



# REPLACEMENT OF MALE MINI-PUBERTY

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## DISCLOSURE STATEMENT

Speakers Name: Dimitrios T. Papadimitriou

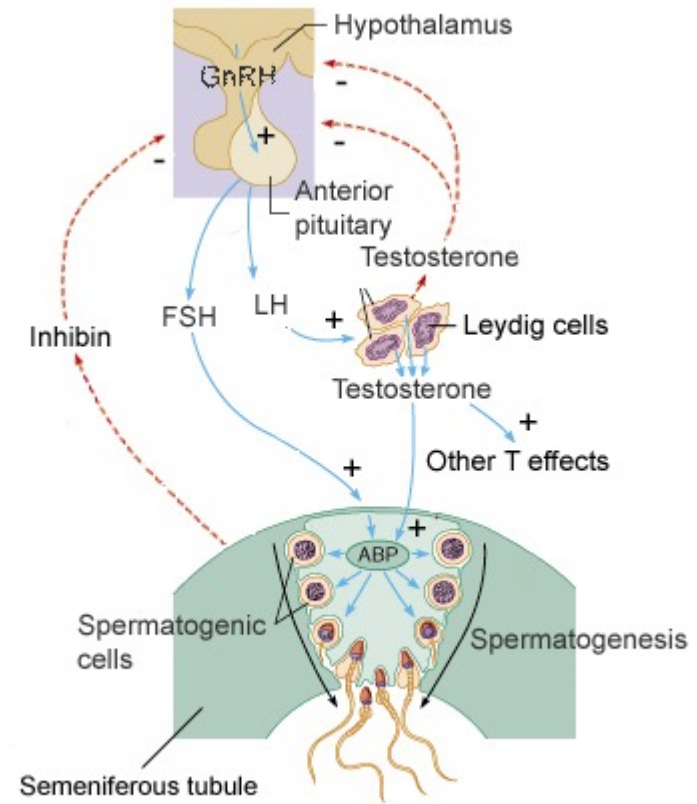
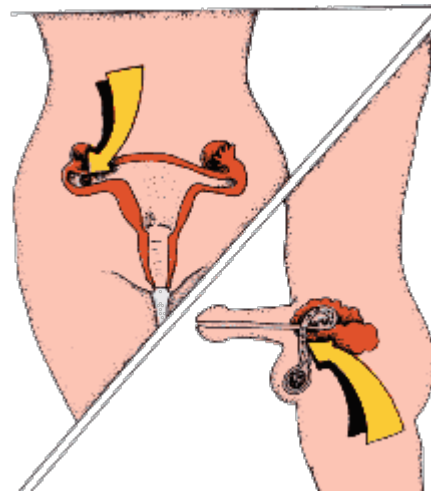
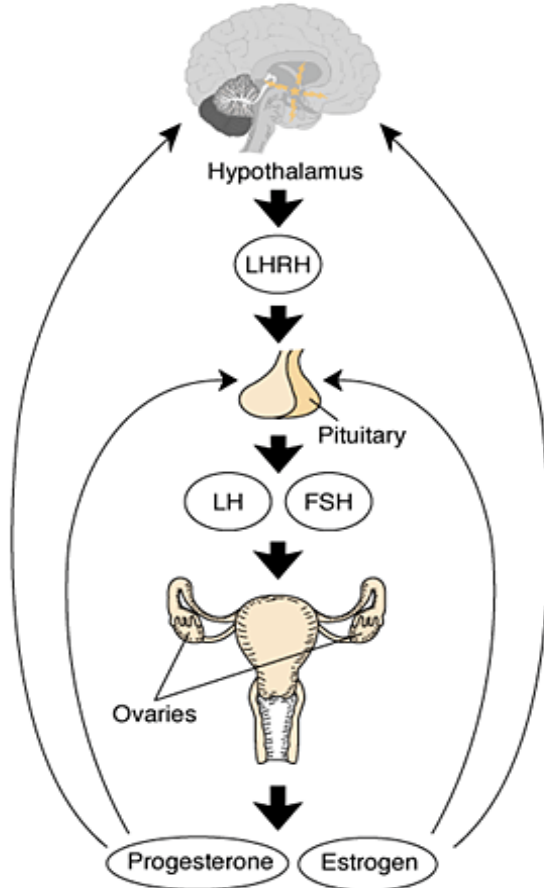
☐ I have the following potential conflicts of interest to report:

- ☐ Research Contracts
- ☐ Consulting
- ☐ Employment in the Industry
- ☐ Stockholder of a healthcare company
- ☐ Owner of a healthcare company
- ☐ Other(s) – *please include details*

*No commercial logos or product names to be included please.*

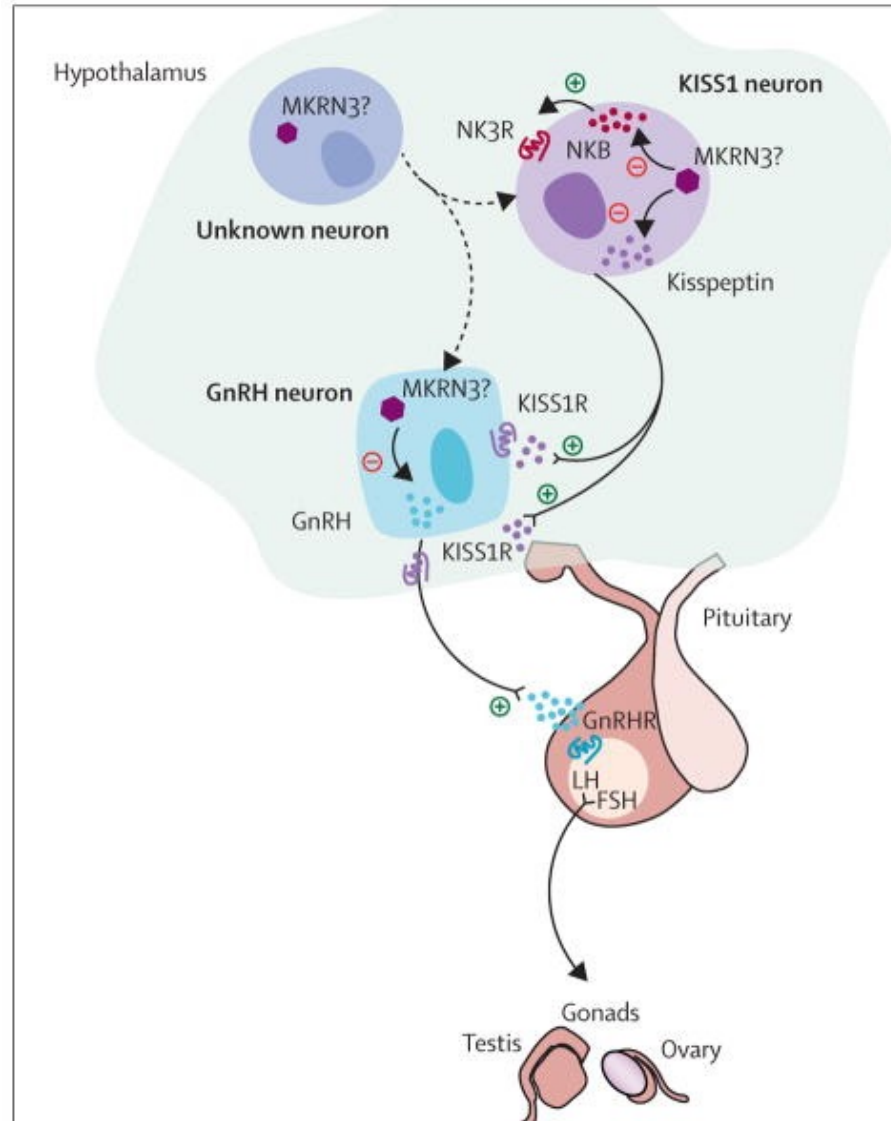
**X** I declare that I have no potential conflict of interest.

# Hypothalamic – Pituitary – Gonadal axis



**Puberty: The transition to an adult, capable of reproduction**

# Essential regulators of GnRH secretion in which mutations have been identified in human beings

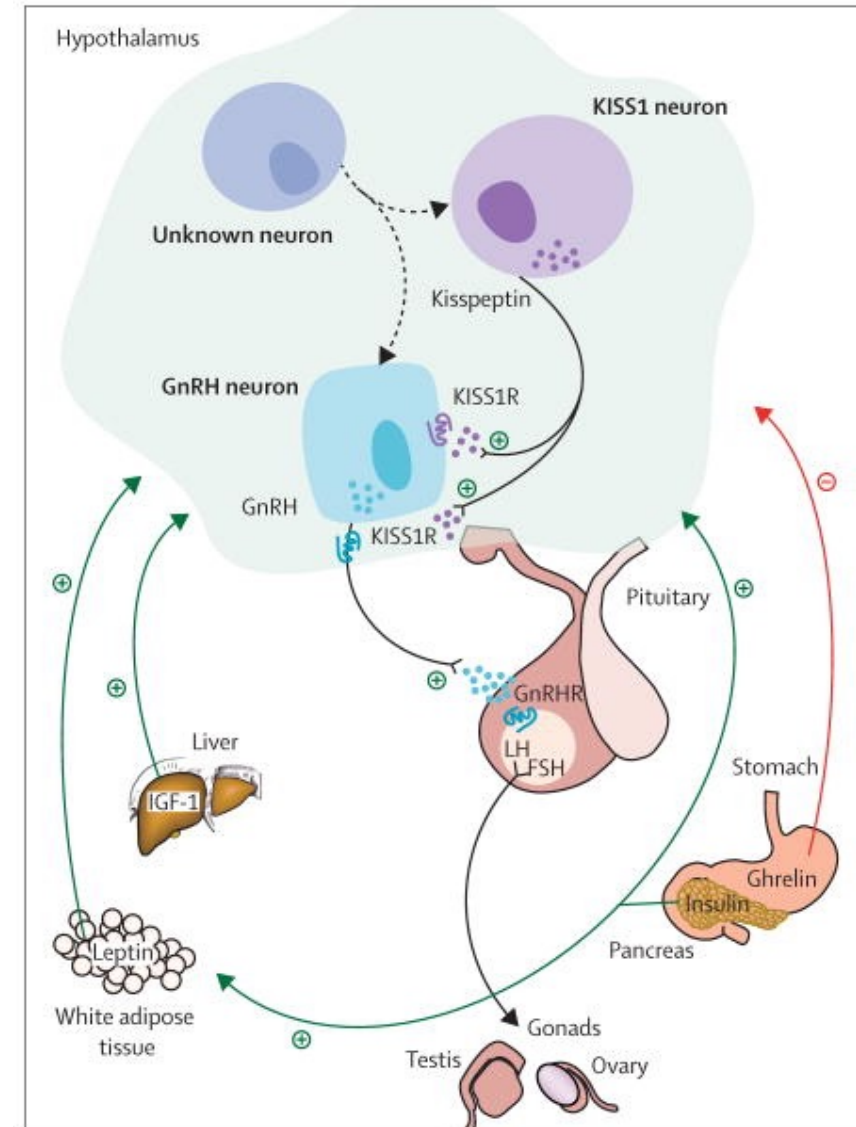


# Control of GnRH secretion by peripheral metabolic hormones

Leptin, a signal for **energy abundance**, is a permissive factor for GnRH secretion.

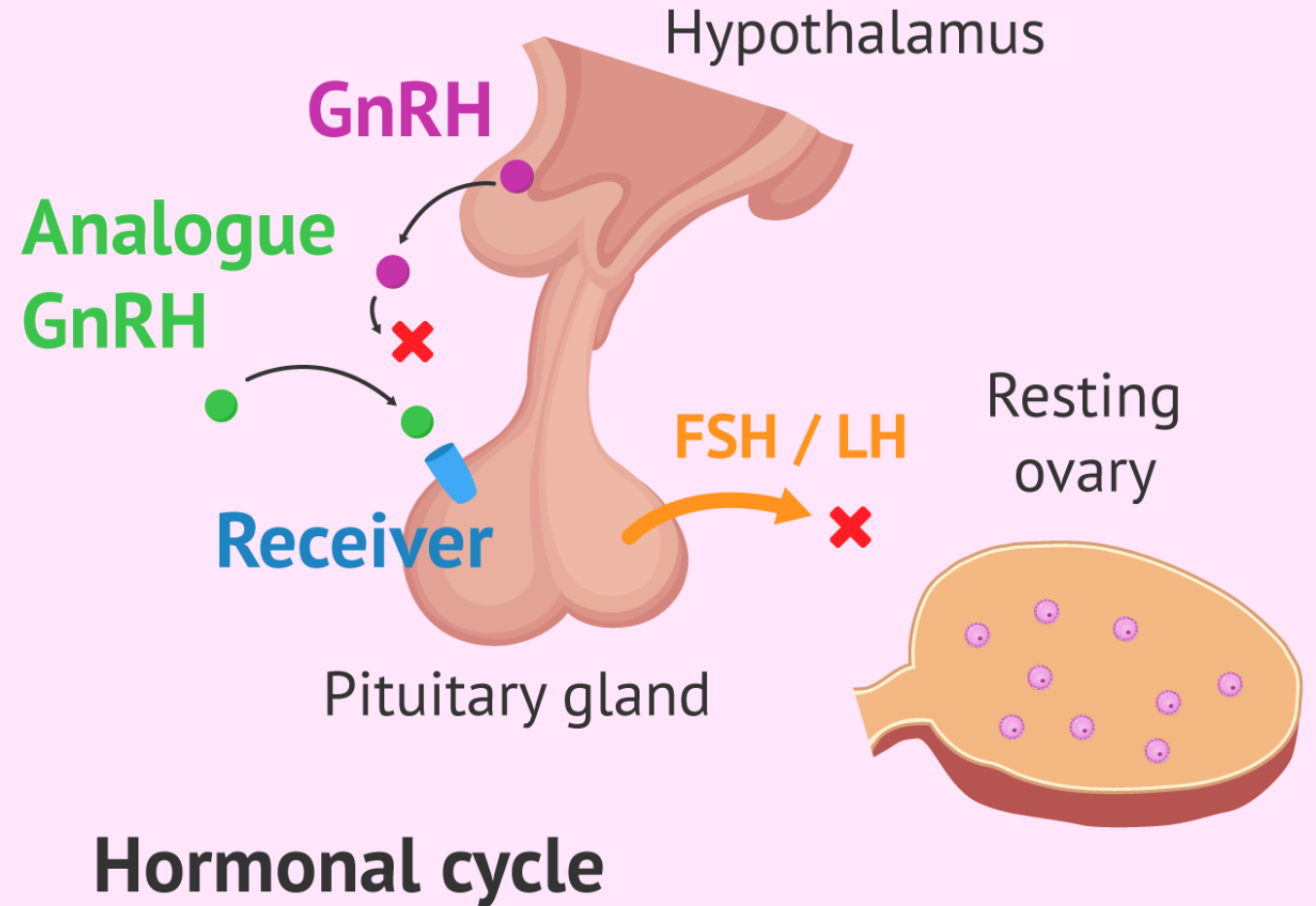
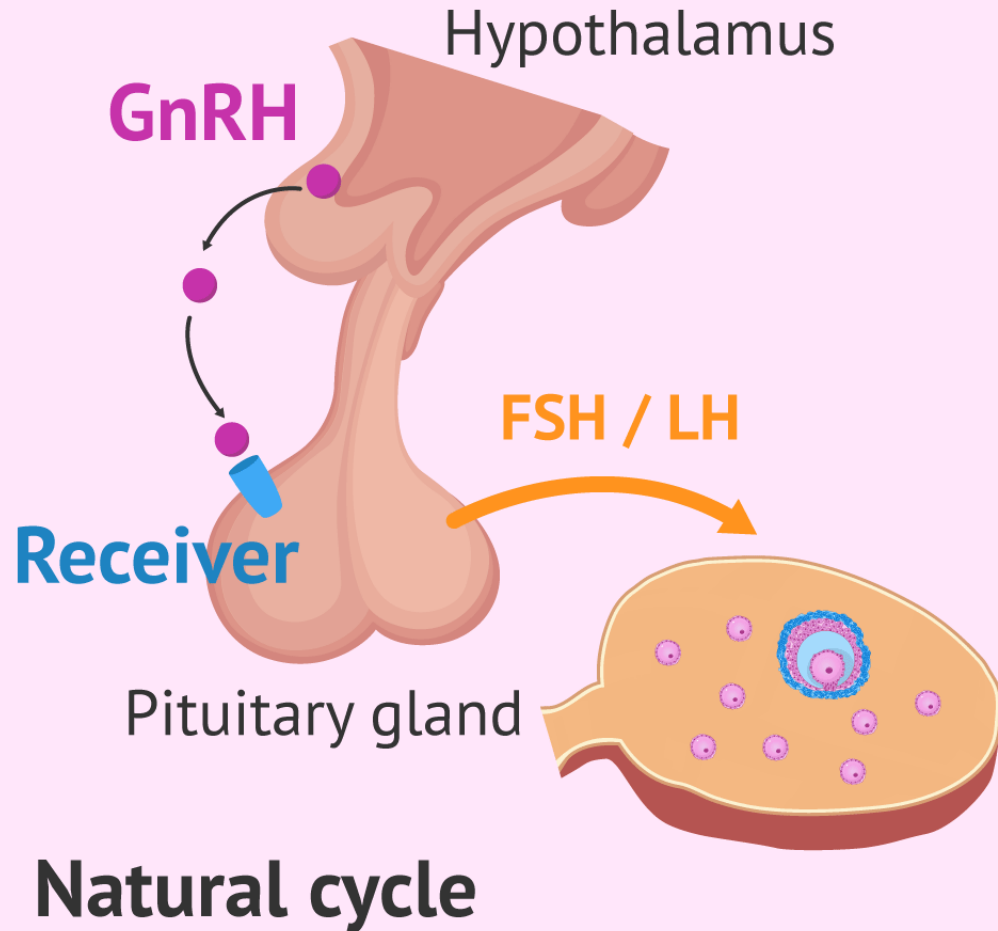
Ghrelin, a putative signal of **energy insufficiency** is an inhibitory factor for GnRH secretion.

**Insulin and IGF-1** have stimulatory effects on the reproductive axis.



Lancet Diabetes Endocrinol.  
2016 Mar; 4(3): 254–264.

## Inhibition of puberty is achieved with long acting GnRH analogs



## GnRH neuron migration/ neurodevelopment

*ANOS1, AXL, CCDC141,  
CHD7, DCC, DMXL2,  
FEZF1, FGFR1, FLRT3,  
HESX1, KAL1, KL, KLB,  
LHX3, OTUD4, PCSK1,  
PNPLA6, POLR3B, PROK2,  
PROKR2, PROP, RAB3GAP1,  
RAB3GAP2, SEMA3A,  
SEMA3E, SOX2, SPRY4,  
WDR11*

## Neuroendocrine function

*AGNRH1, GNRHR, LEPR,  
NR0B1, SRA1, TACR3*

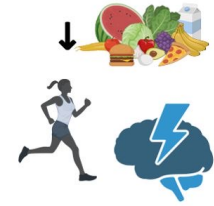
## Genetic vulnerability

Rare or polymorphic  
variants in genes that  
control migration,  
development and/or  
function of GnRH



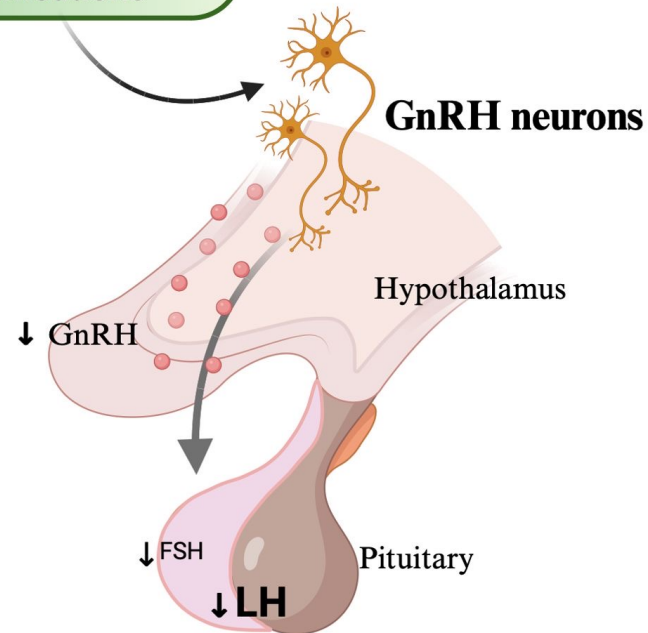
## Environmental stressors

- Energy deficiency due to caloric restriction or excessive energy expenditure
- Intrapersonal characteristic
- Life events



## Epigenetic modifications

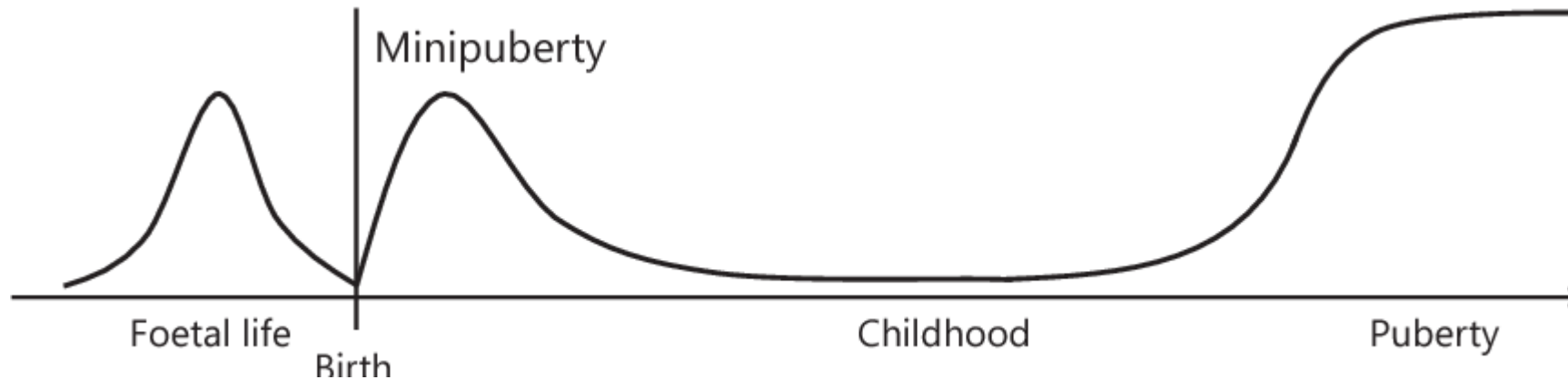
<https://www.frontiersin.org/journals/endocrinology/articles/10.3389/fendo.2024.1423898/full>



## FUNCTIONAL HYPOTHALAMIC AMENORRHEA (FHA)

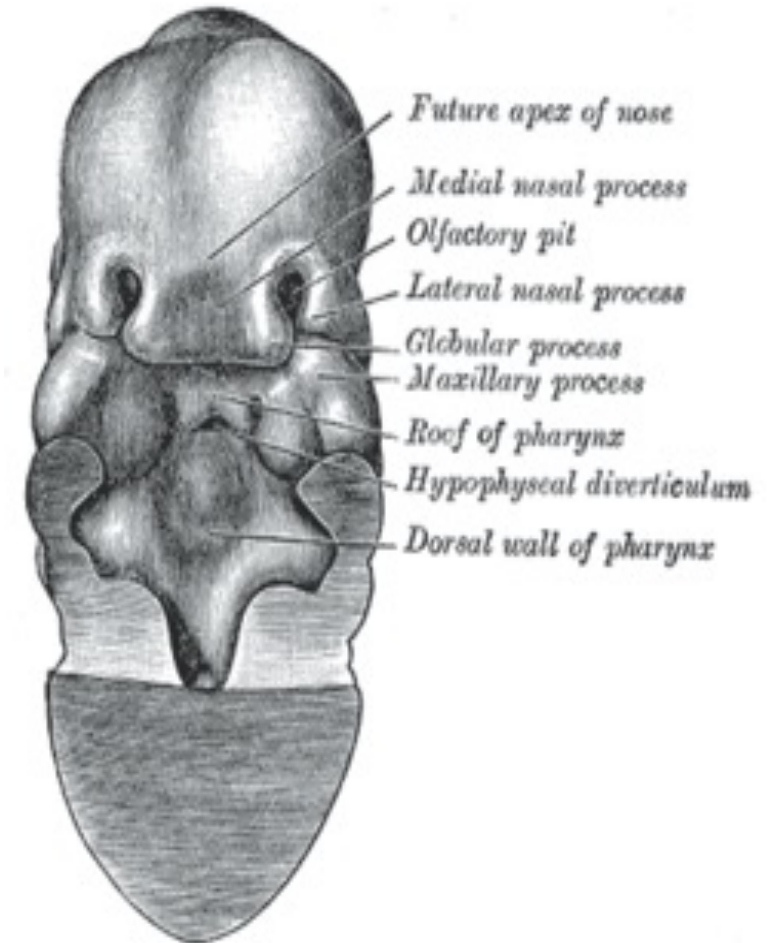
# Humans experience 3 biochemical – endocrine puberties

- Intrauterine (10-24 WG)
- **Neonatal (mini puberty), 15d – 3-6m, peak at 1m**
- No significant changes in Tanner staging
- Not capable in inducing fertility

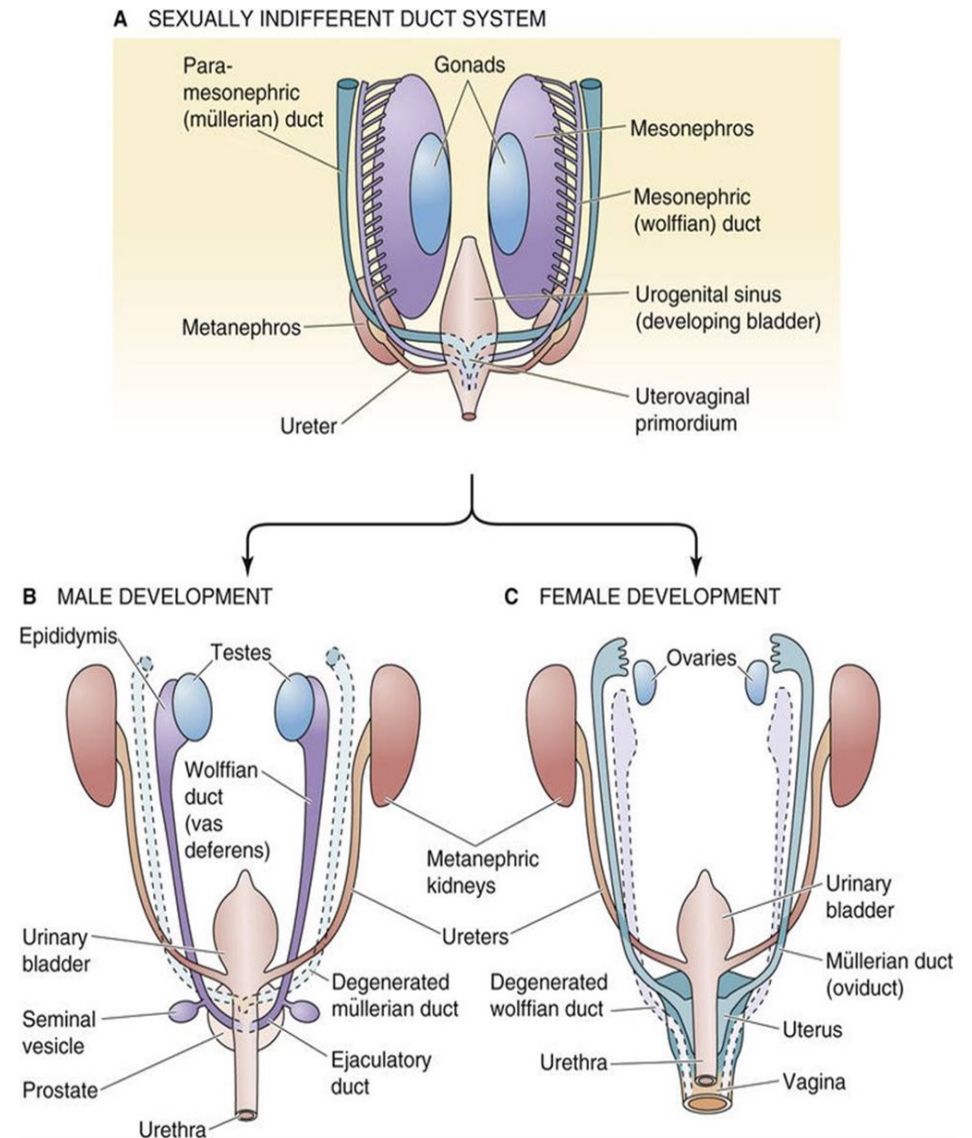


## Intrauterine activation of the H-P-G axis

- At 40 d GnRH producing neurons are developed from the medial nasal process and migrate to the embryonic hypothalamus through neuron lines
- At 9 WG pituitary is developed and synthesizes LH - FSH (measured in embryonic blood at 12-14 WG)
- Until 30-31 WG, LH and FSH secretion is GnRH independent
- Major role in gonadal development, testicular descent, penile growth, linear and mental growth and in defining the sex identity itself.

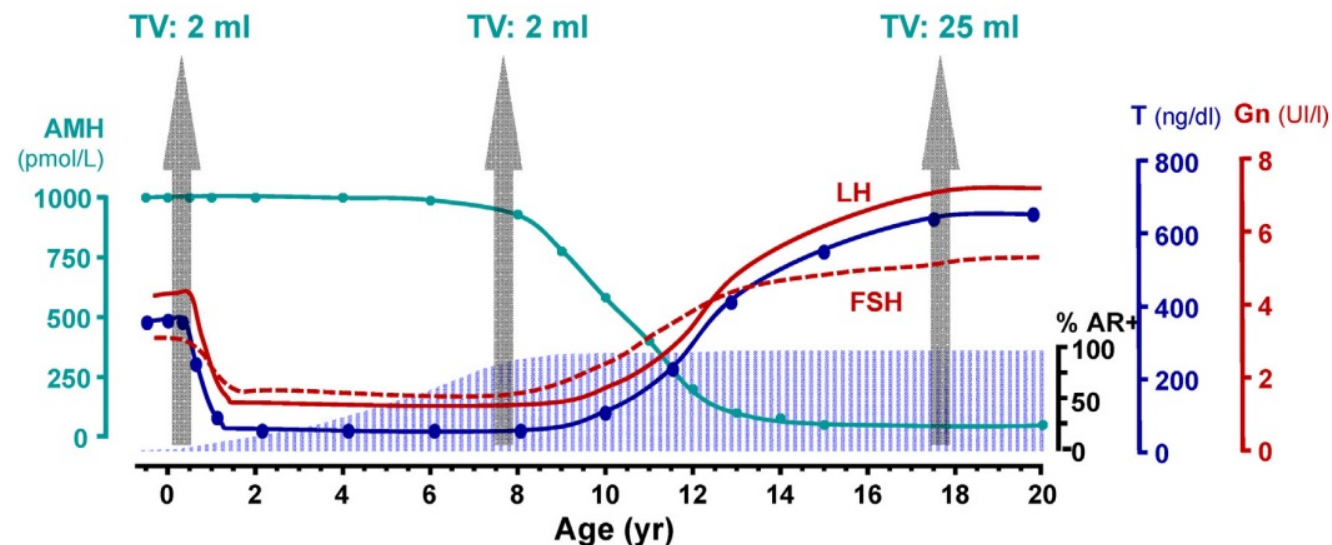


- **FSH** → FSH receptors → Sertoli cell proliferation  
**AMH** → regression of Mullerian ducts (uterus and salpinges)
- Placenta HCG → mesenchymal cells → Leydig cells and lead to TESTO production through the LH/hCG receptor
- 8-11 WG TESTO rises → masculinization
- 20 WG TESTO reaches pubertal levels (0.4–5.8 ng/ml), then gradually falls
- TESTO → seminal vesicles and ducts, epididymis from the mesonephric (Wolfian) duct
- DHT → formation of penis and scrotum



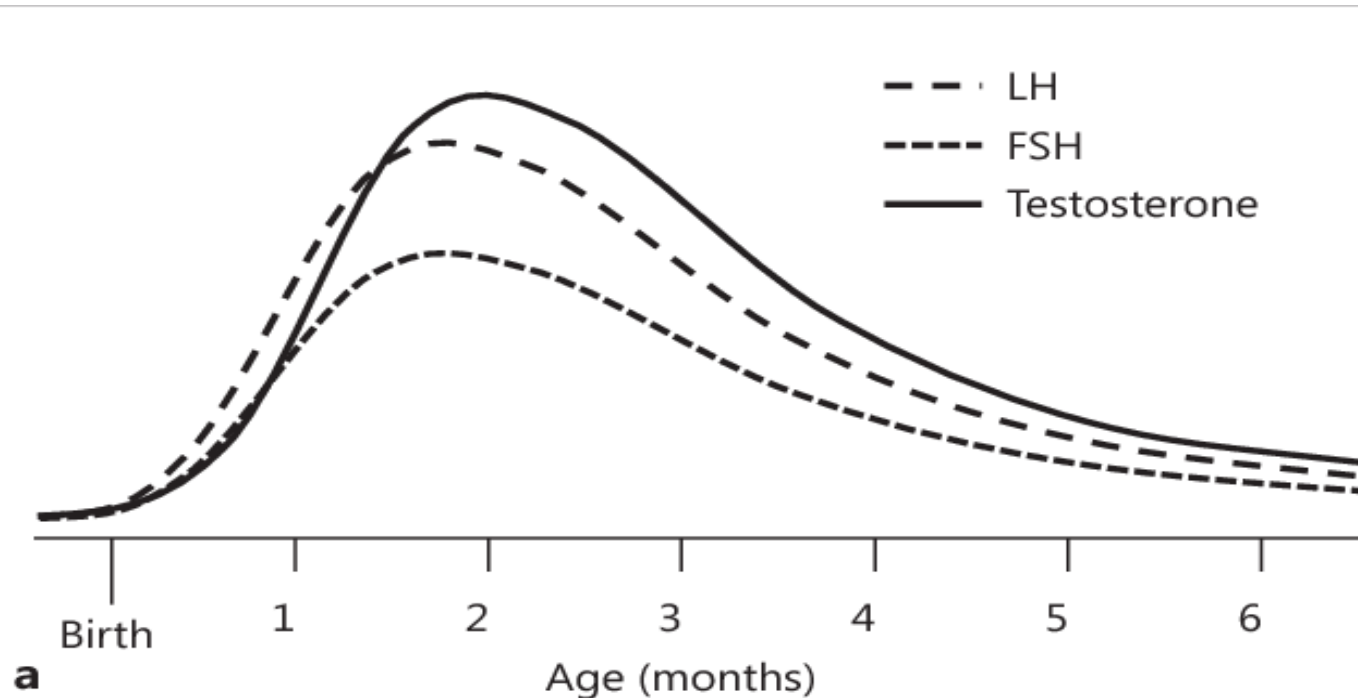
# Mini Puberty is critical and a critical diagnostic window

- The second endocrine puberty **starts at 15 d of life irrespective of prematurity, till 3-6m in the boy** και about 1-6m till even 18-24m in the girl
- Known since 1973
- Critical for
  - **Maturation of the genital system**
  - **Linear growth (+4.1 cm in length for boys the 1<sup>st</sup> month of life)**
  - **Sex differences in body composition emerge in the first 5 months !**
  - **Mental development**
  - **Sex identity**



## Mini Puberty in boys

- **LH** reaches pubertal levels ( $> 0.2$  ng/ml) since 1 Wk → **Leydig cells** → **Testo**
- Peak in 2-10 Wk
- Gradual fall till 4-6 m in prepubertal levels
- FSH follows slightly lower – Sertoli cells do not express the Androgen Receptor at this stage, why spermatogonia remain inactive and despite the rise in TESTO, AMH remains high

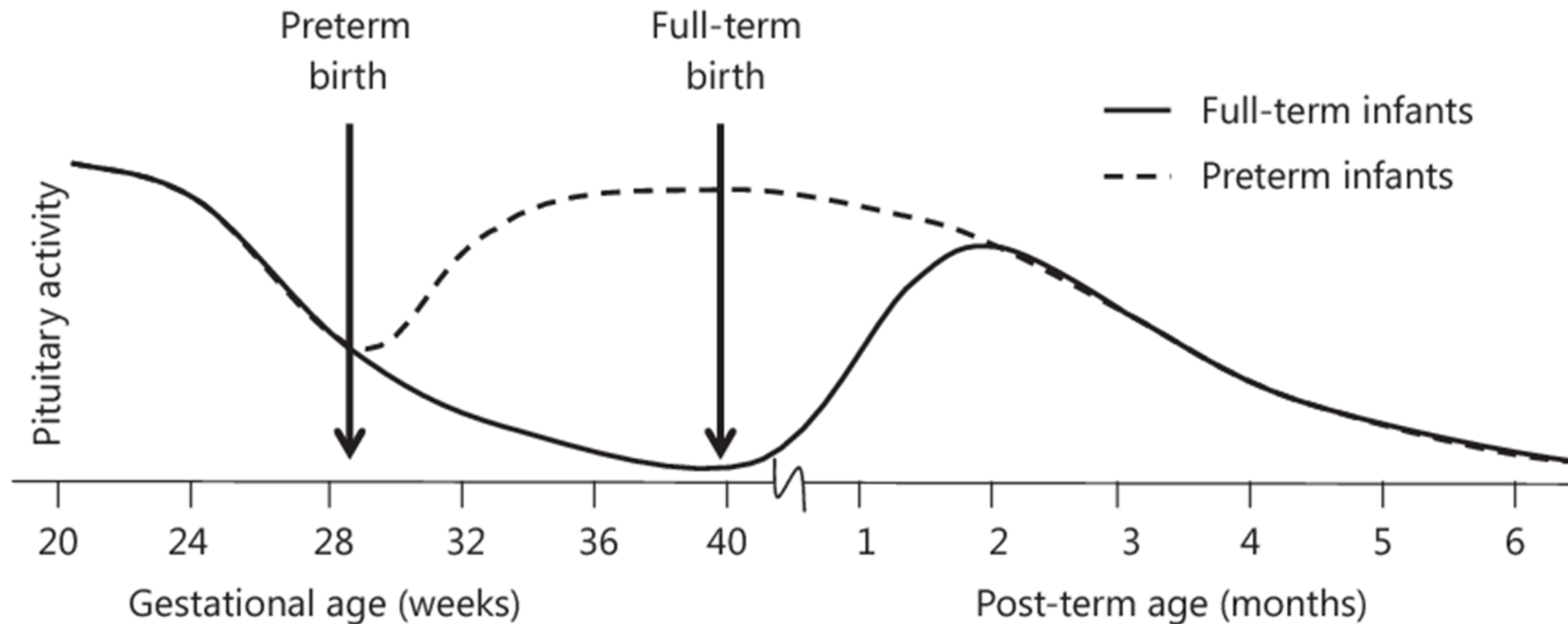


**a**

Horm Res Paediatr 2014;82:73–80  
DOI: 10.1159/000362414

## Mini Puberty in preterm

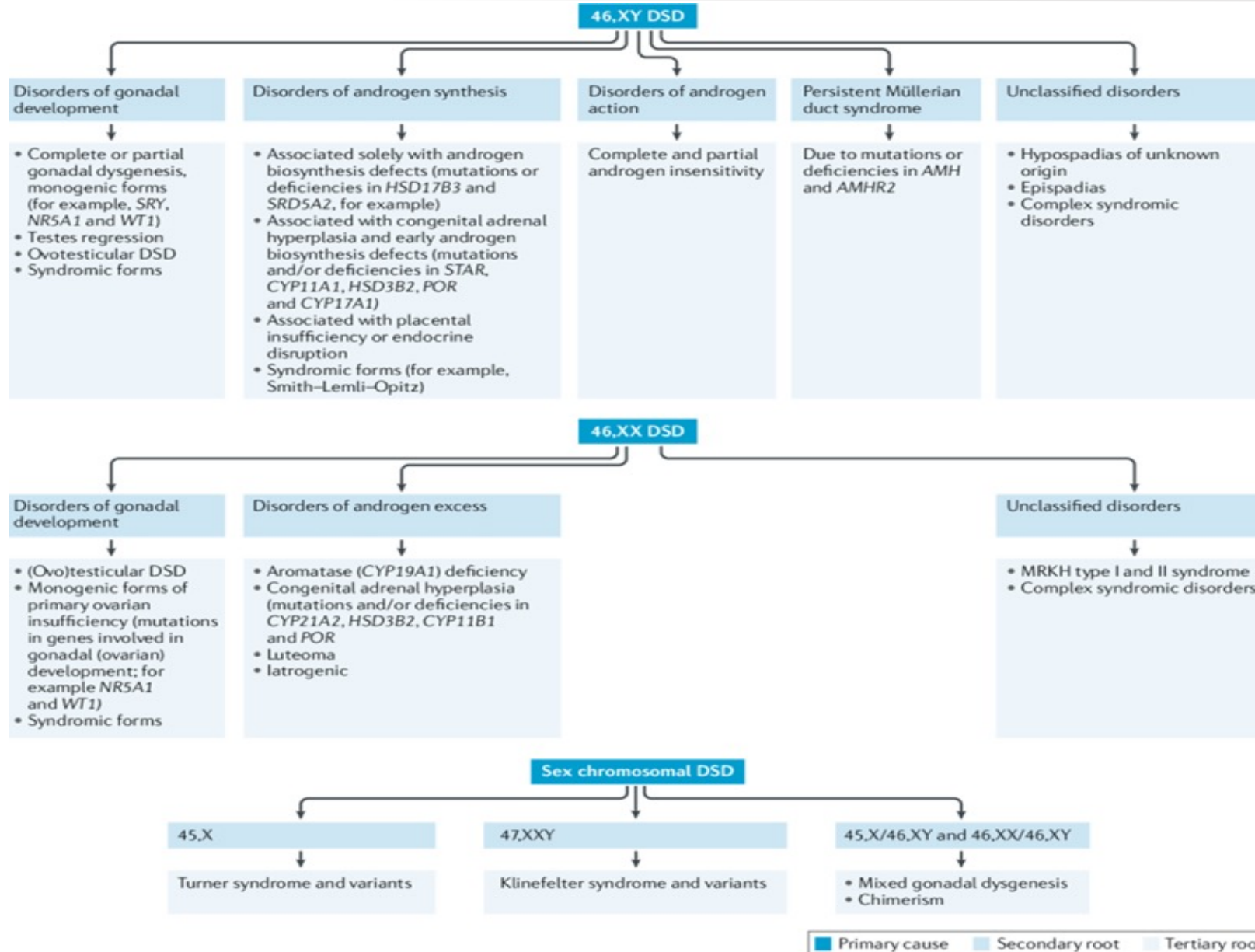
- More intense and prolonged due to immaturity of the axis
- Same biological - not corrected age



# Mini Puberty – clinical importance

- **Leydig cell proliferation and analogous TESTO production the first 3 months of life**
- **Penile growth from** 3.49 +/– 0.4 cm at birth to 4,53+/-0,51 cm at 3 yrs (Eur J Endocrinol. 2006 Jan.)
- **Proliferation of Sertoli cells** (indispensable for spermatogenesis)
- **Testicular volume in U/S augments from** 0.27  $\pm$  0.44 ml the first 6 months, then regresses to 0.31 ml at 9m following the FSH pattern (HumReprod 2008 Apr;23(4):792-6)
- **In bilateral cryptorchidism due to hypogonadotropic hypogonadism, azoospermia will occur despite successful orchiopexy even in babyhood.**
- **Neurobehavioral development (higher TESTO during rapid brain growth periods)**
- **Testosterone measured in infancy predicts subsequent sex-typed behavior in boys and in girls.** (Hormones and Behavior Volume 61, Issue 4, April 2012)
- **Postnatal penile growth concurrent with mini-puberty predicts later sex-typed play behavior: Evidence for neurobehavioral effects of the postnatal androgen surge in typically developing boys.** (Hormones and Behaviour Volume 69, March 2015)

# Mini Puberty = Unique Diagnostic Window for Disorders of Sex Development





# Time Course of the Serum Gonadotropin Surge, Inhibins, and Anti-Müllerian Hormone in Normal Newborn Males during the First Month of Life

Ignacio Bergadá,\* Carlos Milani,\* Patricia Bedecarrás, Luz Andreone, M. Gabriela Ropelato, Silvia Gottlieb, César Bergadá,† Stella Campo, and Rodolfo A. Rey

Bergadá *et al.* • LH, FSH, T, and Gonadal Peptides in Newborns

J Clin Endocrinol Metab, October 2006, 91(10):4092–4098 4095

**TABLE 1.** Serum levels of gonadotropins and gonadal hormones in normal newborns

| Hormone              | d 2                      | d 7                      | d 10                     | d 14                     | d 20                     | d 30                     |
|----------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| LH (IU/liter)        |                          |                          |                          |                          |                          |                          |
| Boys                 | 0.21 ± 0.28 <sup>a</sup> | 3.94 ± 3.19 <sup>b</sup> | 4.81 ± 2.19 <sup>b</sup> | 2.64 ± 1.38 <sup>b</sup> | 2.67 ± 1.64 <sup>b</sup> | 2.95 ± 1.28 <sup>b</sup> |
| Girls                | 0.10 ± 0.11*             |                          |                          |                          |                          | 0.49 ± 0.66**            |
| FSH (IU/liter)       |                          |                          |                          |                          |                          |                          |
| Boys                 | 0.25 ± 0.31 <sup>a</sup> | 2.04 ± 1.67 <sup>b</sup> | 2.30 ± 0.89 <sup>b</sup> | 1.72 ± 1.88 <sup>b</sup> | 1.31 ± 0.61 <sup>b</sup> | 1.48 ± 0.55 <sup>b</sup> |
| Girls                | 0.17 ± 0.15*             |                          |                          |                          |                          | 6.65 ± 7.01*             |
| T (ng/dl)            |                          |                          |                          |                          |                          |                          |
| Boys                 | 66 ± 42 <sup>a</sup>     | 76 ± 40 <sup>a</sup>     | 76 ± 30 <sup>a</sup>     | 98 ± 88 <sup>a</sup>     | 82 ± 24 <sup>a</sup>     | 210 ± 130 <sup>b</sup>   |
| Girls                | 30 ± 9.7*                |                          |                          |                          |                          | 34 ± 7.7*                |
| AMH (pmol/liter)     |                          |                          |                          |                          |                          |                          |
| Boys                 | 371 ± 168 <sup>a</sup>   | 397 ± 152 <sup>a,b</sup> | 427 ± 127 <sup>b</sup>   | 499 ± 139 <sup>b,c</sup> | 523 ± 156 <sup>b,c</sup> | 699 ± 245 <sup>c</sup>   |
| Girls                | 7.4 ± 6.3**              |                          |                          |                          |                          | 18.2 ± 21.3**            |
| Pro-αC (ng/liter)    |                          |                          |                          |                          |                          |                          |
| Boys                 | 892 ± 377 <sup>a</sup>   | 717 ± 232 <sup>a</sup>   | 849 ± 714 <sup>a</sup>   | 872 ± 274 <sup>a</sup>   | 692 ± 529 <sup>a</sup>   | 641 ± 194 <sup>a</sup>   |
| Girls                | 826 ± 553                |                          |                          |                          |                          | 641 ± 522                |
| Inhibin B (ng/liter) |                          |                          |                          |                          |                          |                          |
| Boys                 | 214 ± 86 <sup>a</sup>    | 319 ± 167 <sup>b</sup>   | 300 ± 120 <sup>b</sup>   | 316 ± 89 <sup>b</sup>    | 280 ± 82 <sup>b</sup>    | 361 ± 93 <sup>b</sup>    |
| Girls                | 0 ± 0**                  |                          |                          |                          |                          | 125 ± 41**               |

# Diagnostic window of Mini Puberty

- In every bilateral cryptorchidism (25% in Congenital Hypogonadotropic Hypogonadism) +/- micropenis
- Bilateral cryptorchidism 1-3% in the general population
- CHH is confirmed by the absence of mini-puberty
- Low LH and FSH
- Complete pituitary hormonal profiling necessary

# Mini Puberty and Hypergonadotropic hypogonadism

## Turner (45,X0)

- 1:2130 newborn girls
- Higher **FSH during** mini puberty IF ovaries are involved



## Klinefelter (47,XXY)

- ~1:600 newborn boys
- **Completely normal mini-puberty**



# Every newborn boy even with apparently isolated micropenis with penile length < 2.5 cm needs a karyotype and endocrinological evaluation in mini puberty as CHH may be uncovered

## The same stands for any DSD +/- cryptorchidism +/- hypospadias

**Micropenis** is an unusually small [penis](#). A common criterion is a dorsal (measured on top) erect [penile length](#) of at least 2.5 [standard deviations](#) smaller than the [mean human penis size](#)

A phallic length which is 2.5 or more standard deviations below the mean should be considered as abnormal; for an infant of 0 to 5 months of age, the lower limit is 1.9 cm

*Lee PA, Mazur T, Danish R, Amrhein J, Blizzard RM, Money J, Migeon CJ. Micropenis. I. Criteria, etiologies and classification. Johns Hopkins Med J. 1980 Apr;146(4):156-63. PMID: 7366061.*

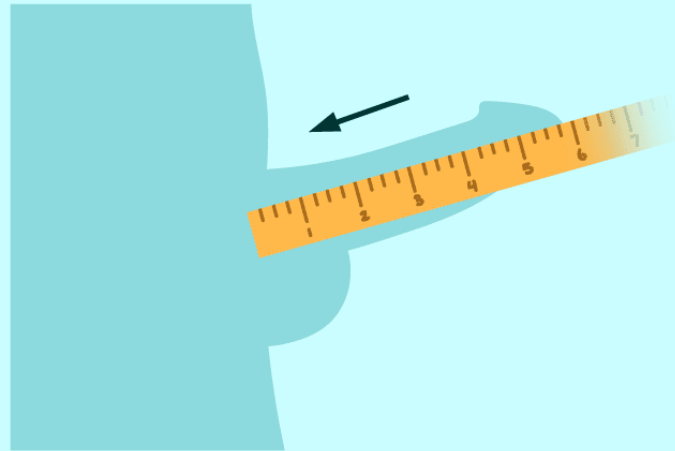
## Etiological evaluation of patients presenting with isolated micropenis to an academic health care center

*Indian J Pediatr. 2014 Aug;81(8):775-9*

In approximately one third of patients the presence of micropenis was not confirmed

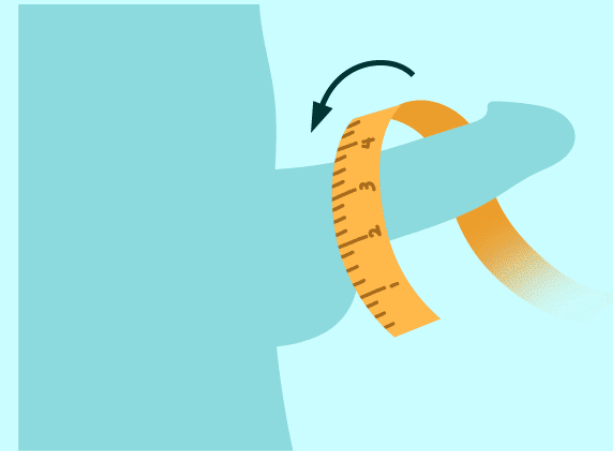
Etiological cause was determined in 29 patients (44 %) with **the most common cause being hypogonadotropic hypogonadism**

## How to Measure a Penis



### Length

- Position measurer at the base
- Press into the pubic bone
- Measure to the end of the tip



### Girth

- Gently wrap measurer around thickest part of shaft
- Note where the ends of the measurer meet

## Establishment of normative data for stretched penile length in Turkish preterm and term newborns

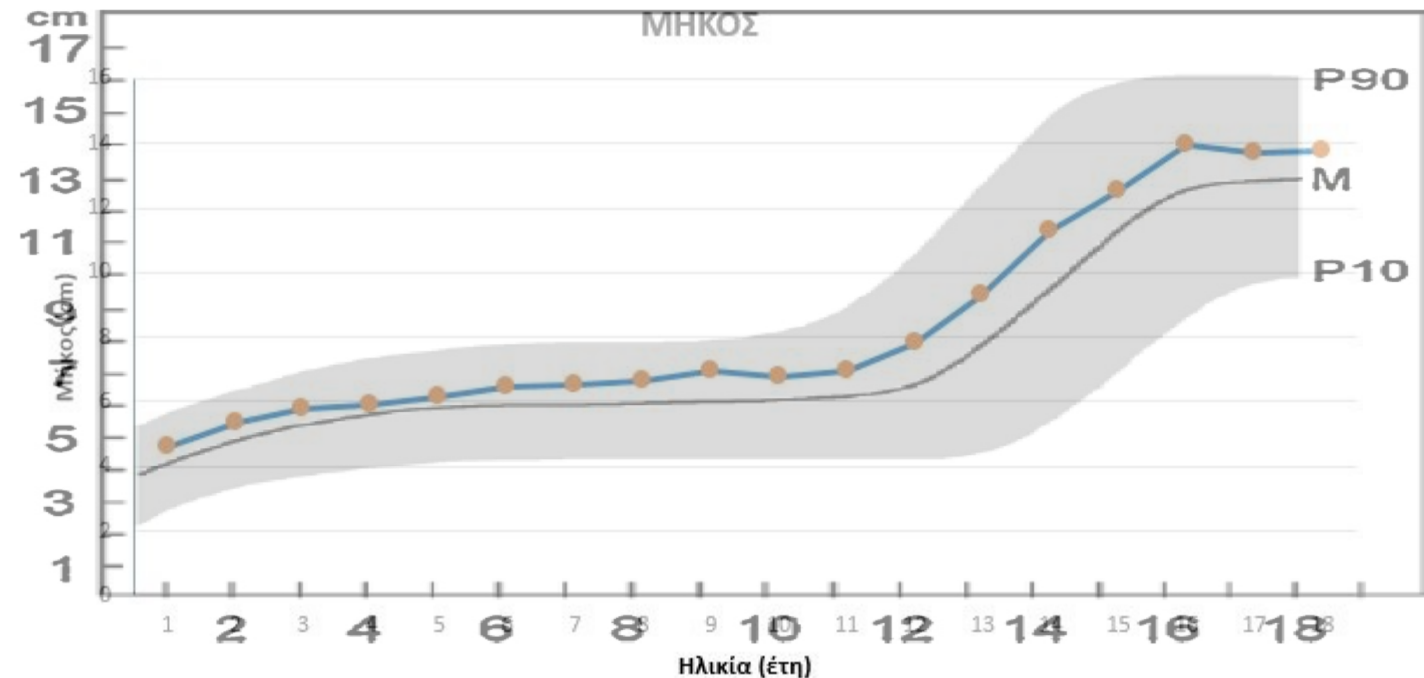
*Turk J Pediatr. 2017;59(3)*

stretched penile length of **preterm  $2.5 \pm 0.565$  cm** and **term neonates  $3.2 \pm 0.551$  cm**

Cross-sectional Hellenic data, K. Kleanthous and A. Papadimitriou shown on Schonfeld's curve on the right

| ΗΛΙΚΙΑ | ΠΛΗΘΟΣ | ΜΕΣΗ ΗΛΙΚΙΑ | ΜΗΚΟΣ        | ΔΙΑΜΕΤΡΟΣ | ΠΕΡΙΜΕΤΡΟΣ |
|--------|--------|-------------|--------------|-----------|------------|
| 0-1    | 62     | 0,38±0,30   | 4,62 ± 0,62  | 1,30±0,17 | 4,67±0,39  |
| 1-2    | 57     | 1,56±0,29   | 5,36 ± 0,71  | 1,41±0,14 | 4,69±0,27  |
| 2-3    | 42     | 2,48±0,31   | 5,79 ± 0,67  | 1,43±0,15 | 4,84±0,44  |
| 3-4    | 48     | 3,58±0,29   | 5,89 ± 0,67  | 1,45±0,16 | 4,89±0,48  |
| 4-5    | 53     | 4,52±0,29   | 6,16 ± 0,75  | 1,51±0,15 | 5,07±0,52  |
| 5-6    | 60     | 5,52±0,31   | 6,43 ± 0,90  | 1,61±0,21 | 5,36±0,51  |
| 6-7    | 51     | 6,52±0,31   | 6,55 ± 0,89  | 1,61±0,15 | 5,27±0,47  |
| 7-8    | 62     | 7,51±0,30   | 6,60 ± 0,93  | 1,62±0,17 | 5,44±0,51  |
| 8-9    | 69     | 8,53±0,32   | 6,91 ± 0,83  | 1,66±0,16 | 5,66±0,55  |
| 9-10   | 82     | 9,53±0,29   | 6,75 ± 0,91  | 1,68±0,15 | 5,65±0,62  |
| 10-11  | 71     | 10,53±0,27  | 6,91 ± 1,02  | 1,73±0,23 | 5,81±0,86  |
| 11-12  | 96     | 11,56±0,28  | 7,83 ± 1,42  | 1,92±0,39 | 6,43±1,09  |
| 12-13  | 83     | 12,55±0,27  | 9,27 ± 2,25  | 2,22±0,45 | 7,34±1,55  |
| 13-14  | 56     | 13,49±0,29  | 11,22 ± 2,41 | 2,56±0,54 | 8,59±1,66  |
| 14-15  | 47     | 14,46±0,26  | 12,27 ± 2,60 | 2,76±0,50 | 9,30±1,53  |
| 15-16  | 37     | 15,46±0,31  | 13,38 ± 1,78 | ±2,970,37 | 9,95±1,08  |
| 16-17  | 20     | 16,56±0,30  | 12,60 ± 1,60 | 2,94±0,43 | 9,31±0,82  |
| 17-18  | 11     | 17,58±0,34  | 12,95 ± 1,99 | 3,04±0,62 | 9,12±0,91  |

*From: Arch Pediatr. 2014 Jun;21(6):665-9 Micropenis*



Schonfeld WA, Beebe GW. Normal growth and variations in the male genitalia from birth to maturity. *J Urol* 1942;48:759–77.

**Male, left cryptorchidism, normal penis, perineal hypospadias,  
hypoplastic vagina, hypoplastic uterus  
endocrine disruptors ?**

**With a proper surgery will be risen as a normal boy**

**46XY, normal mini-puberty,  
Normal DHT/TESTO  $\geq 10\%$   
normal AMH και inhibin-b  
Normal adrenal function  
Normal testes, left undescended**



**3 m declared as girl !**

**Normal penis, normal testes**

**Hypoplastic vagina**

**Scrotal hypospadias**

**Normal mini-puberty**

**Normal TESTO, AMH, inhibin-b**

**This is a boy and needs to be raised as a boy**



**Brain has already been masculinized during the first 2 puberties**

**Just needs a proper surgery !!!**

**While testosterone enanthate I.M. 100 mg/m<sup>2</sup> q 4 wk x 3 completely restores micropenis  
In cases of CHH this does not preserve fertility...**



Early treatment of congenital hypoplasia of the penis with intramuscular delayed-action testosterone. Arch Fr Pediatr. 1984 Aug-Sep;41(7):467-71. PMID: 6497554

**Δεν έχει καμία απώτερη επίπτωση στο τελικό ανάστημα  
λόγω πρόσκαιρης ενδεχόμενης ταχύτερης οστικής ωρίμανσης  
και φυσικά το αποτέλεσμα διατηρείται  
αλλά πρέπει να γίνεται στη σωστή χρονική στιγμή  
(*< 2-4 ετών, ή στην αρχή της ήβης*)**

[Arch Fr Pediatr.](#) 1984 Aug-Sep;41(7):467-71.

**[Early treatment of congenital hypoplasia of the penis with intramuscular delayed-action testosterone].**

[Article in French]

[Landier F](#), [Chaussain JL](#), [Job JC](#).

### **Abstract**

**Three intramuscular injections of 25 to 50 mg of testosterone** hexahydrobenzoate

were prescribed in 37 boys who presented with hypoplastic penis:  
6 with micropenis and normally placed urethra, 21 with hypospadias.  
Ages ranged from 4 months to 9 years.

**In almost all children treated between the ages of 6 and 18 months, penis growth became normal for age.  
Growth and bone maturation were temporarily accelerated but in a parallel fashion,  
so that this very early androgen-therapy need not reduce the adult height of children thus treated.**

PMID: 6497554 [PubMed - indexed for MEDLINE]



#### Start/Search

Browse the Scientific  
and Conference Program

Browse by Author

#### Browse By Day

Friday, June 20

Saturday, June 21

Sunday, June 22

## Origins and Treatment of Reproductive Dysfunction

**Program:** Late-Breaking Abstracts  
**Translational Session**

**Saturday, June 21, 2014: 11:30 AM-1:00 PM**  
W475 (McCormick Place West Building)

#### Chairs:

**Jorma Toppari, MD, PhD**, Institute of Biomedicine, University of Turku, Turku, Finland and **Bernard Robaire, PhD**, McGill Univ, Montreal, Canada

11:30 AM **LB-OR01-1** **Successful Treatment of Neonatal Micropenis and Bilateral Cryptorchidism Due to Hypogonadotropic Hypogonadism (HH) with 3-Month Daily Subcutaneous Injections of the Recombinant LH Plus FSH Preparation (Pergoveris®)**  
**Dimitrios T Papadimitriou, MD, PhD**, Pediatric Endocrinology, 3rd Department of Pediatrics, Attikon University Hospital, Athens Greece, Athens, Greece and **Anastasios Papadimitriou**, Associate Professor of Pediatric Endocrinology, Pediatrics, Attikon University Hospital, Athens, Greece



Registration

## 55th Annual ESPE Meeting ESPE2016

10-12 SEPTEMBER  
PARIS, FRANCE

12:15 13:45

### **RFC & FC 15 : Late Breaking**

Grand Amphithéâtre L2

*Chairs: Sandro Loche (Cagliari, Italy) & Lars Savendahl (Stockholm, Sweden)*

RFC15.8

Replacement Of Male Mini-Puberty

*Dimitrios T. Papadimitriou (Athens, Greece)*



# Replacement of Male Mini-Puberty

Dimitrios T Papadimitriou , Dionysios Chrysis, Georgia Nyktari, George Zoupanos, Eleni Liakou, Anastasios Papadimitriou, George Mastorakos

*Journal of the Endocrine Society*, Volume 3, Issue 7, July 2019, Pages 1275–1282,

<https://doi.org/10.1210/js.2019-00083>

**Published:** 09 May 2019 **Article history** ▼



## Leading the News

### T1D After Age 30 Relatively Common, But Frequently Misdiagnosed As T2D, Study Finds.

[Medwire News](#) (5/10, McDerimid) reported research indicated that “being diagnosed with type 1 diabetes [T1D] after the age of 30 years is relatively common, yet people are often misdiagnosed with type 2 diabetes [T2D], despite rapid progression to insulin dependence.” The [findings](#) were published online in the journal *Diabetologia*.

## The Endocrine Society in the News

### Endocrine Society Has Made Great Strides In Diversity.

[Endocrine News](#) (5/10, Shaw) reported, “From the 1990s to now, the Endocrine Society has made great strides in creating a professional home for all” who belong. The article examined “the evolution of the Society’s Committee on Diversity and Inclusion and how it has steadily grown throughout the years.”

### Advocacy in Action: Obamacare, Drug Pricing, and More.

[Endocrine News](#) shares a quick run down of major issues being discussed by policymakers from an endocrine perspective and the Endocrine Society’s current advocacy work. This week, the Obamacare debate continues, and progress is made on drug pricing transparency and NIH funding.

### Infant Boys Born With Rare Form Of Congenital Hypogonadotropic Hypogonadism May Experience Improvement In Symptoms After Three Months Of Combination Treatment With Two Fertility Hormones, Researchers Say.

[Endocrine Today](#) (5/11, Schaffer) reported, “Infant boys born with a rare form of congenital hypogonadotropic hypogonadism, a condition associated with micropenis and undescended testes, experienced an improvement in symptoms after three months of combination treatment with two fertility hormones,” research indicated. The [findings](#) of the 10-infant study were published in the *Journal of the Endocrine Society*.



## Hormone Therapy

### TOP STORY

### Fertility treatment mimics mini-puberty in infant boys with rare congenital disorder

May 11, 2019

### MEETING NEWS

### Top takeaways from AACE 2019

May 10, 2019

### IN THE JOURNALS

### GH deficiency not observed in adults with Prader-Willi syndrome treated in childhood

May 9, 2019



### International sports authority enforces controversial eligibility rule for female athletes

May 8, 2019



## ESE Daily News Alert - 14 May 2019

### Inducing mini-puberty in infancy improves symptoms of rare disorder

Infant males with congenital hypogonadotropic hypogonadism experience an improvement in symptoms after hormone treatment to induce mini-puberty, according to research published in the *Journal of the Endocrine Society*.

[Healio](#)

### Diabetes and obesity contribute to increasing rates of heart-related deaths

The number of heart disease related deaths in the UK is on the rise for the first time in decades, influenced in-part by rising rates of diabetes and obesity.

[BBC](#)

### Rare genetic variations may contribute to PCOS

New research published in the *Journal of Clinical Endocrinology and Metabolism* has identified rare genetic variations that may contribute to the heritability of PCOS.

[Endocrinology Advisor](#)

### Babies with older fathers are at higher risk of health problems

A study published in *Maturitas* has suggested that fathers over the age of 35 are more likely to experience fertility problems affecting the health of both the child and mother.

[Sun](#)

## Hormonal replacement in boys with congenital Hypogonadotropic Hypogonadism remains a challenge in pediatric endocrinology

**Congenital HH presents clinically with: micropenis + bilateral crypto/microorchidism**

**Micropenis has been traditionally successfully treated** with 3 monthly injections of 25/50 mg of testosterone enanthate in the post-neonatal period or in early infancy, or at the onset of puberty

**Arch Fr Pediatr. 1984 Aug-Sep;41(7):467-71**

**But when bilateral cryptorchidism coincides, surgical intervention – at least needed twice – is required**

**Current recommendations for the treatment of bilateral cryptorchidism**

**(American Urological Association, May 2014)**

**Providers should not use hormonal therapy to induce testicular descent** as evidence shows low response rates and lack of evidence for long-term efficacy (B).

**Non-palpable testes: 4% unsuccessful operation and 2% atrophy**

**Neoadjuvant gonadotropin-releasing hormone therapy before surgery may improve the fertility index in undescended testes in boys younger than < 2 yrs of age.**

**J Urol. 2005 Mar;173(3):974-7**

## Successful surgery but then what ?

Standard treatments, started after puberty, only partially correct genital abnormalities and spermatogenesis.

**Nature Reviews Endocrinology 8, 172-182 (March 2012)**

In congenital HH, even after a successful surgery,  
the deficient proliferation of immature Sertoli cells before and during puberty,  
**due mainly to the lack of the male mini-puberty in the neonatal period,**  
are considered responsible for hypoplastic testes, azoospermia and infertility

Work of reference:

Two neonates: P1 with hypopituitarism and P2 with HH (micropenis + microorchidism)  
received LH and FSH with Continuous Subcutaneous Injection with an insulin pump,  
P1 from the age of 8 wk for 4 months 56 IU LH + 67 IU FSH/day  
P2 from the age of 20 wk for 6 months 50IU LH + 125 IU FSH/day  
Total dose: P1 LH 9000+FSH 22,500-P2 LH 6720+FSH 8,040 IU

**J Clin Endocrinol Metab. 2008 Jun;93(6):2202-5**

# Objective

**To investigate whether early postnatal daily injections for 3 months of the commercially available preparation of rh LH 75 + FSH 150 IU could mimic the physiological male mini puberty**

**10 neonates with bilateral cryptorchidism, non-palpable testes in intra-abdominal position and micropenis (< 2 cm) with absence of neonatal male mini-puberty:**

LH < 0.44, FSH < 0.73 IU/L and undetectable basal Testosterone measured repeatedly from age 15 days up to 3-6 months.

**All received for 3 months daily s.c. injections of Pergoveris® (LH 75 + FSH 150 IU)**

**Total dose: LH 6,750 and FSH 13,500 IU - monthly follow-up**

**Parents were trained and performed the injections**

**The Greek National Organization for Medicines (EOF) issued permission for the off-label use of Pergoveris and the primary health insurance covered 100% the cost of the injections (6,100 €)**

**5 patients had Kallmann syndrome [8]** diagnosed at the neonatal period before bilateral cryptorchidism (abdominal in two cases and inguinal position in three cases) and micropenis

**1 patient had syndromic features and neurodevelopmental delay [16],**

**1 had normosmic idiopathic hypogonadotropic hypogonadism [17]** (nIHH) (testes in inguinal position),

**1 CHARGE syndrome [18]** (coloboma, heart defects, atresia of the choanae, retarded growth and development, genital-urinary anomalies, and ear defects) diagnosed at birth before choanal atresia (testes in abdominal position)

**2 had septo-optic dysplasia [19]** (testes in abdominal position) diagnosed in the Neonatal Intensive Care Unit (one because of symptomatic hypoglycemia and cholestatic jaundice and one due to severe diabetes insipidus with a sodium of 174 mmol/L at 12 hours of life), and

**1 had congenital panhypopituitarism** diagnosed before hypogonadism and cholestatic jaundice (one testicle in the abdominal position and one in the inguinal position).

showed unilateral hypoplasia/absence of the olfactory tract in three cases  
and unilateral/complete absence of the olfactory bulbs in the other two cases of Kallmann syndrome  
normal in the patient with normosmic IHH

Hypoplastic pituitary and optic nerve atrophy was noted in the septo-optic dysplasia cases,  
aplastic pituitary [20] in the panhypopituitarism case, and  
cerebellar hypoplasia in the CHARGE syndrome case.

### Treatment

All subjects started treatment at the median age of 0.35 years (0.19 to 0.78) for 3 months

with daily subcutaneous injections of Pergoveris (recombinant human LH 75 IU and FSH 150 IU),  
receiving a total dose of 6750 IU of LH and 13,500 IU of FSH, and were monitored  
clinically monthly. Parents were trained and performed the injections at home.

# Results

- **All testes descended in scrotal position** reaching 1.5-2.5 ml by the end of the 1<sup>st</sup>(3)-2<sup>nd</sup>(4)-3<sup>rd</sup> month (3)
- **Penile length** increased from < 2 cm to a median of 3.8 cm
- During therapy, **all infants initiated catch-up growth**
- **Median LH** from undetectable reached **high normal 4.45 IU/L** and **FSH supranormal levels 83 IU/L**
- **Inhibin b** and **AMH** from subnormal, reached **high normal levels: 365 pg/ml** and **1071 pmol/L**
- **Testosterone** increased from undetectable to a **median of 3.3 ng/ml**
- **After a follow-up of 1-10 yrs testes** have slightly regressed to 0.5 -1.5 ml but **are still in scrotal position**
- In 2 case **1 testicle regressed to low inguinal position within 1yr - successfully operated**
- **None presented any adverse events or reactions**
- **Ultrasound** examination of the testes at the end of therapy **was normal**

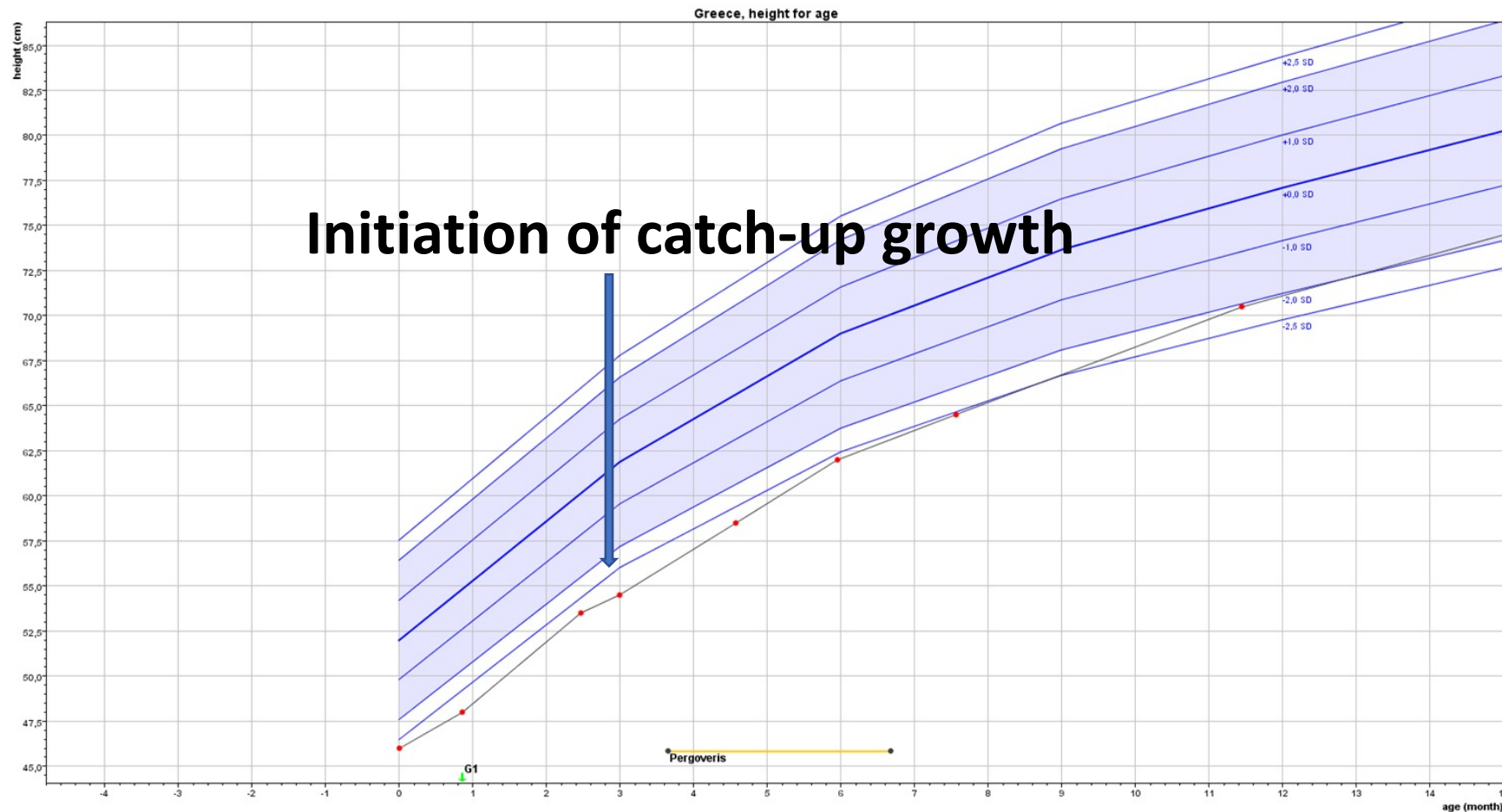
## Conclusions (1)

**Treatment for 3 months with daily s.c. injections  
of the commercially available preparation of LH 75 / FSH 150 IU**

- **mimics neonatal male mini puberty repairing micropenis and cryptorchidism**
- **induces normal/high activation of Leydig and Sertoli cells respectively**
- **may be as well as beneficial to the brain as to the testes**
- **seems to stimulate initiation of catch-up growth**

## Conclusions (2)

➤ seems to stimulate initiation of catch-up growth



## Conclusions (3)

- **This treatment is a non-invasive strategy that mimics physiology**
- **Costs much less than two surgical operations (~6000€/patient)**
- **Not being able to measure the cost of an unsuccessful surgery or future infertility**
- **Even if it proves partially unsuccessful in some cases, the work of the surgeon will be much easier, and the potential for future fertility preserved**

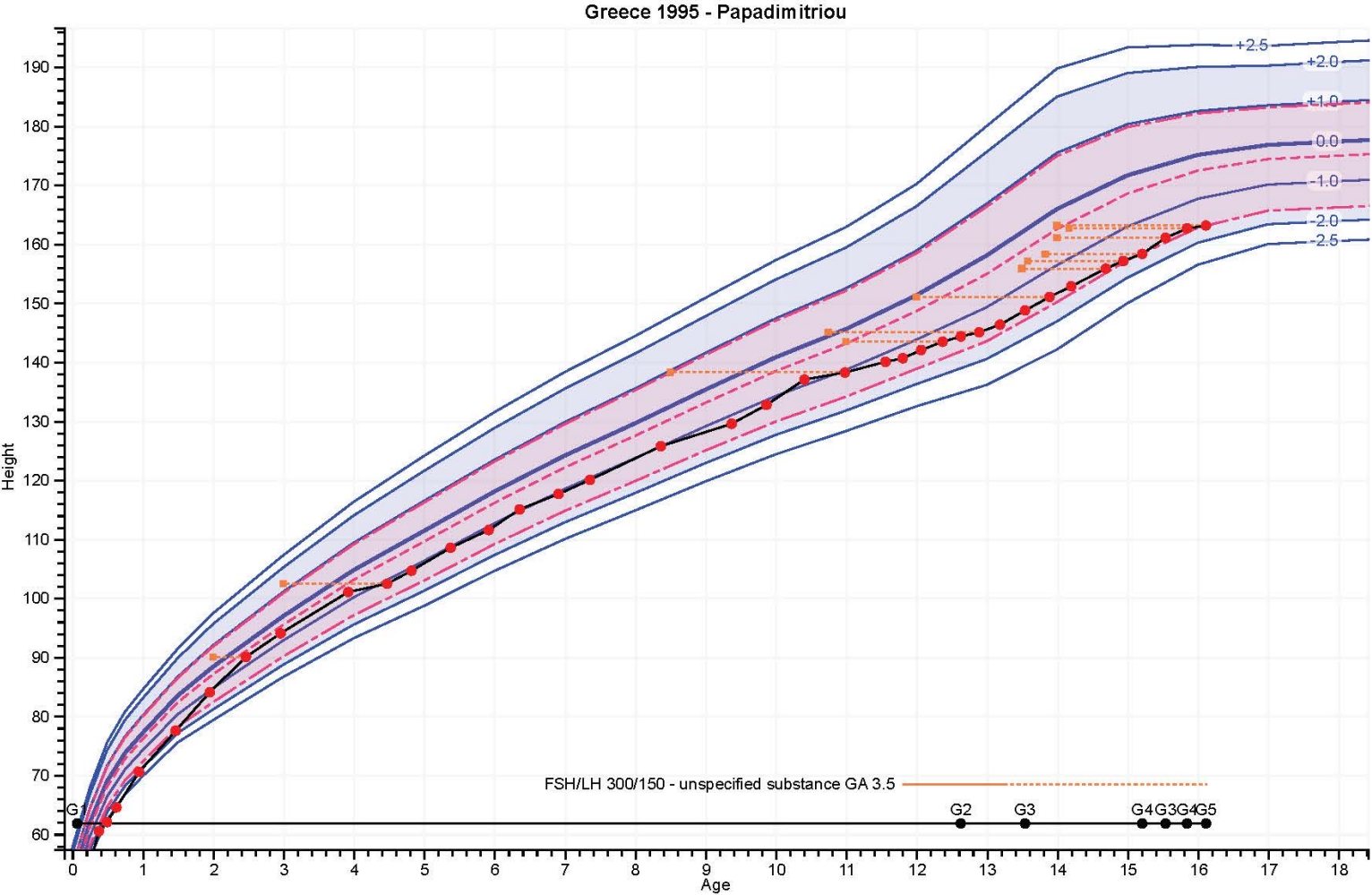


## Future implications

- Further studies are needed to optimize this strategy (maybe a 1:1 or 2:1 preparation should be tested)
- Can be tried in idiopathic or even secondary bilateral cryptorchidism (i.e. Prader-Willi syndrome)
- The importance and the benefits of the postnatal physiological gonadotropin surge - given that that the 1<sup>st</sup> in the fetal life (8-24 wks) was missed - **in the male gender development as well in normal growth** should be further investigated and seriously considered
- Puberty induction protocols with the combination of LH/FSH in gradually increasing doses may be developed



# Induction of puberty with daily rLH/FSH (Pergoveris pen)



G5P5A3  
 PL = 9 cm  
 Age 16 yrs  
 Bone Age 14 yrs

|         |                                                                              |                        |  |  |            |
|---------|------------------------------------------------------------------------------|------------------------|--|--|------------|
| Active  | FSH/LH 300/150 - unspecified substance GA 3.5 (unspecified substance GA 3.5) | 1 time per day 300 iU  |  |  | 03/11/2022 |
| Stopped | FSH/LH 300/150 - unspecified substance GA 3.5 (unspecified substance GA 3.5) | 1 time per day 150 iU  |  |  | 20/04/2022 |
| Stopped | FSH/LH 300/150 - unspecified substance GA 3.5 (unspecified substance GA 3.5) | 1 time per day 100 iU  |  |  | 24/03/2022 |
| Stopped | FSH/LH 300/150 - unspecified substance GA 3.5 (unspecified substance GA 3.5) | 1 time per day 75 iU   |  |  | 30/08/2021 |
| Stopped | FSH/LH 300/150 - unspecified substance GA 3.5 (unspecified substance GA 3.5) | 1 time per day 50 iU   |  |  | 29/07/2021 |
| Stopped | FSH/LH 300/150 - unspecified substance GA 3.5 (unspecified substance GA 3.5) | 1 time per day 12.5 iU |  |  | 27/05/2021 |
| Stopped | FSH/LH 300/150 - unspecified substance GA 3.5 (unspecified substance GA 3.5) | 1 time per day 25 iU   |  |  | 27/05/2021 |

**This strategy mimics physiology  
corrects genital hypotrophy,  
restores testicular endocrine function,  
and may improve the response to future  
treatments intended to induce fertility**



# REPLACEMENT OF MALE MINI-PUBERTY

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