

An Introduction to Central Precocious Puberty

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Disclosures

Honoraria

- Ipsen Ltd
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Introduction

Key terms

Normal puberty overview

What does Central Precocious Puberty mean?

Girls

Boys

Treatment

Key terms

Puberty

- Development of secondary sexual characteristics
- Attain reproductive capacity



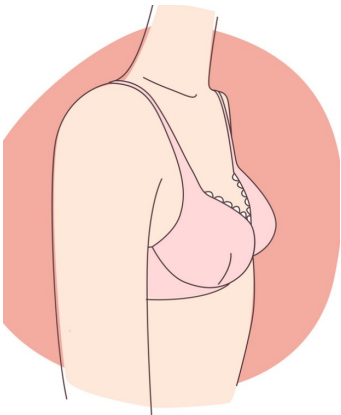
Adrenarche

- Onset of androgen dependent changes



Thelarche

- Onset of female breast development



Blair, J. C. and M. O. Savage (2002). Normal and Abnormal Puberty. Comprehensive Clinical Endocrinology. G. M. Besser and M. Thorner. Michigan, Mosby.

Key terms

Gonadarche

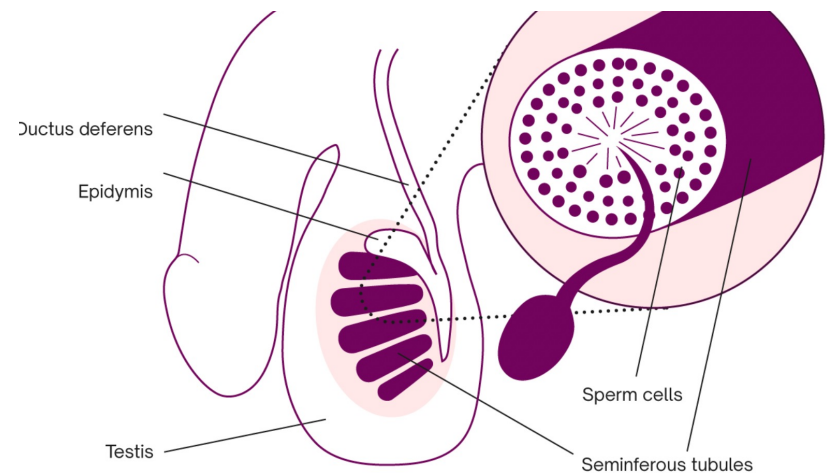
- Activation of reproductive glands by LH and FSH

Menarche






- Onset of menstruation

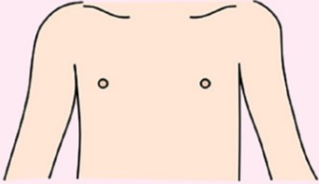
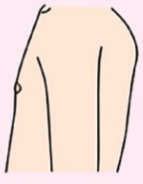

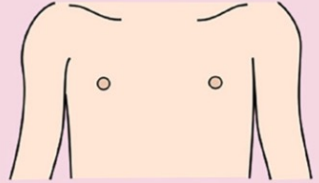
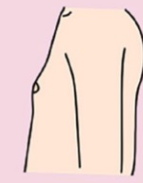

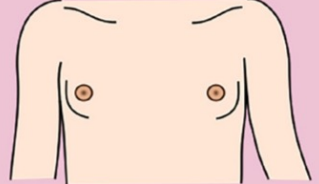
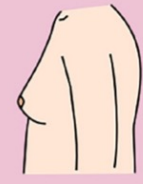
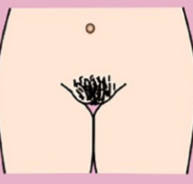
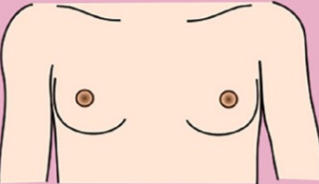


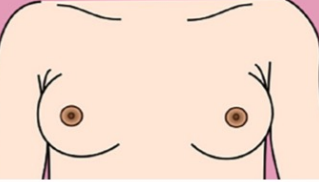


Spermarche

- Development of sperm in the testes



Tanner staging

I		3 ↕ <2,5
II		4 ↕ 2,5-3,2
III		10 ↕ 3,6
IV		16 ↕ 4,1-4,5
V		25 ↕ >4,5

I			
II			
III			
IV			
V			

Davies, K. (2020). "Biological basis of child health 7: growth, development and the reproductive system."
Nurs Child Young People.

Normal puberty?

Girls

Starting pubertal development after the age of 8 years
(average is 10 years)

Boys

Starting pubertal development after the age of 9 years
(average is 12 years)

Hypothalamic Pituitary Gonadal (HPG) axis

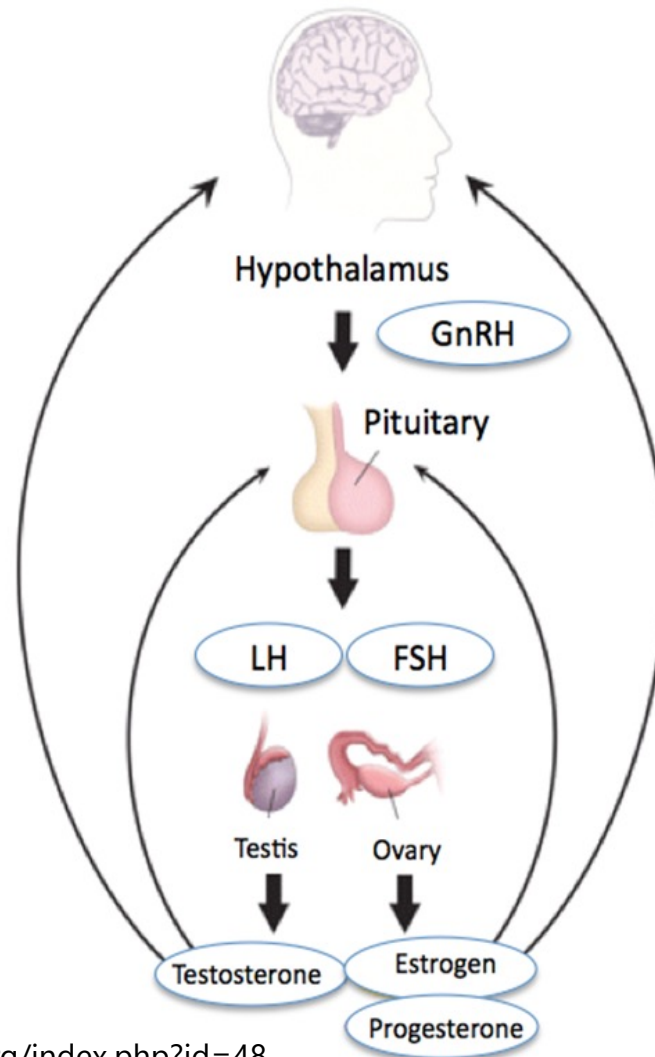


Image from <https://www.dsdgenetics.org/index.php?id=48>.

Consonant puberty: girls

Breast growth



Acceleration in height velocity



Pubic and axillary hair growth



Menarche

Consonant puberty in boys

Testicular growth



Growth of penis, pubic and axillary hair growth

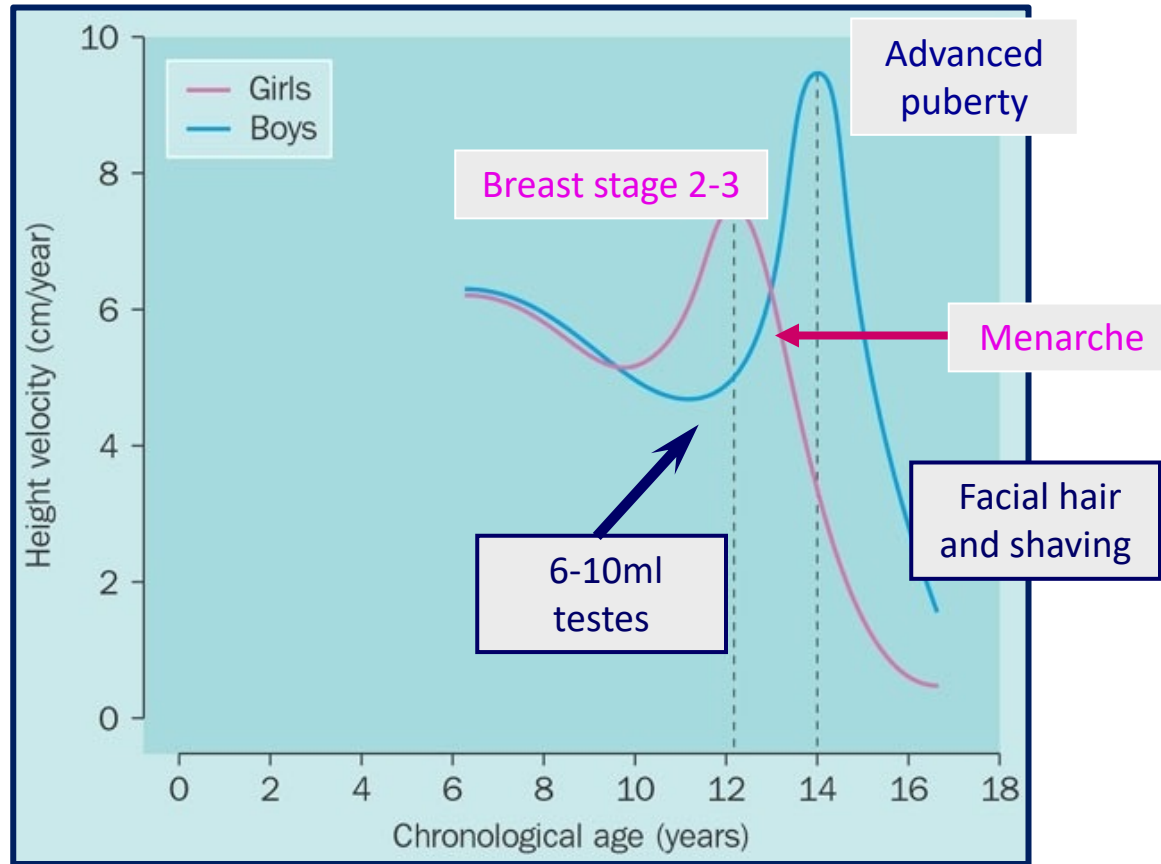


Acceleration in height velocity



Voice deepens, facial hair growth

Boys and girls normal puberty



Pubertal timing influences

Genetics

General health of the child

Environmental factors

Genetics

Genetics of Pubertal Timing

Jia Zhu¹, Temitope Kusa², and Yee-Ming Chan^{1,2}

Family history

Mother – Age at menarche

Father – Delayed growth spurt
- Voice breaking

Siblings - pubertal milestones



- **FSHR**

- Gene that encodes the FSH receptor
- Variants
 - Later testicular growth
 - Later Thelarche

- **MKRN3 / DLK1 / Kisspeptin**

- Central precocious puberty

- **IGFS10**

- Delayed puberty

General health of the child

- Adequate nutrition
- Obesity – increased BMI
- Emotional and behavioural difficulties
- Chronic disease



- Full History
 - Craniospinal / gonadal / abdominal irradiation
 - Gonadal treatment
 - Testicular damage
 - Congenital anomalies
 - Chromosomal disorders

Environment

Effects of Environmental Endocrine Disruptors on Pubertal Development

Samim Özen¹, Şükran Darcan²

¹Pediatric Endocrinology Unit, Mersin Children Hospital, Mersin, Turkey

²Department of Pediatric Endocrinology and Metabolism, Ege University School of Medicine, Izmir, Turkey

Phytoestrogens

- Carrots, garlic, apple, coffee, cherry

Pesticides, herbicides, fungicides

DDT

BPA (Bisphenol A)

- Baby feeding bottles

J Clin Res Ped Endo (2011) 3:1 pp1-6



What about Central Precocious Puberty?

Onset of clinical signs of puberty before the age of

- 8 years in girls
- 9.5 years in boys

CAUSES?

CNS lesions

Lesions of the central nervous system

Cerebral malformations

Trauma

Radiation



Pyra, E. & Schwarz, W. (2019) Puberty: Normal, Delayed and Precocious. Advanced Practice in Endocrinology Nursing. S. Llahana, C. Follin, C. Yedinak et al. Cham, Springer. 1: 63 - 84.

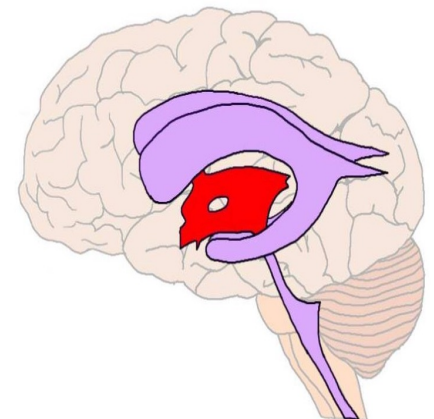
The most common cause?

Hypothalamic Hamartoma

- Congenital
- Benign
- Collection of neural tissue
Base of third ventricle



Incidence: 1: 100,000 children



(Soriano-Guillen, L., & Argente, J. (2019). Central precocious puberty, functional and tumor-related. Best Pract Res Clin Endocrinol Metab, 33(3), 101262. doi:10.1016/j.beem.2019.01.003)

Idiopathic CPP – no CNS lesion

92% of girls

- No cause in up to 2/3 of girls

50% of boys

- Identifiable cause more likely

History of familial CPP or adoption may be present

CPP occurs 4 to 10 times
more frequently in girls than in boys.²



What are the signs of CPP in girls?

Breast development before 8 yrs

Pubic hair before 8 yrs

Menarche before 10 yrs

**Breast development between 8 – 9yrs –
Investigate if:**

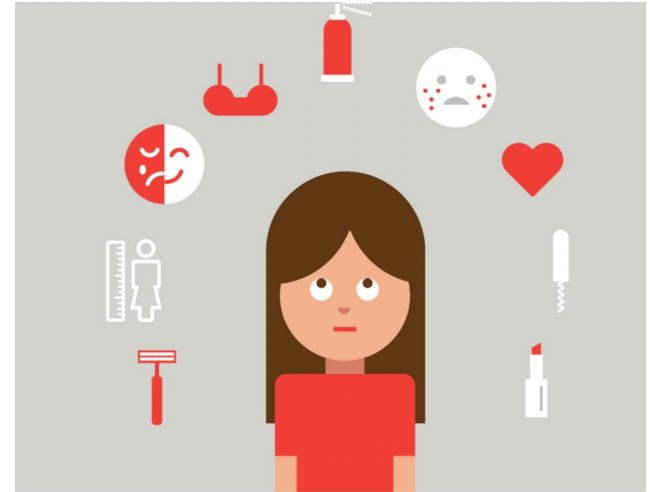
Onset of development before 8 yrs

HV >6cm/yr

- Adult height prognosis below target height

Rapid progression of pubertal development (from one stage to another in less than 6 months)

Clinical evidence of a neurogenic aetiology



What are the signs of CPP in boys?

Increase in testicular volume before the age of 9.5 yrs
Increased FSH production
Testosterone stimulation

Pubic hair before the age of 9.5 yrs

**Pubertal development before 10 yrs –
Investigate if:**

HV >6cm/yr
- Adult height prognosis below target height

Rapid progression of pubertal development

Clinical evidence of a neurogenic aetiology

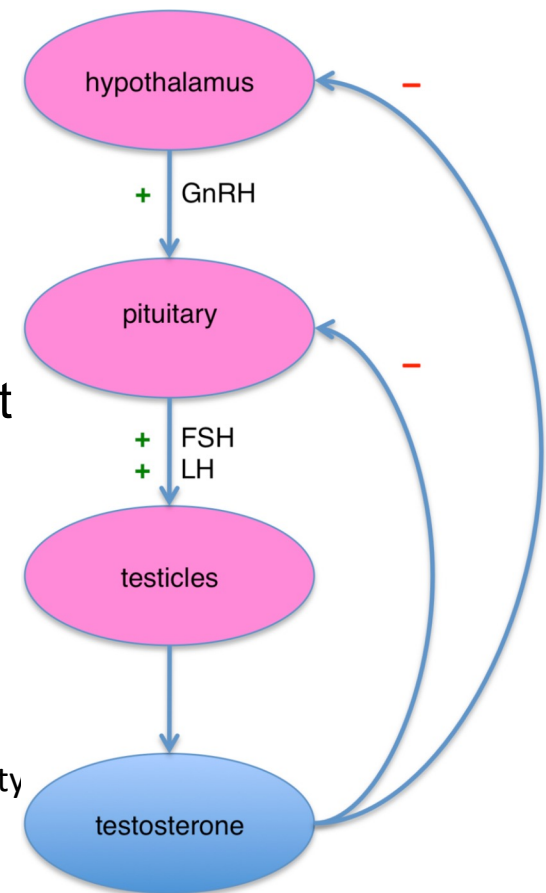


Figure adapted from (Synovitz, L., & Chopak-Foss, J. (2013). Precocious puberty Pathology, related risks, and support strategies. Open Journal of Preventive Medicine, 03(09), 504-509. doi:10.4236/ojpm.2013.39068)

Familial CPP

Genetics
MKRN3



Journal of Pediatric Nursing 48 (2019) 127–128



Contents lists available at ScienceDirect

Journal of Pediatric Nursing

journal homepage: www.pediatricnursing.org



Pediatric Endocrinology Nursing Society Department

Genetic Competencies for Effective Pediatric Endocrine
Nursing Practice☆☆☆

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Nursing Children and Young People, March 2020

Biological basis of child health 1: understanding the cell and genetics

Kate Davies and Eirini Meimaridou

Trends in pubertal development

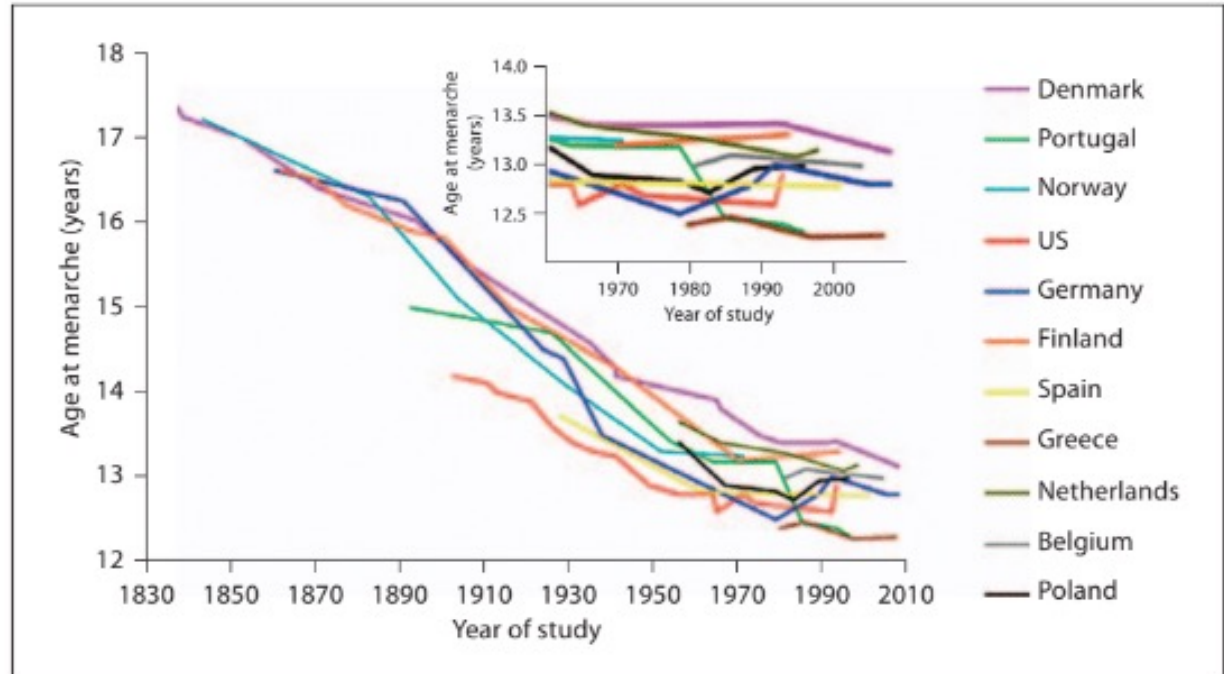
Mini Review

HORMONE RESEARCH IN PÆDIATRICS

Recent Secular Trends in Pubertal Development: Implications for Evaluation and Diagnosis of Precocious Puberty

Kaspar Sørensen Annette Mouridsen
Signe Sloth Mogensen Anders Juul

Department of Growth and Reproduction, Rigshospitalet
Copenhagen, Denmark



Boys

- Not received the same attention
- 1940s - Genitalia developmental trends been consistent

Why?

THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL
ARTICLES

Incidence and Prevalence of Central Precocious Puberty in Korea: An Epidemiologic Study Based on a National Database

Ye Jin Kim, MD¹, Ahreum Kwon, MD², Mo Kyung Jung, MD³, Ki Eun Kim, MD⁴, Jungwhan Suh, MD²,
Hyun Wook Chae, MD, PhD², Duk Hee Kim, MD, PhD⁵, Sangmi Ha, MD⁶, Gi Hyeon Seo, MD⁶, and Ho-Seong Kim, MD, PhD²

Incidence of CPP risen

Unclear why

Contributing factors

Genetics

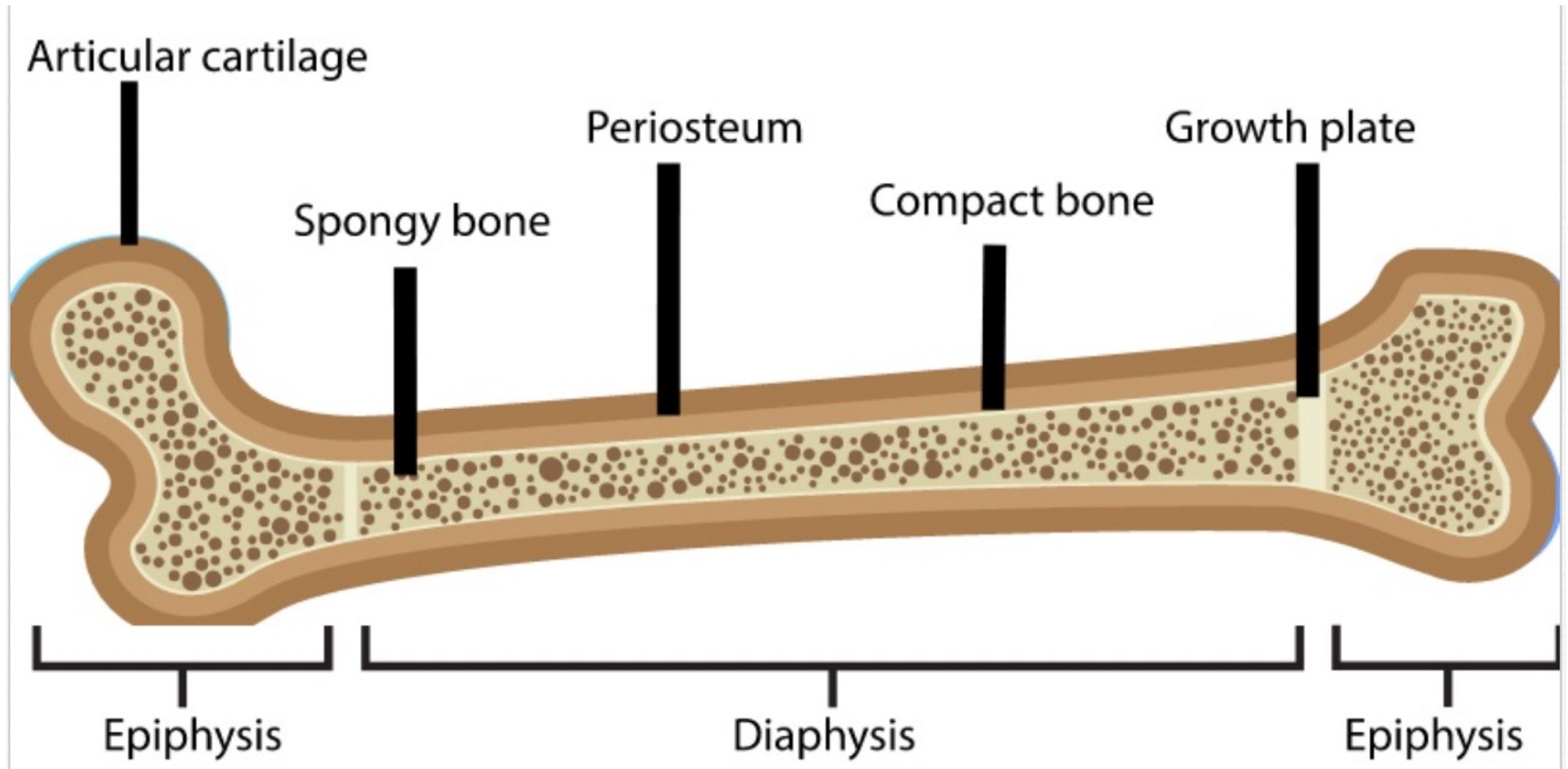
Environmental factors

Increase in obesity



Management

Main goal is to prevent early fusion of the epiphyseal growth plates

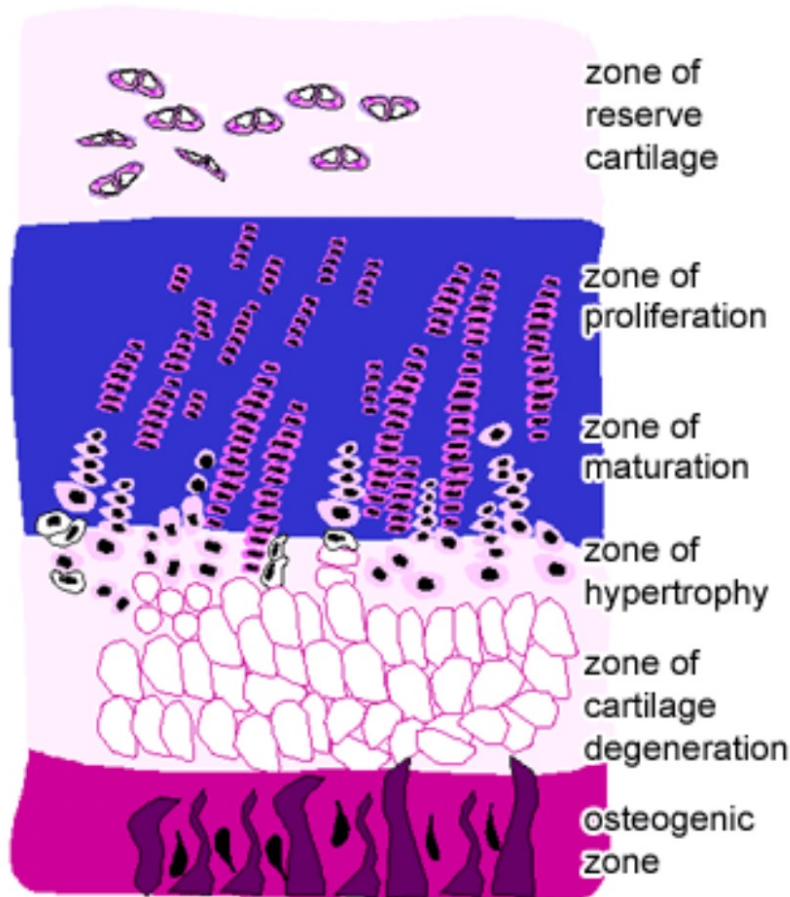


Epiphyseal growth plate

Cartilaginous tissue with specific functions since growth begins until epiphysis is closed after puberty

Three different zones

- **The resting zone**
 - Stem cells slowly replicate
- **The proliferative zone**
 - Generate clones of chondrocytes
 - Replicate at high rate
 - Align in columns
 - Replication decreases as move away from epiphysis, and form
- **Hypertrophic zone**
 - Cartilage attracts the blood vessels, osteoclasts, and differentiating osteoblasts, which remodel the newly formed cartilage into bone tissue.

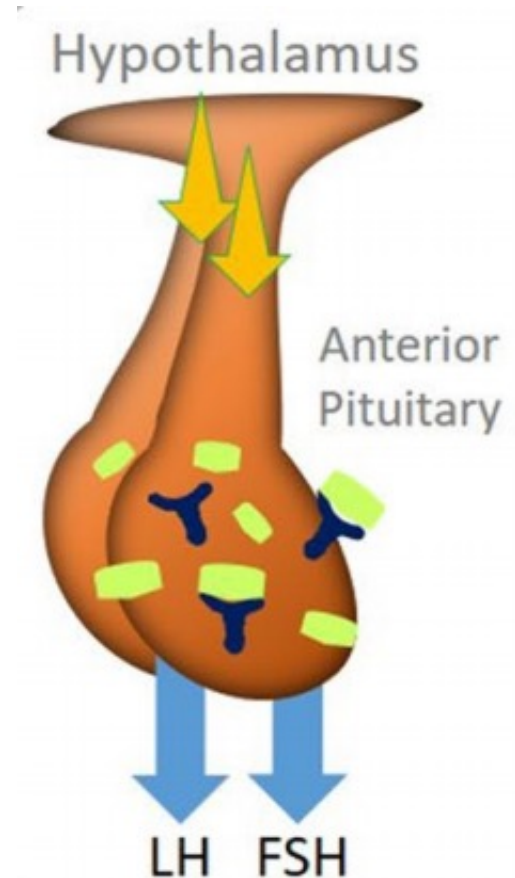


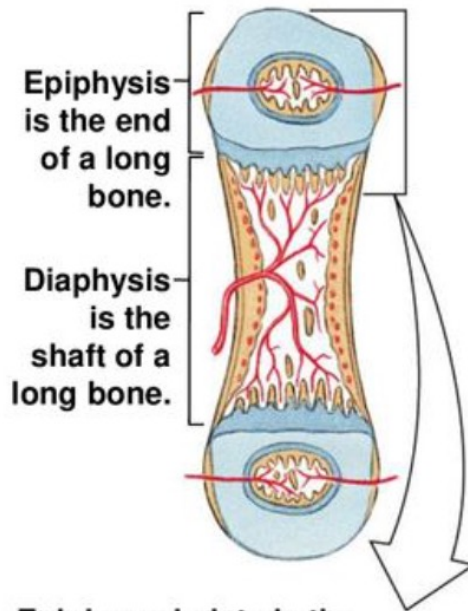
GnRH analogues

Artificially created molecules

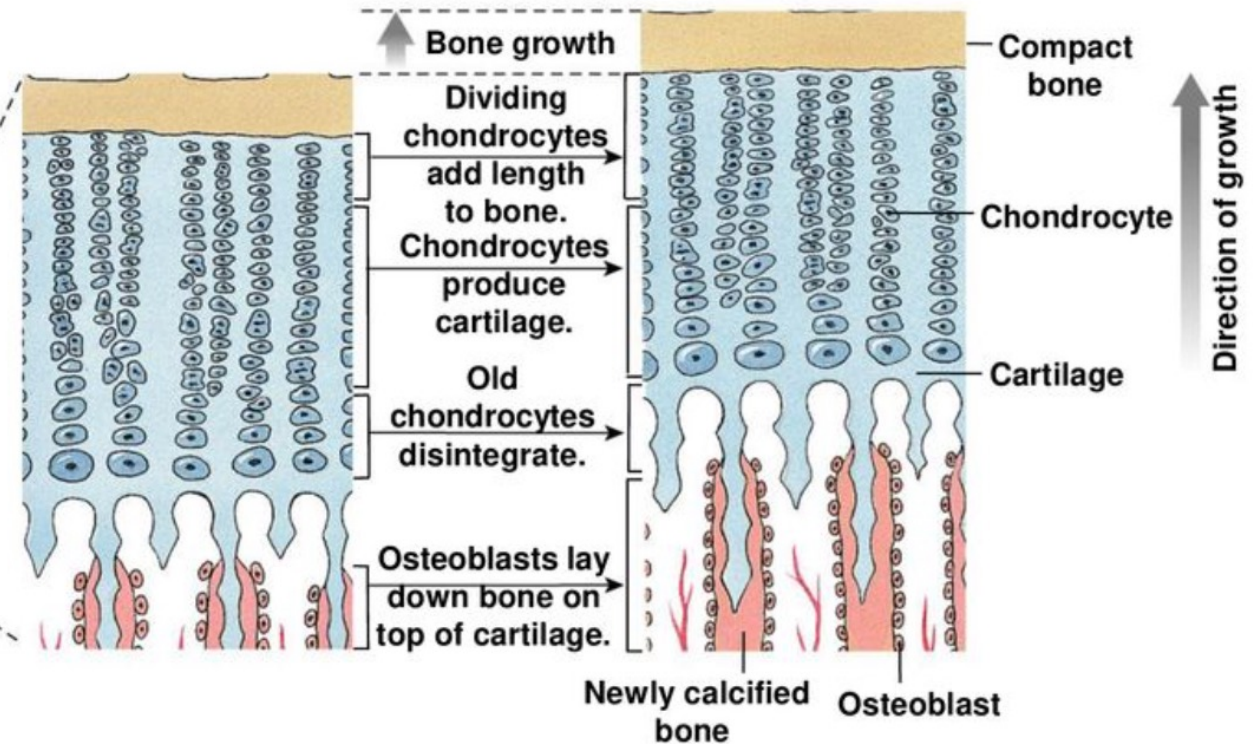
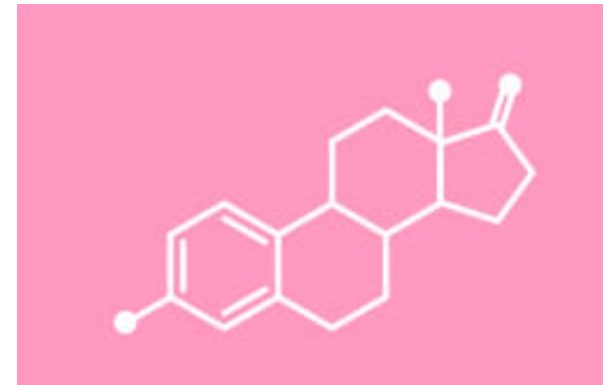
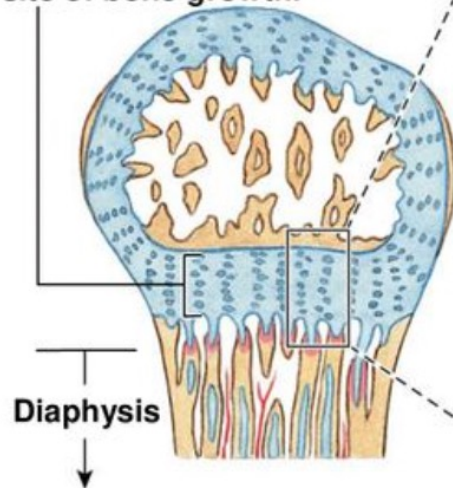
Similar to the actual GnRH

Affinity for GnRH receptors in the pituitary gland

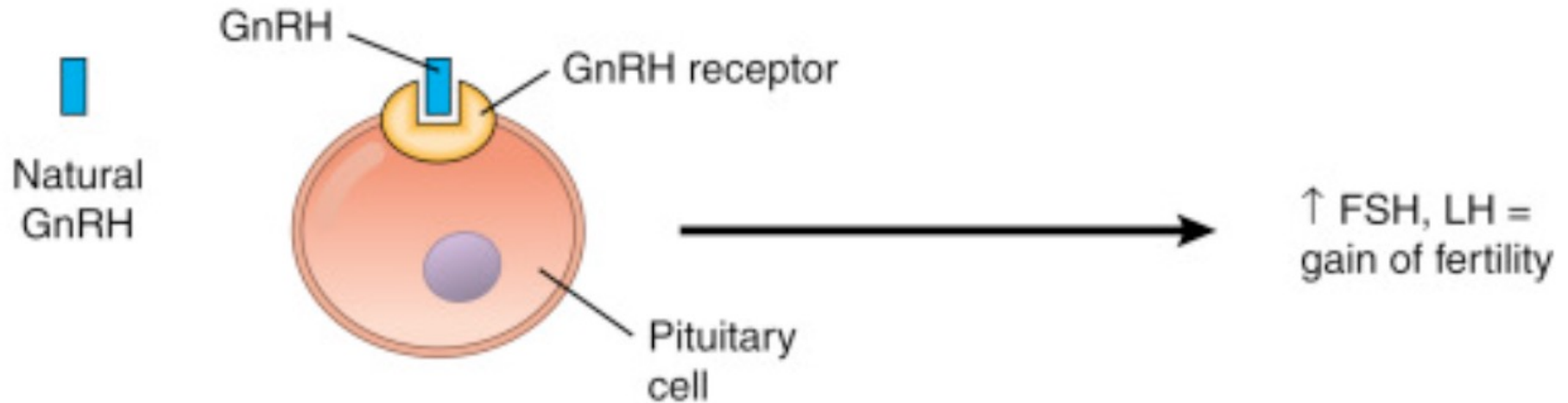




Epiphyseal plate is the site of bone growth.



Normal physiology



AGONIST

- A drug that binds to a receptor
 - Causes activation and then cellular changes

One simulates the intended reaction, where an antagonist binds to the receptor, and stops/ slows responses

ANTAGONIST

- Reduces the effect of an agonist
- Type of drug that blocks or dampens the biological response

GnRH agonist

More potent than native GnRH

Longer half life than 'native' GnRH

Produce initial stimulation of pituitary gonadotrophs ➤

- Secretion of FSH and LH ➤
- Expected gonadal response
- Down regulation and inhibition of HPG axis

Suppression of spontaneous ovulation

- Ovarian stimulation – IVF - ICSI
- Assisted reproductive technology
- PP...?



GnRH antagonist

‘Antagonize’ the GnRH receptor

Used for short periods to prevent the LH surge and ovulation

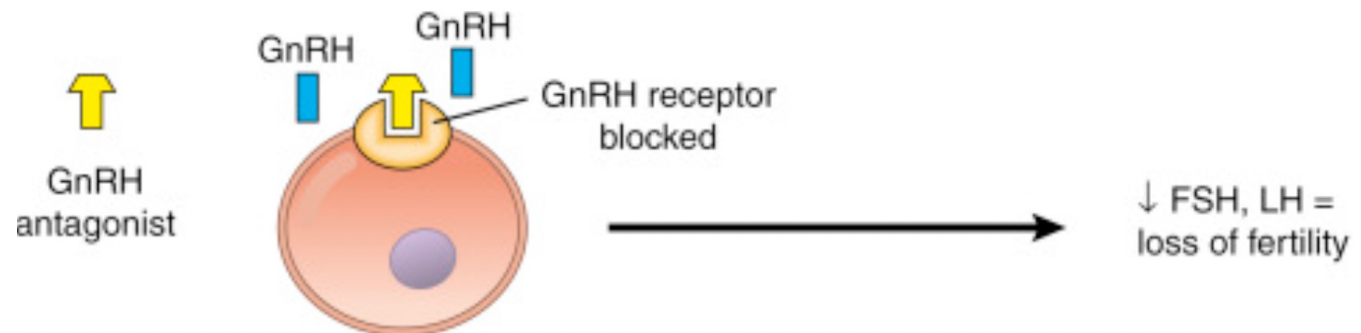
PROMPTLY suppress pituitary gonadotrophins by GnRH receptor competition

- Avoids initial stimulatory phase of the agonists

Discontinuation

- Rapid and predictable recovery of HPG axis

Potential tool for ‘chemical hypophysectomy’



Which one?

GnRH AGONIST

Daily injections of agonists
- Desensitizing effects

Now have longer lasting antagonist analogues
- Block the LH surge
- Therefore longer desensitization

Kumar, P & Sharma, A. (2014) Gonadotrophin releasing hormone analogs: understanding advantages and limitations
Journal of Human Reproductive Sciences 7;3 July – Sept pp.170
- 174



GnRHa	Starting dose, per day
Leuprorelin	3.75 mg every month or 11.25 mg every 3 months
Triptorelin	11.25 mg every 3 months 22.5mg SR every 6 months

<https://www.medicines.org.uk/emc/product/5906/smpc>
<https://www.medicines.org.uk/emc/product/780/smpc>
<https://www.medicines.org.uk/emc/product/4650/smpc>
<https://www.medicines.org.uk/emc/product/4651/smpc>

Conclusion

CPP

- Differences in boys and girls
- Causes
- Presenting signs and symptoms

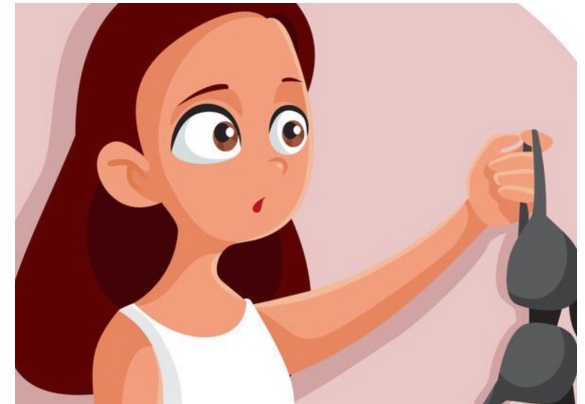
Management

- Pathophysiology
- GnRH analogues

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@LSBU_Prescribe



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