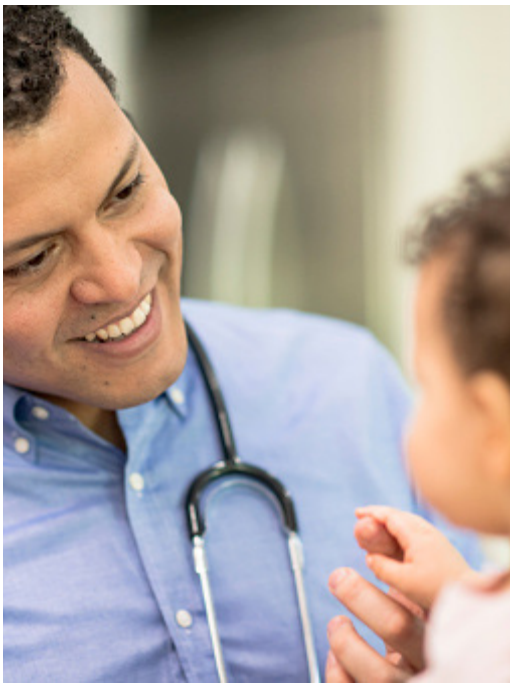
The assessment of premature thelarche



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Background
Premature thelarche (PT) is defined as early breast development without other signs of pubertal maturation. It is frequently considered to be a normal variant of pubertal growth in girls. When premature thelarche presents under the age of two years, most infants will have spontaneous remission.

Objective
Progression to precocious puberty (PP) can be seen in infants with PT, especially when breast development commences after the age of five years. With consequences on bone maturation and final height, it is imperative that general practitioners (GPs) confidently differentiate isolated benign PT from that which might progress to PP.

Discussion
This article emphasises the importance of simple baseline investigations, referral red flags and judicious follow-up to allay parental anxiety or expedite treatment of PT for those children who need it.

THE WORD 'THELARCHE' comes from the Greek definition of two words: *thele* for 'nipple' and *arche* meaning 'beginning'.

Thelarche is the beginning of breast development.

The normal age range at which breasts begin to develop is at ages 8–12 years. Breast development that occurs before the age of eight years in girls is considered early.[1,2]

The most common condition to cause early breast development in girls is isolated premature thelarche (PT). First defined by Wilkins in 1957 this condition refers to 'isolated breast development in the absence of any other clinical signs of pubertal maturation in girls younger than eight years, predominantly in the first two years of life'.[3]

PT occurs only in females. Breast development in male children is termed gynaecomastia.

Aim

This article aims to equip general practitioners (GPs) with a comprehensive understanding of the clinical manifestations, natural history, recommended investigations and follow-up guidelines for the assessment of PT.

A systemised approach enables GPs to distinguish benign PT from those progressing to precocious puberty (PP). This allows for appropriate reassurance while avoiding any unnecessary investigations for most families, and timely referrals for others.

Girls with isolated PT have a significant degree of anxiety and depression, with reduced quality-of-life scores.[4] By addressing both their physical and mental health concerns, GPs can play a vital role in improving overall health outcomes.

Clinical implications

Girls with isolated PT typically exhibit isolated breast development without signs of pubarche (pubic hair) or menarche (menstruation). They maintain normal growth velocity and bone age. In contrast, girls with PP might have PT along with additional signs of puberty, such as pubarche and menarche, often accompanied by advanced growth and advanced bone age. Figure 1 shows the age onset of pubertal stages.

Because PT usually precedes the other manifestations of PP, it is an important 'canary in the coalmine' for GPs to recognise red flags and prompt early intervention to prevent early epiphyseal fusion, altered growth trajectories and significant lifelong impacts.

Classification

Two primary age groups present with isolated PT: under age two years and ages 5–7 years. The former is often classified as classical benign PT, while the latter is referred to as atypical or exaggerated PT.

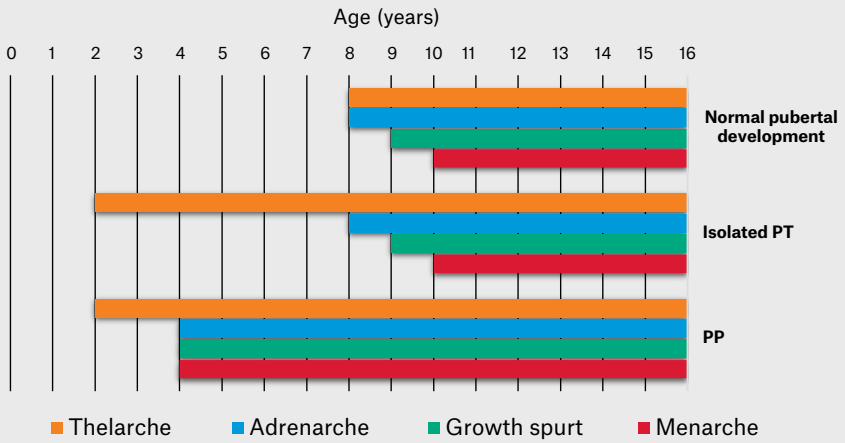

Figure 1. Age onset of pubertal stages for girls.[1,2,6]
PP, precocious puberty; PT, premature thelarche.

Classical benign PT occurs in girls under age two years, with typically minimal bilateral breast tissue development. They commonly present with Tanner stage 2 breast development.[2] Studies indicate 60–89% of these cases regress or stabilise by age three years.[5,7–10] However, Volta,[5] Wang[11] and Zheng[12] have reported this seemingly indolent presentation has a 9–29% risk of progressing to PP, highlighting the need for careful monitoring.[5,7,11,12]

Atypical or exaggerated PT refers to breast development that has not regressed by age three years or that has commenced after the age of three years, most commonly seen in the group aged 5–7-years. Although breast development remains small, it might show a cyclical pattern or might progress, with a 21–36% risk of transitioning to PP.[6]

Prevalence and risk factors

There are no reported incidence or prevalence figures for isolated PT within Australia, but international studies report rates between 0.4–8.9% of all females born.[11,13–16] Puerto Rico has the highest incidence of benign PT (<2 years) and atypical PT (>3 years) with an annual rate of 6.2 per 1000 live births and 1.6 per 1000 live births respectively.[16]

There are no reliable tests that can distinguish PT cases that will regress versus those that progress to PP. However, there are several risk factors which are statistically significant for progression to PP, including:[12,17,18]

- breast development which commences after ages 5–6 years
- girls presenting with Tanner stage 3 breast score, which has a seven-fold increased risk
- larger ovarian volume on pelvic ultrasound.

See Table 1 for the distinguishing features of PP and PT.[7,13,14,18–21]

Aetiology

The aetiology of isolated PT remains largely unknown.[22] In girls under age two years, the cause is mostly idiopathic, while in girls over age three years, it might relate to partial activation of the hypothalamic-pituitary axis, increased oestrogen secretion from ovarian follicular cysts and increased body fat mass.[15]

The following lists some of the identified causes.[15–17,20,22–24]

Common causes include:

- idiopathic
- higher body mass index (BMI)
- ethnicity – higher prevalence in Black African-American and Hispanic girls.

Less common but important not to miss are:

- primary hypothyroidism
- exogenous oestrogens and oestrogenic agonists, such as:
  - child's exposure to their caregiver's use of topical oestrogen/testosterone creams
  - lavender oil
  - herbal medicines used for colic (eg *Foeniculum vulgare*)
  - tea tree oil
  - phthalate esters (found in food, water, soil, plastic products, pesticides and stock feeds)
  - phytoestrogens (eg soy-based food sources).

Clinical evaluation and assessment of premature thelarche

Early breast development in girls can cause parental concern. It is important to systematically evaluate this to determine if it is isolated benign PT or PT requiring prompt intervention (see Figure 2 for a flow chart on the evaluation of breast development). Providing parental reassurance or appropriate guidance based on these findings is essential.

History

A detailed history of both the child and mother's health, and parental pubertal and growth history, should be obtained (Box 1). Determine the age of onset of the child's breast development, evaluate if it is stable, cyclical or progressive, and inquire about any accompanying signs, such as pubic hair development or growth spurts. Breast, pubertal development and growth spurts that are out of keeping with parental history or in keeping with a family history of PP might indicate an increased risk of PP for the child.

Assess for possible reversible causes including a caregiver's use of transdermal hormones and natural therapies used for colic. It is also important to assess the family's anxiety levels, as addressing psychological distress can improve quality-of-life scores.[4]

Table 1. Distinguishing clinical features of PT and PP[7,13,14,18–21]

	Classical benign PT	Atypical or exaggerated PT	PP
Age onset	6 months – 2 years	Typically, ages 5–7 years but can commence after age 3 years	Can be from age 6 months
Breast development under age 8 years	Yes	Yes	Yes, plus at least one additional feature (adrenarche/menarche/accelerated growth)
Breast (Tanner stage)	Stage 2 stable or regressing	Stage 2 or 3 stable, cyclical or progressive	Stages 2–4 and progressing
Early adrenarche	No	May be present	May be present
Early menarche	No	No	May be present
Accelerated growth velocity	No	May be present	May be present
Accelerated bone age	No	No	Yes
Prevalence	0.4–8.9%	6–15%	Incidence of 415 per 10,000 population and increasing
Breast bud regression	60–89% by age 3 years	No	No
Rate of progression to PP	9–29%	• 21–36% • Higher rates of progression with later age of onset	
Long-term sequelae	• Normal height • Normal puberty onset • Psychological distress	• Normal height • Normal to slightly early puberty onset	• Shortened height • Early puberty onset • Psychological distress • Early sexual activity • Possible increased risk of breast cancer

PP, precocious puberty; PT, premature thelarche.

Examination

Assessing breast developmental stage

Breast development should be classified using Tanner stages,[2] which describe the expected timing and sequence of normal pubertal development (Figure 3). The average onset of breast development (Tanner stage 2) is around age 10–11 years , with pubic hair developing before, simultaneously or just after thelarche. Menarche usually occurs within two years of the onset of breast development, at an average age of 12–13 years.[1,2]

Correct staging of breast and secondary sexual characteristics compared with chronological age enables GPs to reassure children and their parents in situations of normal developmental progress. Deviations in this sequence, which might indicate a physiological problem, can be quickly recognised and acted upon.

After seeking appropriate permissions and with the child's parents present, perform an examination with the child lying down. Determine if the breast enlargement is glandular tissue or lipomastia, and assess the breast Tanner stage. Tanner stage 2 breast development has a small breast bud mound. Tanner stage 3 has further enlargement of the breast mound and areola.

Assess for additional secondary sexual characteristics if indicated.

A breast ultrasound scan (USS) might be indicated if galactorrhea or any additional primary breast, chest wall or vascular pathology is noted at examination.

Monitoring growth

A standardised technique must be used when assessing growth. Equipment and standardised growth charts must be accurate and appropriate for the child's age.

The Queensland Child and Youth Clinical Network (QCYCN) provides a platform for health professionals to access resources and clinical guidance frameworks that improve the wellbeing of infants and children. Its key publications 'Assessing infant/child nutrition, growth and development within the primary health care setting'[30] and 'Child and Youth Health Practice Manual'[31] provide the current guidelines on assessing growth and recognising deviations that require further investigation and/or referral.

Length is measured in the recumbent (lying) position for infants aged younger than 24 months or children aged 24–36 months who cannot stand unassisted.

Use a calibrated digital or mechanical Infantometer with a fixed headboard and a smoothly moving footboard.

Height is measured for infants aged over two years and is measured in the

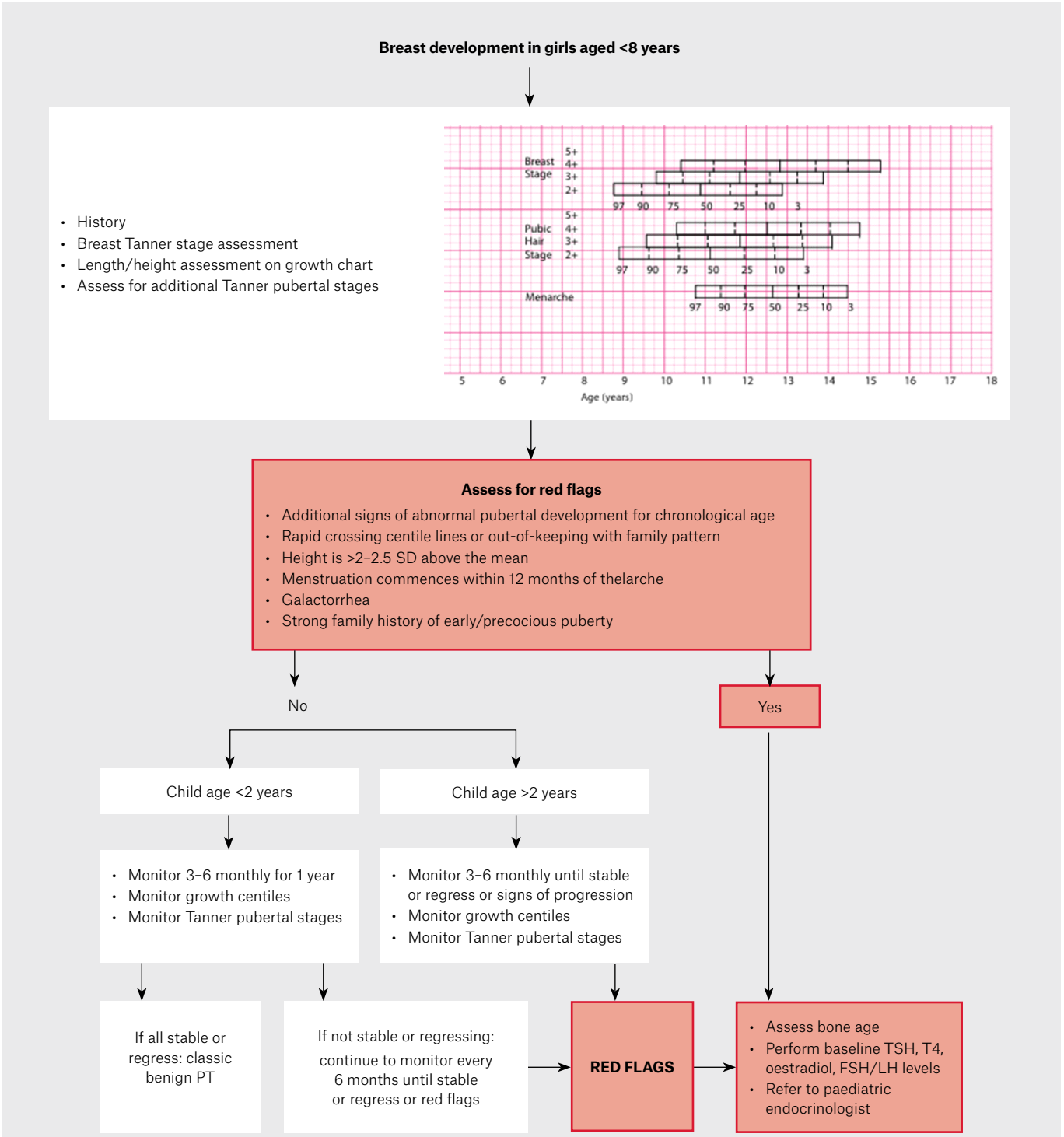

Figure 2. Flow chart for the evaluation of breast development in girls aged under 8 years.[6,25,26]

Pubertal stages reproduced with permission from Australia and New Zealand Society for Paediatric Endocrinology and Diabetes. Girls 2–18 years. ANZSPED, 2023.

FSH, follicle-stimulating hormone; LH, luteinising hormone; PP, precocious puberty; PT, premature thelarche; SD, standard deviation; T4, thyroxine; TSH, thyroid stimulating hormone.

standing position using a stadiometer (height measurer) or a correctly installed 'pull-down' measure.

Perform regular and consistent monitoring at three- to six-month intervals to analyse the pattern or trend of growth when plotted on a growth chart.[28,29]

Follow-up of premature thelarche

Most children with Tanner stage 2 breast development can be assessed and monitored with a history, physical examination and review of their growth chart, with regular observation at three- to six-month intervals. Emotional wellbeing should also be evaluated as girls with benign isolated PT have a higher Revised Child Anxiety and Depression Scale (RCADS) score and a lower physical Pediatric Quality of Life Inventory (PedsQL) psychosocial score.[4]

In the age-under-two-years group, stable or regressing breast development over 12 months with height centiles following expected centile lines and no additional signs of abnormal pubertal development for chronological age typically indicates benign isolated PT, and no additional hormonal studies or bone age assessments are needed.[32] These children can be reassured of progressing to predicted menarche consistent with maternal age of menses[33] and obtaining a final height consistent with, or slightly higher than, predicted final height.[34]

For cases that have not regressed by age three years, or which present later, ongoing three-monthly assessments of pubertal stages and growth should occur (see Figure 2) until normal development is observed or red flags emerge that require further investigation and referral.[7,33]

Parents can be educated on the normal and abnormal pubertal signs to monitor and should be advised on when to present for an earlier review.

Box 1. History and examination[26-29]

Detailed medical history

- Mother/caregiver: current medications (transdermal hormones)
- Parents:
  - Parental height and puberty history
  - Known familial genetic conditions (neurofibromatosis)
  - Strong family history of early/precocious puberty
- Child:
  - Growth in utero
  - Birth weight, length and head circumference
  - Age of onset and progression of breast development
  - Is it unilateral?
  - Is there associated galactorrhea?
  - Appearance of additional signs of abnormal secondary sexual development for chronological age – Tanner stages
  - Nutrition (eg soy-based formula)
  - Relevant medical history
  - Medications
  - Exposure to exogenous oestrogens, including estrogenic environmental pollution (eg lavender oil, tea tree oil, natural therapies). Breast development is reversible on stopping these

Detailed physical examination in partnership with parent/caregiver

- Length/height and plot data on appropriate growth charts:
  - WHO growth standard up to age 2 years
  - CDC growth charts for ages 2–20 years
  - Weight and plot data on appropriate growth charts
- Head circumference
- Tanner stages for breast development
- If unilateral breast development, exclude chest/muscular/vascular/ lipoma abnormalities
- Assess and plot the development of secondary sexual characteristics against chronological age charts.

CDC, Centers for Disease Control and Prevention; WHO, World Health Organization.

Investigations

Bone age

Bone age is the most reliable method to distinguish isolated PT from PP.[35,36]

An X-ray of the left hand and wrist compared with a standardised bone age atlas will determine if bone age is advanced. A bone age more than one year or two standard deviations greater than chronological age warrants referral.

Bloods

Investigations are not required unless there are additional signs of PP and specialist referral is required. Baseline thyroid stimulating hormone (TSH), thyroxine (T4), follicle-stimulating hormone (FSH)/luteinising hormone (LH) and oestradiol would be recommended in this scenario.[37]

Pelvic USS

While ovarian volume and uterine length can predict an increased risk of progression to PP,[12] a paediatric pelvic USS is best left to the paediatrician to arrange.

Breast USS

A breast USS may be indicated if galactorrhea or any additional primary breast, chest wall or vascular pathology is noted at examination. However, a breast USS is not a recommended investigation for distinguishing PT from PP.[35,38]

Conclusion

Disorders of puberty can profoundly affect a child's physical and psychological wellbeing. Girls presenting with precocious breast

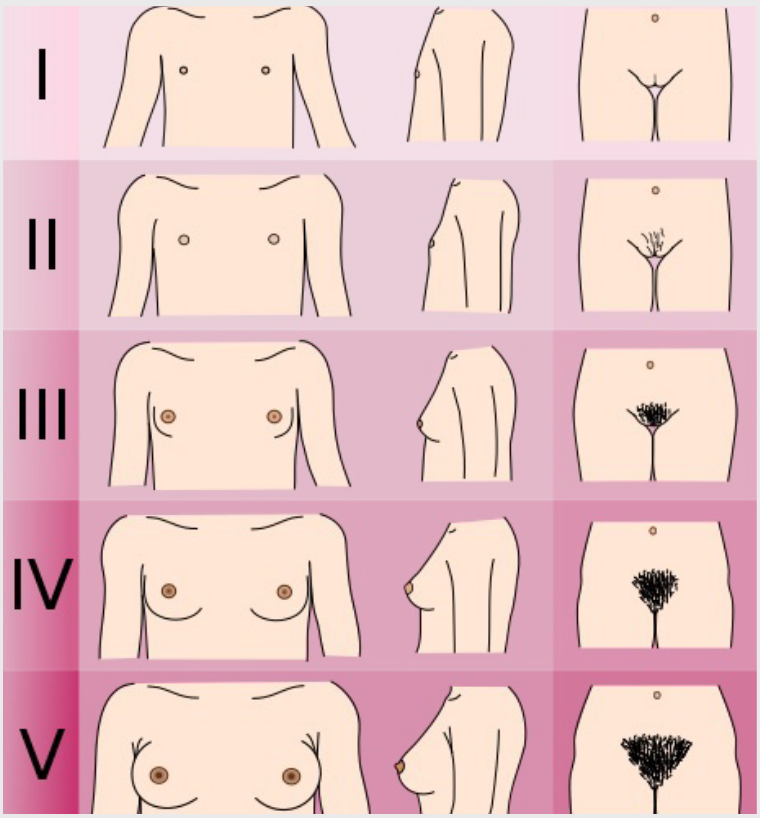

Figure 3. The Tanner scale – female.

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development before age eight years, without additional pubertal signs and who maintain normal growth percentiles, typically fall into the benign isolated PT category.

GPs can reassure families about the self-limiting nature of the condition and its expected normal pubertal progression. A patient flyer on premature thelarche is available from the Australia and New Zealand Society for Paediatric Endocrinology and Diabetes (ANZPED) at https://media.anzsped.org/2022/11/12102910/J-4741-ANZSPEDSandoz-Premature-Thelarche-A4.pdf.

Despite its mostly benign, self-limiting and reversible nature, GPs and parents/caregivers need to remain vigilant for deviating clinical signs and manage the potential physical and psychosocial impacts of PT. Parents might feel concerned or responsible for their child's development, while older children might experience anxiety and social challenges due to their physical differences.

It is essential to provide support and consider referrals to child psychologists to prevent secondary psychosocial harm and referral to paediatricians if red flags develop that suggest progression to PP.

Key points

- PT is considered a benign condition; however, up to 36% of girls will progress to PP.
- Regularly follow-up until there is regression, stability or red flags that suggest progression to PP.
- The greatest risk for progression to PP is the age of onset of early breast development.
- Bone age is the most accurate investigation to distinguish benign PT from PP.
- Benign PT can have significant mental health impacts on the child and caregiver.

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References

1. Wheeler MD. Physical changes of puberty. Endocrinol Metab Clin North Am 1991;20(1):1–14. doi: 10.1016/S0889-8529(18)30279-2.
2. Tanner JM. Growth at adolescence. 2nd edn. Thomas, 1962.
3. Wilkins L, Thomas CC. Endocrine disorders in childhood and adolescence. Obstetrical & Gynecological Survey 1957;12(5):791. doi: 10.1097/00006254-195710000-00062.
4. Donbaloglu Z, Bostan R. Assessing psychiatric evaluations in premature thelarche and idiopathic central precocious puberty cases: Exploring depression, anxiety, quality of life, and coping challenges. Cureus 2024;16(8):e68123. doi: 10.7759/cureus.68123.
5. Volta C, Bernasconi S, Cisternino M, et al. Isolated premature thelarche and thelarche variant: Clinical and auxological follow-up of 119 girls. J Endocrinol Invest 1998;21(3):180–83. doi: 10.1007/BF03347298.
6. Berberoğlu M. Precocious puberty and normal variant puberty: Definition, etiology, diagnosis and current management. J Clin Res Pediatr Endocrinol 2009;1(4):164–74. doi: 10.4274/jcrpe.v1i4.3.
7. Wang YM, Liang L, Fang YL, Fu JF, Dong GP, Wang CL. [A clinical follow-up study of premature thelarche in infants under two years of age]. Zhongguo Dang Dai Er Ke Za Zhi 2013;15(4):285–88. doi: 10.1186/1687-9856-2013-S1-P129.
8. Januszek-Trzciakowska A, Małecka-Tendera E, Lewin-Kowalik J. Przedwczesny rozwój gruczołów piersiowych u dziewczat--współczesne poglady na patogeneze i postepowanie diagnostyczne [Thelarche praecox in young girls: Recent approaches to the pathogenesis and clinical evaluation]. Wiad Lek 2000;53(5-6):312–17.
9. Chiabotto P, Costante L, de Sanctis C. Premature thelarche and environmental pollutants. Minerva Med 2006;97(3):277–85.

10. Stanhope R. Premature thelarche: Clinical follow-up and indication for treatment. J Pediatr Endocrinol Metab 2000;13 Suppl 1:827–30. doi: 10.1515/JPEM.2000.13.S1.827.
11. Wang Y, Wang A, Kong L, et al. [Multi-center study of premature thelarche and gynecomastia in Chinese infants and toddlers]. Zhonghua Er Ke Za Zhi 2014;52(1):5–10.
12. Zheng X, Su H, Huang S, et al. Secondary oxidized di-2-ethylhexyl phthalate metabolites may be associated with progression from isolated premature thelarche to central precocious or early puberty. Sci Rep 2023;13(1):5560. doi: 10.1038/s41598-023-32768-1.
13. Pasquino AM, Pucarelli I, Passeri F, Segni M, Mancini MA, Municchi G. Progression of premature thelarche to central precocious puberty. J Pediatr 1995;126(1):11–14. doi: 10.1016/S0022-3476(95)70492-2.
14. Curfman ALBS, Reljanovic SMBA, McNelis KMBABS, et al. Premature thelarche in infants and toddlers: Prevalence, natural history and environmental determinants. J Pediatr Adolesc Gynecol 2011;24(6):338–41. doi: 10.1016/j.jpag.2011.01.003.
15. Kihtir, HS, Akçay, T. Retrospective analysis of cases with premature thelarche. Bagcilar Med Bull. 2020;5(2):24–27. doi: 10.4274/BMB.galenos.2020.03.08.
16. Colón I, Caro D, Bourdony CJ, Rosario O. Identification of phthalate esters in the serum of young Puerto Rican girls with premature breast development. Environ Health Perspect 2000;108(9):895–900. doi: 10.1289/ehp.108-2556932.
17. Bizzarri C, Spadoni GL, Bottaro G, et al. The response to gonadotropin releasing hormone (GnRH) stimulation test does not predict the progression to true precocious puberty in girls with onset of premature thelarche in the first three years of life. J Clin Endocrinol Metab 2014;99(2):433–39. doi: 10.1210/jc.2013-3292.
18. Verrotti A, Ferrari M, Morgese G, Chiarelli F. Premature thelarche: A long-term follow-up. Gynecol Endocrinol 1996;10(4):241–47. doi: 10.3109/09513599609012315.
19. Beştaş A, Unal E, Aktar Karakaya A, Demiral M, Haspolat YK. Evaluation of clinical and laboratory findings in the differential diagnosis of central precocious puberty and premature thelarche. Indian J Endocrinol Metab 2023;27(3):237–41. doi: 10.4103/ijem.ijem_245_22.
20. Atay Z, Turan S, Guran T, Furman A, Bereket A. The prevalence and risk factors of premature thelarche and pubarche in 4- to 8-year-old girls. Acta Paediatr 2012;101(2):e71–75. doi: 10.1111/j.1651-2227.2011.02444.x.
21. Burlo F, Lorenzon B, Tamaro G, et al. Prevalence and characteristics of thelarche variant. Front Endocrinol. 2023;14:1303989. doi: 10.3389/fendo.2023.1303989.
22. Uçar A, Saka N, Baş F, Bundak R, Günöz H, Darendeliler F. Is premature thelarche in the first two years of life transient? J Clin Res Pediatr Endocrinol 2012;4(3):140–45. doi: 10.4274/Jcrpe.709.
23. Türkyilmaz Z, Karabulut R, Sönmez K, Can Başaklar A. A striking and frequent cause of premature thelarche in children: Foeniculum vulgare. J Pediatr Surg 2008;43(11):2109–11. doi: 10.1016/j.jpedsurg.2008.07.027.
24. Ramsey JT, Li Y, Arao Y, et al. Lavender products associated with premature thelarche and prepubertal gynecomastia: Case reports and endocrine-disrupting chemical activities. J Clin Endocrinol Metab 2019;104(11):5393–405. doi: 10.1210/jc.2018-01880.
25. Khokhar A, Mojica A. Premature Thelarche. Pediatr Ann 2018;47(1):e12–15. doi: 10.3928/19382359-20171214-01.
26. ANZSPED; Pfizer Australia Pty Ltd. Australian and New Zealand Growth Charts: Girls 2–18 years. Pfizer, 2023.
27. Braunstein EW, Braunstein GD. Are prepubertal gynaecomastia and premature thelarche linked to topical lavender and tea tree oil use? TouchREV Endocrinol 2023;19(2):60–68. doi: 10.17925/EE.2023.19.2.9.
28. Group WMGRS. WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. World Health Organization, 2006.
29. Centers for Disease Control and Prevention & National Centre for Health Statistics. 2 to 20 years: Girls Stature-for-age and Weight-for-age percentiles. CDC, 2000.
30. Children's Health Queensland. Assessing infant/child nutrition, growth and development within the primary health care setting. Queensland Health, 2023.
31. Queensland Child and Youth Clinical Network – Child Health Sub-Network. Child and Youth Health Practice Manual. Children's Health Queensland Hospital and Health Service, 2020.
32. Kaplowitz PB. For Premature thelarche and premature adrenarche, the case for waiting before testing. Horm Res Paediatr 2020;93(9-10):573–76. doi: 10.1159/000512764.
33. Kaplowitz P. Diagnosing children with signs of early puberty: Knowing when to test and when to just monitor. Expert Rev Endocrinol Metab 2016;11(4):297–99. doi: 10.1080/17446651.2016.1191350.
34. Salardi S, Cacciari E, Mainetti B, Mazzanti L, Pirazzoli P. Outcome of premature thelarche: Relation to puberty and final height. Arch Dis Child 1998;79(2):173–74. doi: 10.1136/adc.79.2.173.
35. Youn I, Park SH, Lim IS, Kim SJ. Ultrasound assessment of breast development: Distinction between premature thelarche and precocious puberty. AJR Am J Roentgenol 2015;204(3):620–24. doi: 10.2214/AJR.14.12565.
36. Latronico AC, Brito VN, Carel JC. Causes, diagnosis, and treatment of central precocious puberty. Lancet Diabetes Endocrinol 2016;4(3):265–74. doi: 10.1016/S2213-8587(15)00380-0.
37. Government of Western Australia Child and Adolescent Health Service. Puberty concerns in girls. Perth Children's Hospital, 2021.
38. Keçeli M, Akyürek N. Early breast development in girls: The power of greyscale sonography and sonoelastography. Br J Radiol 2024;97(1155):594–99. doi: 10.1093/bjr/tqae020.

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