can be congenital or acquired abnormalities of the central nervous system (CNS), monogenic defects, and can also be idiopathic. Idiopathic CPP is the most common type of CPP. From the research that has been done, it is estimated that metabolic and environmental factors affect the occurrence of idiopathic CPP. From metabolic factors, leptin, which is adipocytokine, has an important role in the onset of puberty by stimulating the release of kisspeptin (Felício et al., 2021; Hvidt et al., 2021).

Some studies say that nutrients obtained early in life affect the incidence of CPP. Other factors such as stress and exposure to endocrine-disrupting substances also influence the occurrence of CPP in children. In addition to idiopathic, lesions of the CNS are another fairly frequent cause of CPP. Lesions on the CNS are more common in males compared to females. The most common CNS lesion causing CPP is the hypothalamic hamartoma. Hamartomas usually appear before a child is 4 years old and can cause precocious gonadotropin-dependent puberty (Shi et al., 2022).

The diagnosis of precocious puberty is made by accurate history of personal and family history, a complete physical examination, and hormonal and radiological examinations. It is important in the history to know the age of puberty of the parents, the onset of puberty in the child, the possibility of steroid exposure, and signs of the occurrence of lesions in the CNS. A thorough physical examination should focus on antopometric examination and secondary sex assessment using the Marshall and Tanner classification (Wood et al., 2019).

Breast milk as a protective factor against precocious puberty

Nutrition is one of the important factors that influence the occurrence of puberty. One of the influences on puberty is nutrition early in life. Early life nutrition cannot be separated from breastfeeding in infants (Felício et al., 2021; Hvidt et al., 2021).

There have been several studies evaluating the effect of breastfeeding on the onset of puberty, but the results are not always coherent. In the study conducted, a significant association was found between the short period of breastfeeding and the earlier onset of puberty, especially in boys. Other studies have also shown that breastfeeding in girls causes slower sex maturation compared to children who do not breastfeed (Calcaterra et al., 2021; Felício et al., 2021).

Breast milk has a protective factor from the onset of precocious puberty, this is thought to be because breastfeeding has benefits in preventing obesity, while obesity itself is a risk factor for precocious puberty. In another study, similar results were obtained by women who had an overweight and obese body mass index (BMI) reached puberty onset faster than women with normal BMI (Hui et al., 2019; Tambalis et al., 2019).

The association between breast milk and the prevalence of obesity and precocious puberty is levels *of insulinlike growth factor (IGF)-1* and leptin. Increased IGF-1 levels can be seen in infants who are not breastfed and only get formula milk, as well as in children who gain weight rapidly in the early months of birth. Both of these correlate with faster production of sex steroids. This condition will facilitate secretion of GnRH, resulting in an accelerated onset of puberty (English et al., 2020; Felício et al., 2021; Schraw et al., 2015).

Exclusive breastfeeding can prevent early introduction to foods that can promote excess weight. Studies show that protein and total energy intake are lower in children with exclusive breastfeeding compared to children with formula feeding. Another study also added that children with formula milk have a higher body weight. High protein intake of excess weight early in life is associated with the incidence of childhood obesity. Children who are given formula milk have higher levels of insulin in plasma compared to children who are exclusively breastfed. High levels of insulin in plasma will stimulate fat deposition and adipocyte formation more quickly (Aghaee et al., 2019; Rito et al., 2019; Sadauskaitė-Kuehne et al., 2004).

The mechanisms of obesity and puberty are complex and are still being studied. Some studies have found that early puberty in overweight and obese children is thought to be associated with higher leptin levels and lower adiponectin levels. It can stimulate the production of sex hormones. Leptin was the first adipose cytokine identified and is a peptide hormone (16kDa) encoded by the obesity gene product (ob), as well as secreted from adipocytes into the circulation. Leptin levels are directly related to the amount of body fat (Reinehr &; Roth, 2019).

Physiologically, circulating leptin is a sensitive marker of metabolic status. The circulating leptin will then transport signals to the hypothalamus. After binding to leptin receptors (LepRb) in the hypothalamus, leptin activates pathways such as JAK2/STAT3, PI3K/IRS/AKT, and SHP2MAPK, then uses anorexigenic and thermogenic functions to

ease the metabolic load in the periphery. Simultaneously, accumulation of phosphorylated STAT3 dimers will induce SOCS3 transcription, which inhibits the JAK2/STAT3 pathway. The efficient work of this leptin signaling feedback mechanism guarantees metabolic homeostasis (Huang &; Roth, 2021; Shi et al., 2022; Tambalis et al., 2018).

Leptin is also a permissive factor for neurosecretory activation of GnRH at puberty. Kisspeptin produced by Kiss1 neurons in the hypothalamus is the basic regulator of GnRH. Leptin deficiency has been found to cause decreased expression of Kiss1 in the hypothalamus, whereas addition of exogenous leptin will increase expression of Kiss1. Clinical investigations reported that serum leptin levels were seen higher in girls who developed CPP compared to controls. Consistently, individuals with malnutrition have low leptin levels with delayed onset of puberty, whereas individuals who are overweight or obese have high leptin levels and have a faster onset of puberty. Individuals with obesity show high leptin concentrations due to adipose tissue expansion, but these high leptin concentrations fail to elicit the expected suppression of food intake and increased energy expenditure. This leads to a phenomenon called leptin resistance (Shi et al., 2022; Uwaezuoke et al., 2017).

Leptin resistance is a hallmark of obesity. It displays high circulating and central leptin concentrations. The lack of feedback from leptin signals in leptin resistance will continuously stimulate Kiss1 expression, and damage the balance of NKB and Dyn modulation in kisspeptin secretion (Nsamba et al., 2019; Shi et al., 2022; Uwaezuoke et al., 2017).

Other studies have also shown that an increase in adipose tissue leads to insulin resistance, thereby reducing the concentration of sex hormone-binding proteins and increasing the bioavailability of sex hormones (Liu et al., 2021). The study, conducted by Liu et al, showed that prolonged overweight and/or obesity, for 1 year or more in girls, and more than 2 years in boys, can affect the incidence of CPP. This suggests that aggressive weight loss interventions may be an important strategy for CPP prevention in overweight and obese patients. In addition to weight loss interventions, many studies have shown that exclusive breastfeeding for more than 6 months, has been shown to be protective for obesity and precocious puberty (Liu et al., 2021; Wagner et al., 2021).

Conclusion

Exclusive breastfeeding has many benefits, including increasing children's immunity, preventing children from respiratory and digestive infections, preventing obesity in children, helping children's mental and psychomotor growth and development. In recent studies that the authors compiled, it was found that breast milk has a protective effect on the incidence of precocious puberty, especially CPP. Obesity in children is one of the risk factors for precocious puberty. Obesity in childhood can be prevented by exclusive breastfeeding up to the age of 6 months. Exclusive breastfeeding can be associated with the prevention of precocious puberty.

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