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Pubertal Disorders in Girls

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Sally Radovick, M.D
Professor of Pediatrics
Rutgers-RWJ Medical School

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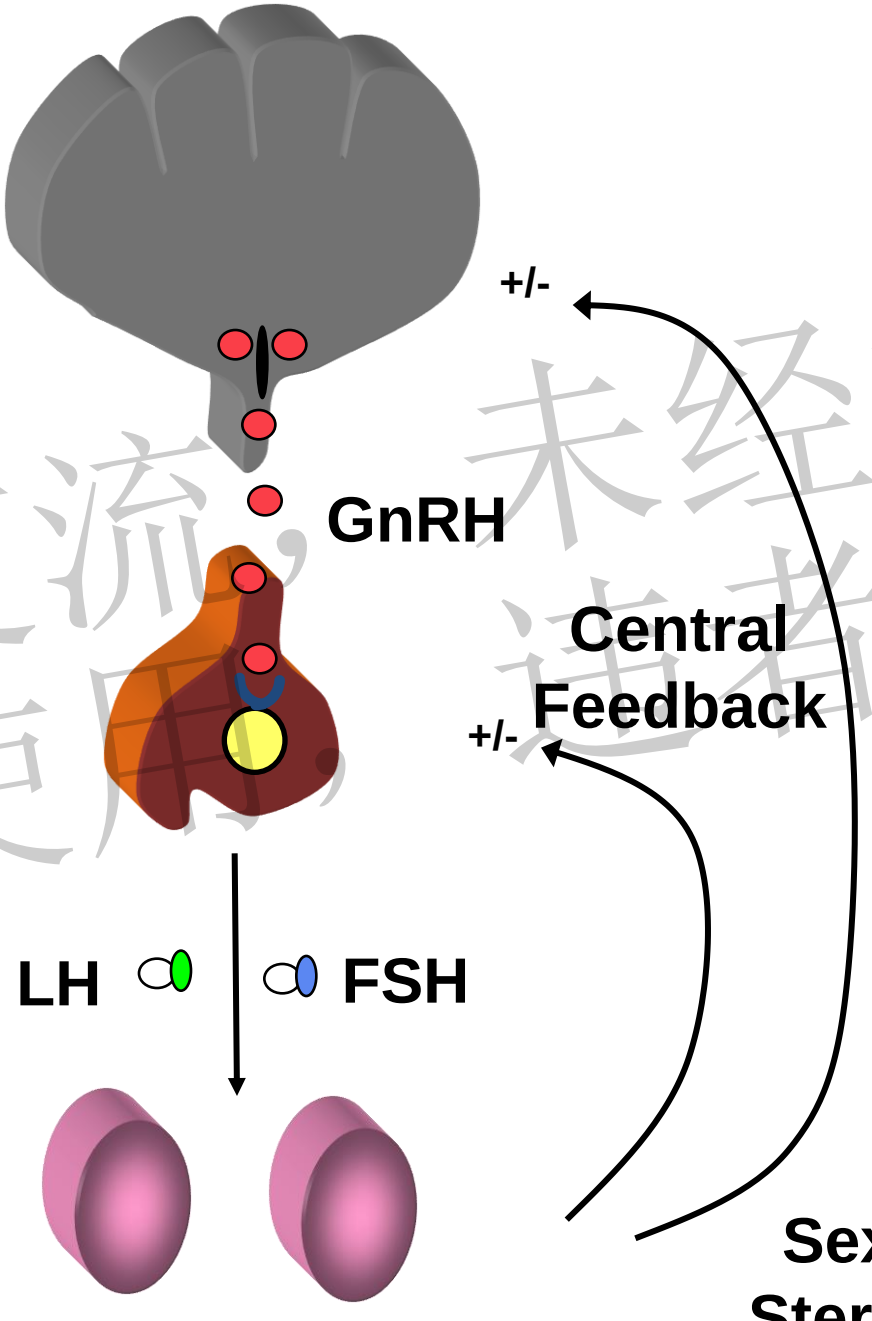
The Reproductive Axis



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Case 1. A 7 year-old presents with onset of breast development 6 months ago.

- History:
  - Normal prenatal course, AGA
  - Normal developmental milestones
  - Mom is concerned that she is ‘hanging around’ older girls
- Family History:
  - Mom’s menarche 11½.
- Physical Examination:
  - Height 75th percentile, weight 90th%ile for age
  - Mid-parental height 50th%ile
  - Tanner II breast development, stage 1 pubic hair
  - Normal neurologic exam
- Laboratory Studies:
  - LH 2.2 U/L, FSH < 0.2 U/L (AM)
  - Estradiol 40 pg/ml
  - Bone age 8 years

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Case 1. A 7 year-old Latina presents with onset of breast development 6 months ago.

The best next step in evaluating this child would be:

A. Brain MRI
B. Pelvic ultrasound
C. Reassurance and follow-up in 3 – 6 months
D. GnRH agonist stimulation test

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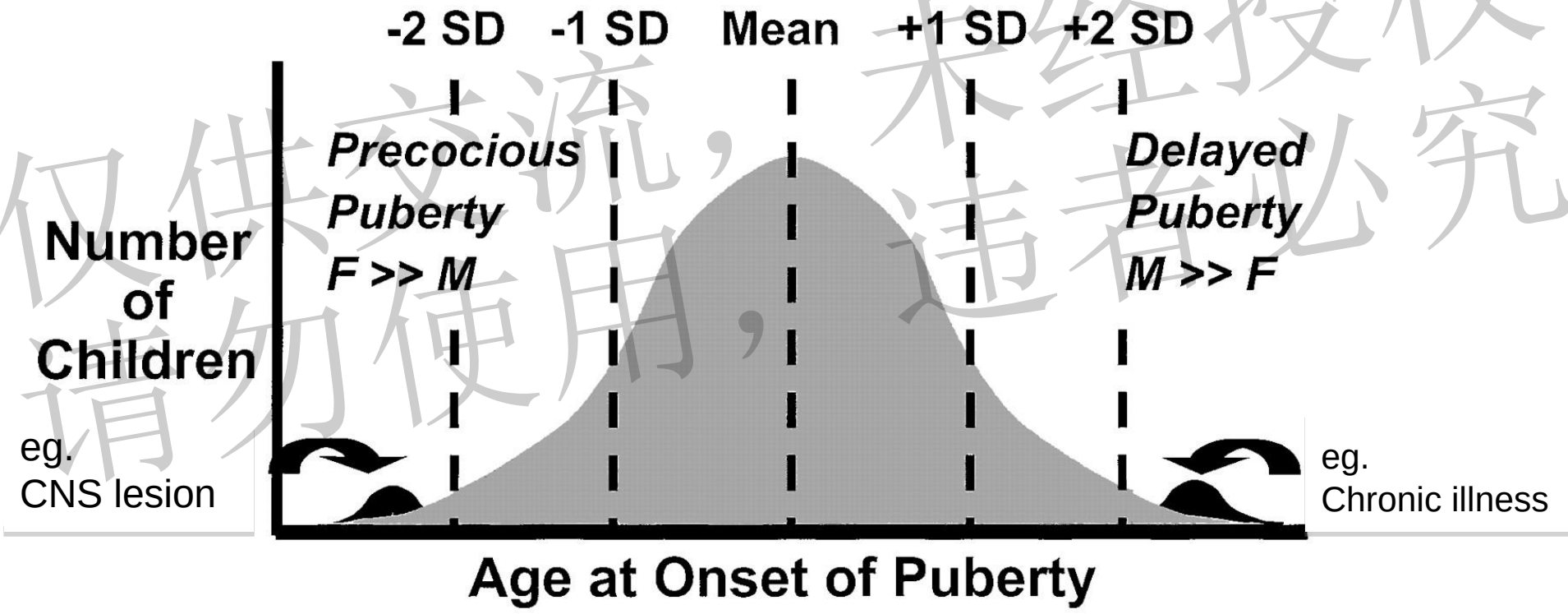
Normal Variation in the Onset of Puberty



Palmert and Boepple, JCEM 86 (2001)

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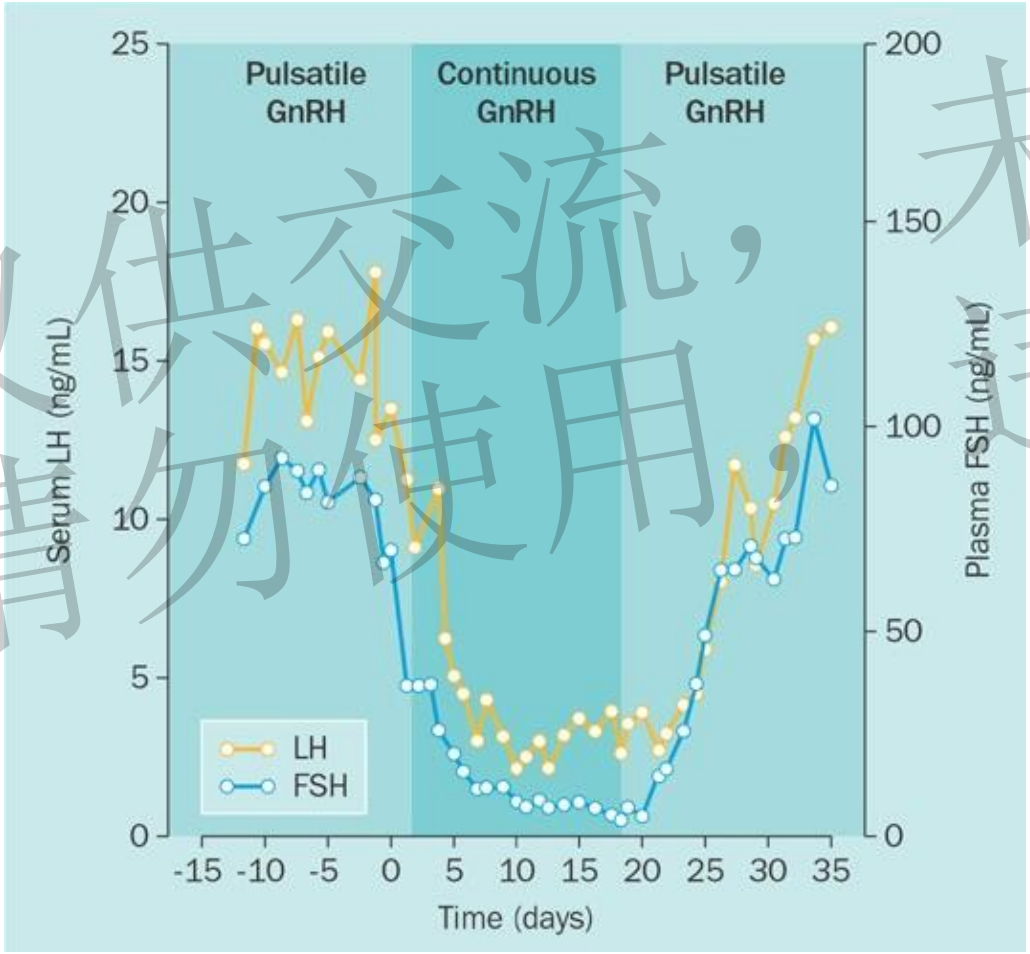
Groundbreaking Studies in Puberty: The Use of GnRH Agonists to Treat Precocious Puberty



- Pulsatile GnRH is required for LH secretion
- Continuous GnRH suppresses LH

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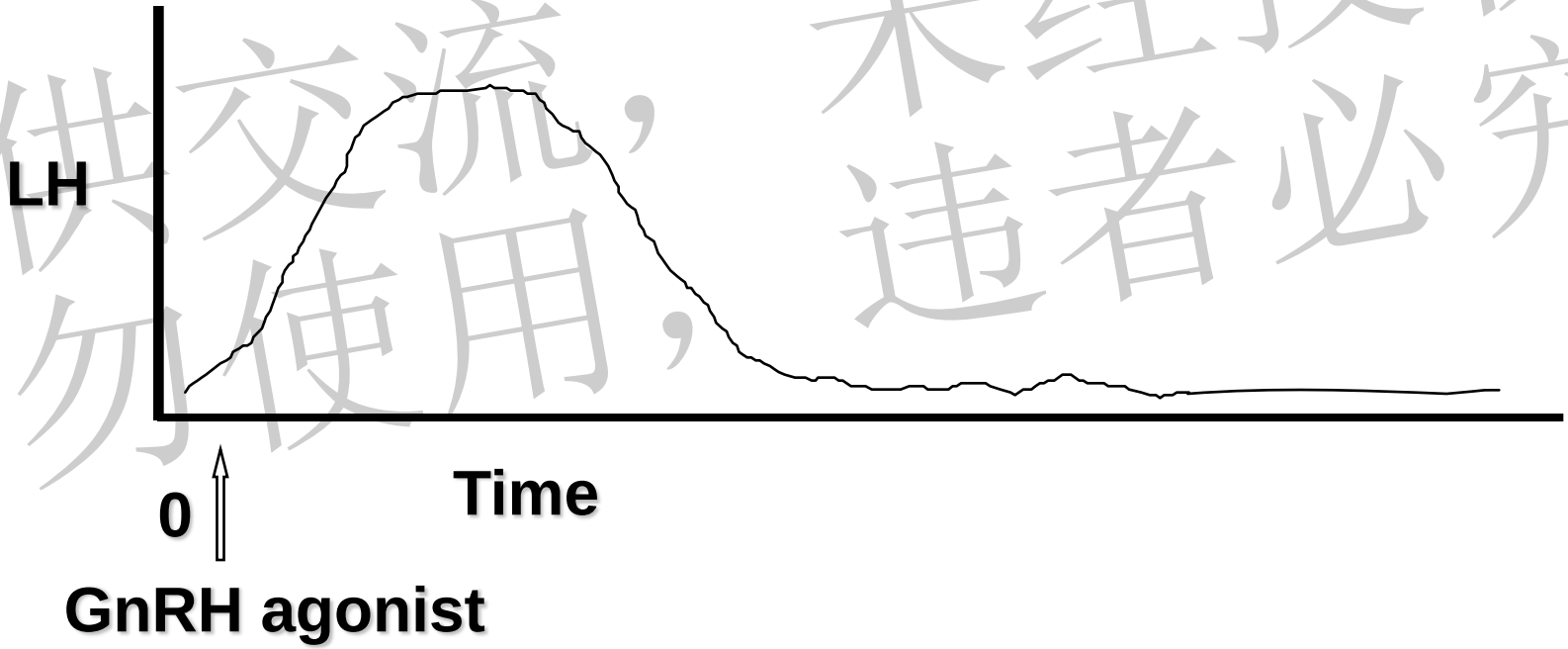
Treatment of Central Precocious Puberty

- GnRH agonists (analogues)
- Induce pituitary desensitization



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Patient Presentation

4 y/o female patient presents with vaginal bleeding.

Hx: Full term infant reaching normal childhood milestones. She developed breast buds at the age of 18 months that were diagnosed as ‘benign premature thelarchy.’ She developed pubic hair at 3 years of age.

PE: Height >95%ile. Tanner 4 breasts, Stage 3 pubic hair, pink vaginal mucosa.

Laboratories: midpubertal LH, E2. GnRH stimulation test: rise in LH consistent with puberty

BA 12 years; predicted height:55”

MRI: normal hypothalamus and pituitary

Rx: GnRH agonist

Treatment course: vaginal bleeding x1 after initiating therapy. Within 1 year, prepubertal breasts, Tanner 2 pubic hair.

Age 11: stopped luprolide therapy

Menses resumed at 11years 6 months. Final height 60” (mid-parental 66”)

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At what age should we evaluate girls for precocious puberty (PP)?

Classic definition:

- CPP - activation of the HPG axis before 8 years of age in girls
    - The diagnosis may be considered in girls who have progressive breast development and who cross percentiles upward on the linear growth chart

Risks:

- Psychosocial
- Short stature
- Pathology

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At what age should we evaluate girls for precocious puberty (PP)?

- Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network.
  - Mean age of onset of breast development was nearly 10 years in Caucasian girls and about 9 years in African American girls
- 15% of African American girls and 5% of Caucasian girls between 7 and 8 years of age had breast development.

- NHANES showed similar data from 1988 to 1994

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Herman-Giddens ME, et al. *Pediatrics*. 1997;99(4):505–512
Wu T, et al. *Pediatrics*. 2002;110(4):752–757

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At what age should we evaluate girls for precocious puberty (PP)?

Risks

The Pediatric Endocrine Society 1999

1. Evaluation need not be performed for white girls older than 7 years of age or for African-American girls older than 6 years of age.
2. Use of GnRH therapy to suppress puberty in 6- to 8-year-old girls with slowly progressive puberty and/or an acceptable predicted adult height has not been proven to have an effect in improving adult height.
   [Girls with earlier thelarche may have a longer period of time before menarche]

© 2007 Thomson - Kaplowitz PB, Oberfield SE, Pediatrics.1999;104 :936– 941.

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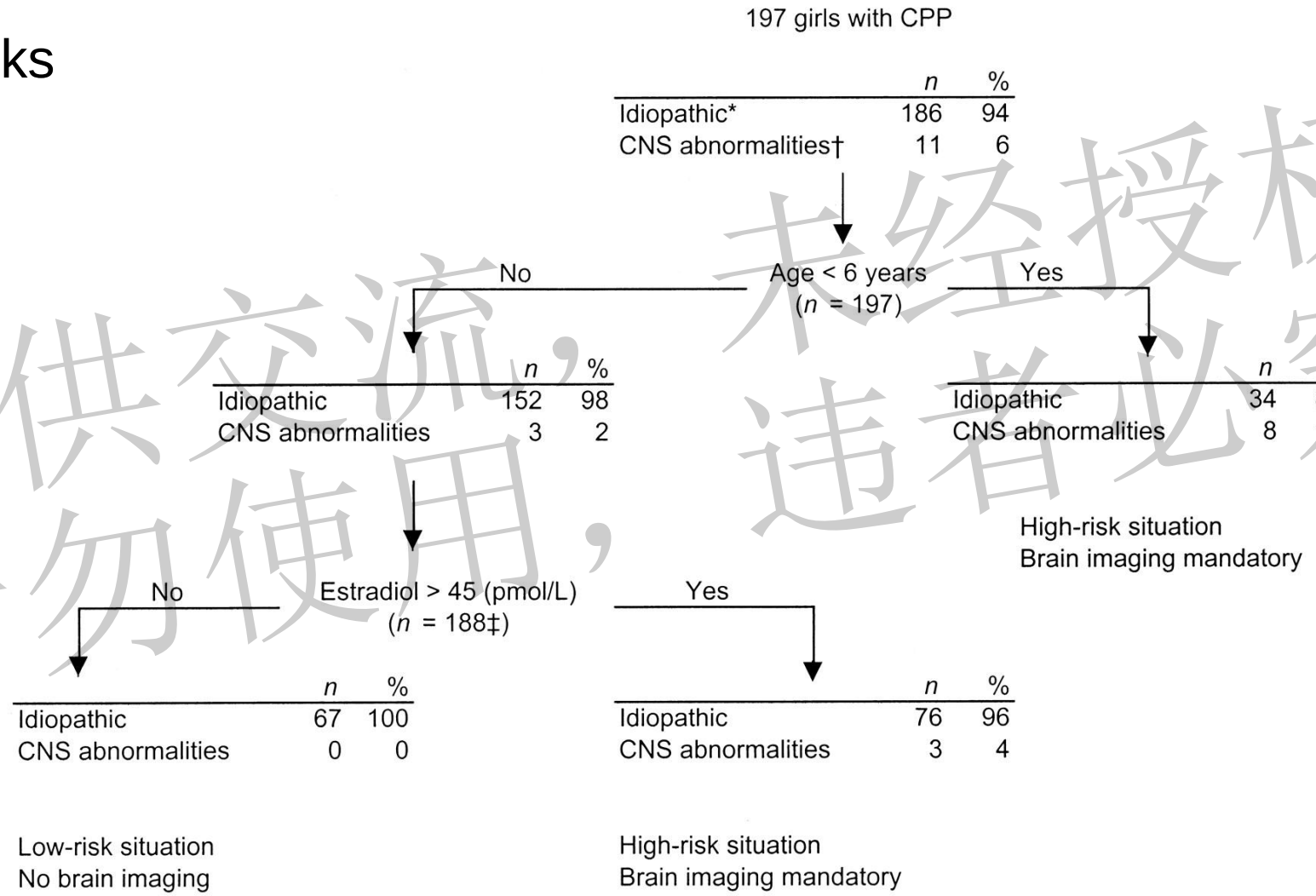
Diagnosis tree to predict low or high risk of CNS abnormalities for girls with CPP [France]

Risks



Martin Chalumeau et al. Pediatrics 2002;109:61-67

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At what age should we evaluate girls for precocious puberty (PP)?

Risks:

- 13 out of 208 Danish girls (6.3%) between 6-9 years old with early or precocious puberty and no other CNS symptom had pathological CNS findings upon MRI, which were causally related to CPP.

Conclusion: A high frequency of 6–8 year old girls with precocious puberty had a pathological brain MRI, which could not be predicted from any clinical nor biochemical parameters.

Mogensen SS, et al. 2012 *PLoS ONE*, 7 (1), e29829

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At what age should we evaluate girls for precocious puberty (PP)?

- Longitudinal study with breast development assessed by palpation
  - 23% of African American, 15% of Hispanic, and 10% of Caucasian girls between 7 and 8 years of age had breast development.
  - evaluation of girls with signs of early puberty has to take into account increased BMI as well as race/ethnicity.

Biro FM, et al. *Pediatrics*. 2010;126(3).

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At what age should we evaluate girls for precocious puberty (PP)?

- .[NHANES III]
- Normal weight, breast and pubic hair (by inspection) are unusual before 8 years of age
- Elevated BMI associated with breast development in younger girls (? true breast tissue vs adipomastia)
- African American and Mexican American girls with normal BMI achieved all of the pubertal landmarks earlier than NHW girls with normal BMI.

Conclusion:
Although the appearance of breasts before 8 years of age *can be considered premature in* NHW girls with normal BMI, occurring in <5% of them, it *seems* to be normal in 7-year-old NHB and MA girls with normal BMI.

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Rosenfield R et al. *Pediatrics*. 2009;123:84-88

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At what age should we evaluate girls for precocious puberty (PP)?

- The diagnostic evaluation of suspected CPP :
  - bone age
  - FSH, LH, estradiol
  - TFTs (hypothyroidism is rare)

An LH of >0.3 IU/L is the most reliable screening test for CPP
if it is <0.3 and CPP is suspected, proceed to a stimulation test with a GnRH analog
In selected cases, pelvic ultrasonography may be helpful because increased ovarian and uterine volumes relative to age are diagnostic of CPP

Once the diagnosis of CPP is established, a CT or MRI is performed

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At what age should we evaluate girls for precocious puberty (PP)?

Additional considerations:
Ethnic/racial differences
Increased BMI

- African American girls who enter puberty after their sixth birthday and Caucasian girls who enter puberty after their seventh birthday in the absence of any predisposing disease are now considered to be normal by many authorities, rather than precocious.

- A dissenting view that still considers 8 years of age as the lower limits of onset of female puberty: for maximum safety it appears best to use the 8-year guideline for girls being evaluated by providers in general practice, and pediatric endocrinologists can best determine which of those require in-depth evaluation and perhaps treatment.

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Case 2: A 16-year-old girl presents with amenorrhea.

- History:
  - Menarche at age 15 years, one bleeding episode since
  - Runs for exercise and sport at since 14 years of age, 3-5 miles/day, lost about 5 lb
  - No galactorrhea, headache, visual changes
  - Ankle pain for the last few weeks
- Family medical History:
  - Mother's menarche at 16 years, aunt never had children
- Physical exam:
  - BMI is 20
  - Tanner 3 breasts, stage 2 pubic hair, normal bimanual exam
- Laboratory studies:
  - CBC blood chemistry panel, HCG - normal
  - TSH, fT4 - low
- Medications:
  - levothyroxine

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Case 2: A 16-year-old girl presents with amenorrhea.

What should be the next step in the evaluation?

A. Progesterone challenge test
B. LH, FSH, E, prolactin
C. Free testosterone and DHEAS
D. MRI
E. Karyotype

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Delayed Puberty and Hypogonadism

- Delayed puberty - no breast development by 13 years of age
  - 0.6% enter puberty spontaneously at an age outside this range
  - Permanent gonadotropin deficiency is most likely if a patient does not start puberty spontaneously by 18 years of age
  - Primary amenorrhea is failure to begin menses by 15 years of age or within 3 years of thelarche
- Risks:
  - Pathologic etiology
  - Bone mineralization
  - Psychosocial

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Evaluation of Delayed Puberty, Hypogonadism

- Risks:
  - Pathologic etiology
    - Screening at an age prior to 15 years to include eating disorders, excessive androgen, outflow tract disorders, gonadal dysgenesis. This may include an FSH level.
  - Bone mineralization
  - Psychosocial

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Treatment of delayed puberty, hypogonadism

- Very low estrogen doses may be started at 11–12 years of age
- Transdermal estradiol (no cardiovascular risk and optimizes bone health)
  - 25 □g daily for 2 - 3 weeks monthly;
  - to reach adult dose of 100 □g
- Cyclic progestin is added for 7–10 days during the latter portion of the estrogen re-placement cycle after 2 years of estrogen therapy or after unpredictable bleeding

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Rosenfield RL, et al. J Clin Endocrinol Metab. 2005;90:6424–6430
Ross JL, et al. N Engl J Med. 2011;364:1230–1242

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Case 3: A 16-year-old girl is seen for evaluation of hirsuitism and obesity

- History:
  - Sports-related injuries hampering activity
  - Menarche at 12 years of age; 3-4 menstrual periods/year
  - OCPs recommended by PMD but declined by her mother
- Family Medical History:
  - Mother and father have type 2 diabetes
- Physical Exam:
  - BMI is 32, BP 135/75
  - Feriman Gallway score is 12, acanthosis nigricans
- Laboratory Studies:
  - Total testosterone 0.7 ng/ml (70 ng/dl, elevated)
  - HDL cholesterol 28 mg/dl, triglycerides 140 mg/dl
  - GTT: glucose at 2 hours 128 mg/dl

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Case 3: A 16-year-old girl is seen for evaluation of hirsuitism and obesity

1. Which of the following is the best next diagnostic step in this patient's evaluation?:

A. Pelvic ultrasound
B. Serum LH level
C. Adrenal androgens (DHEAS), AM 17-hydroxyprogesterone
D. All of the above
E. B and C

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Case 3: A 16-year-old girl is seen for evaluation of hirsuitism and obesity

2. What treatment would you suggest:

A. Diet and exercise
B. Metformin
C. Antiandrogen, ie spironolactone
D. A and B

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How do we diagnose and how should we manage girls with hyperandrogenism and metabolic syndrome?

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How do we diagnose girls with hyperandrogenism and metabolic syndrome?

- Exclude nonclassical CAH, hyperprolactinemia, virilizing tumor, cortisol excess

  - Hyperandrogenism: hirsuitism, acne (common), androgenic alopecia (rare)
    - Ferriman-Gallwey score >8 in adults; ethnically variable and may not be fully manifested in adolescence
      - Progressive hirsuitism
    - The lower limit of T may be lower in adolescents;
      - Measure T 8-10AM during follicular phase, use LC-MS/MS

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92 Kushnir MM,. Clin Chem 2010;56(7):1138–1147
93 Fanelli F, J Clin Endocrinol Metab 2013;98(7): 3058–3067

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How do we diagnose girls with hyperandrogenism and metabolic syndrome? –cont'd

- Menstrual abnormalities, hyperinsulinism are common in normal puberty
  - Adolescent girls may have menstrual irregularity with anovulatory cycles and varied cycle length for1– 2 years postmenarche
- Ovarian morphology in adolescents is varied and normative data is minimal
  - Ovarian volume >10.8 cc or > 10 follicles (2-9 mm), but about 5-% adolescents meet this criteria
- Anti-Mullerian hormone, secreted by growing follicles; may lack sensitivity and specificity to dx PCOS

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92 Kushnir MM,. Clin Chem 2010;56(7):1138–1147
93 Fanelli F, J Clin Endocrinol Metab 2013;98(7): 3058–3067

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How should we manage girls with hyperandrogenism and metabolic syndrome?

- First line: Weight loss and lifestyle modification
- Second line: OCPs, +/- antiandrogen
- Third line: Metformin
- Also:
  - Cosmetic
  - Evaluate and treat glucose and lipid abnormalities, hypertension, sleep apnea
  - Screen family members
  - Screen for depression

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Treatment of PCOS

- OCs have 4-fold increased risk of venous thromboembolism
  - This risk may be slightly higher in OCs containing the antiandrogenic/antimineralocorticoid progestin vs the biochemically androgenic levonorgestrel or other progestins
  - OCs containing □20 g ethinyl estradiol
    - Low cardiovascular risk
    - Inadequate accrual of bone mass
    - Less effective in controlling irregular menstrual bleeding
    - Consider OCs with 30 –35 □g ethinyl estradiol.
- progestin-only contraceptives where OCs are risky,
  - less reliable control of menses or androgen excess

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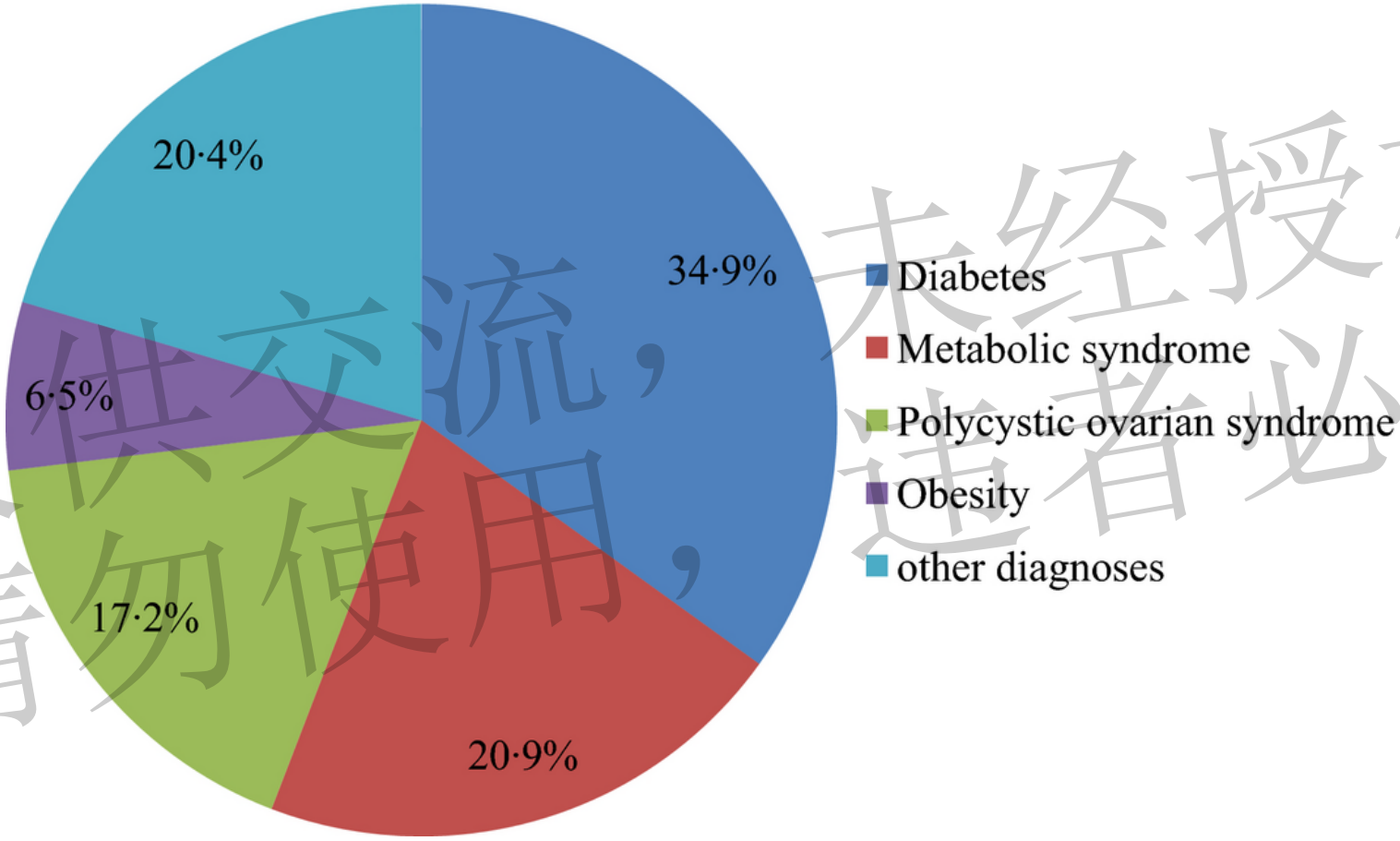
Metformin prescription patterns among US adolescents aged 10–19 years: 2009–2013



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Journal of Clinical Pharmacy and Therapeutics
9 MAR 2016 DOI: 10.1111/jcpt.12379

METFORMIN

- Review of the use of insulin sensitizers in PCOS
  - ‘evidence supports the use of metformin in obese/overweight and lean adolescent girls to help reduce androgen excess and improve ovarian function’ (Geller DH, et al. Int J Pediatr Endocrinol. 2011;2011:9)

- Small randomized, placebo-controlled study of obese adolescents with insulin resistance and PCOS treated with metformin
  - restored menses
  - improved hyperandrogenemia
  - improved HDL cholesterol
  - no weight loss
  - no improvements in insulin sensitivity

(Bridger T, et al. Arch Pediatr Adolesc Med.2006;160:241-246)

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METFORMIN

- Retrospective study in overweight/obese adolescents with PCOS metformin vs metfomin with OCPs over 10 months
  - Metformin group,
    - decrease in BMI and
    - improvement in total and LDL cholesterol, no changes in TGs
  - Metformin with an OCP,
    - No change in total and LDL cholesterol, TGs; increase in HDL

  (Bredella MA, et Clin Endocrinol (Oxf). 2013;79:199-203)

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METFORMIN

- 10 normal-weight girls with a history of precocious puberty and PCOS were treated with metformin
  - •decreased biochemical and clinical hyperandrogenism
  - •improved cyclic menses
  - •decreased hyperinsulinemia, improved lipid profiles

  (Ibáñez L, Endocr Rev. 2000;21:671-696)

- Early intervention in high-risk prepubertal and early menarchal girls can prevent the metabolic and clinical sequelae of PCOS

  (Ibáñez L. *J Pediatr*. 2004;144:23-29 and Ibáñez L. *J Clin Endocrinol Metab*. 2011;96:E1262-E1267)

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