hpf diferentiata pana in sapt 11 VIU

pana atunci, au migrat neuronii GnRH din placardele olfactive in nucleii paraventriculari, arcuat

in sapt 20, 24 valori de FSH, LH similare cu adultul, in ovulatie, apoi incep sa scada dat hh placentari

Daca nu functioneaza hpf, ovarul nu se dezvolta corect

Celulele granuloase sunt similare cel sertuli, -> sursa de estrogeni din androgenii techali.

cel tecale, hilare si intrestitiale sunt similare cu cel Leydig -> sursa de androgeni

dupa luteinizare – ambele produc si progesteron

Ovarele se formeaza in creasta urogenitala si sunt colonizate de cel germinale din sacul vitelin in prima luna de viu/ cel geminale se inconjoara de cel granuloase -> foliculi primordiali; cele care nu gasesc cel granuloase - apoptoza

Gene: WT-1, LIM-1, SF-1, and possibly DAX-1 gene. Pentru a se dezvolta in ovar si nu in testicol e necesara

SRY. Altfel, Wnt-4 induce dezv de ovogonii si cel granuloase

Oogonia then undergo oogenesis, entering the prophase of meiosis to become primary oocytes during the fi nal 5 to 6 months of gestation.When oocytes enter the diplotene stage of meiotic prophase they must be furnished with granulosa cells to form a primordial follicle. Otherwise, they undergo atresia.

Primordial follicles appear in the fourth month, when the epithelium of the secondary sex cords provides granulosa ccells to the oocytes—and they peak in number between the fifth and ninth months. They become primary follicles

when the encircling granulosa cells become cuboidal. Primordial and small primary follicles are resting follicles that are the major repository of germ cells.

Preantral follicles contain as many as 300 granulosa cells, and their diameter ranges from 50 to 200 m. The oocyte diameter increases from 25 or less to 80 m. Antral (graafi an, tertiary, or vesicular) follicles have a fl uid-fi lled antrum and a full-grown oocyte, are lined with more than 300 granulosa cells, and have a well-developed theca. They are greater than 200 m in diameter. The dimensions of the mature ovary are approximately 1.25 x 2.75 4 cm.

Ovocitele necesita ambii crz X activi pt a supravietui.

Dupa nastere, ca raspuns la scaderea estradiolului, FSH si LH cresc la valori pubertare, cu raspuns la diphereline

Pubertar – mica pubertate. La copii agonadici valorile ajung in domeniul menopauzei.

La prematuri cresterile sunt mai mari si se normalizeaza prin sapt 40 (echivalent de VIU).

Dupa 4 luni, valorile incep sa scada, cu un minim la 6 ani, chiar si la copii agonadici. Creste nr de receptori pt e2 si

dihidroTST la nivel hpt/hpf.

Dupa 7 ani incepe sa se modifice patternul secretor, cu o crestere de secretie

Ovarul - 5 foliculi antrali de 5-6 mm in copilarie. Sufera atrezie ce determina cresterea stromei ovariene vol ovarian 4 cc la 7 ani si 5,5 la 9 ani

Estradiolul este crescut la valori de pubertate precoce in primele luni de viata, apoi scade. FSH, LHsunt si ei mai crescuti apoi scad. Prepubertar avem cresteri de pana la pentru e2 de 6-12 pg/ml, pe testele ultrasensibile

In PUBERTATE,

Initial in preadolescenta apar cresteri (initial nocturne ) de pulsuri de GnRH. apoi incep sa creasca gonadotropii si se declanseaza act ovariana, initial anovulatorie. Pulsurile GnRH la f. 2000 pg/ml, la b. 200 pg/ml.

Initial creste preponderent FSH ( mai putin dep de GnRH, timp de injumatatire mai lung). induce formare foliculara si secretie de e2, cu menstre anovulatorii. estradiolul determina crestere somatica.

Apoi incep si pulsurile de LH. In plus creste si bioactivitatea LH, mai mult decat cantitatea de LH.

Estradiol output increases rapidly in the year approaching menarche

The CNS is stimulated by preovulatory levels of estradiol to increase GnRH pulse size. At the pituitary level, there is the self-priming effect of GnRH whereby a pulse of GnRH sensitizes the pituitary to have a greater LH response to a subsequent identical GnRH pulse.Critical patterns of estradiol and progesterone secretion enhance the pituitary LH and FSH responsiveness to GnRH. At the gonadal level, the cascade of events is augmented by the FSH induction of aromatase activity and progestin production in granulosa cells—phenomena in which androgens play a synergistic role. Furthermore, FSH stimulates granulosa cell mitosis and induces LH receptors—phenomena in which estradiol may play a synergistic role. Subsequently, LH is able to further enhance the aromatase and progesterone effects. Progesterone itself plays a synergistic role in stimulating granulosa cell progesterone and prostaglandin synthesis in concert with FSH and LH.

Ecografic 25% din adolescente au 4-10 foliculi de pana in 10 mm diam, doar 10% din cele cu menstre ritmice au peste 10 foliculi.

Adult

Gonadotropin and sex hormone levels are low during the premenstrual phase of the mature cycle (Figure 14-14A). Gonadotropin concentrations then increase at the time of menstruation, FSH predominating in the early follicular phase while nocturnal LH pulsation is slow120 (Figure 14-14B). Luteinizing hormone pulsation increases to a circhoral pattern around a stable baseline, and estradiol production slowly begins (Figure 14-14C). Estradiol levels gradually increase, and serum FSH levels fall reciprocally (Figure 14-14D). The subsequent geometric increase in plasma estradiolconcentrations then selectively amplifi es the pituitary’s LH response to GnRH as estradiol reaches about 90 pg/mL for longer than 3 days103-105 (Figure 14-14E). When the plasma estradiol rises to greater than 200 to 300 pg/mL for 36 hr, the positive feedback mechanism is activated and the midcycle gonadotropin surge commences (Figure 14-14F). Estradiol then induces progesterone receptor (PR) expression in the hypothalamus and pituitary.100 Progesterone increasing to 100 ng/dL facilitates the LH surge, shortens the duration of time over which estradiol is required for the surge to 24 hours, and brings about an FSH surge. The mechanism of progesterone action involves inhibition of GnRH cleavage.106 Androgens may also play a role in facilitating FSH and GnRH release.121,122 The LH surge is then primarily responsible for luteinizing the preovulatory ovarian follicle (Figure 14-14F). At this time, LH pulses become larger in amplitude but slower in frequency and their apparent bioactivity increases. Ovulation then results. Estrogen levels fall when the follicle is disrupted (Figure 14-14G). As the corpus luteum begins to form, progesterone increases steadily to be sustained at very high levels for several days—along with lesser but substantial increases in estradiol and 17-hydroxyprogesterone levels (Figure 14-14H). In response to the high progesterone level, gonadotropin pulsation slows.120 In the absence of increasing human chorionic gonadotropin (hCG) from a conceptus, the corpus luteus dies. Menses follow.

TIMING PUBERTATE NORMALA LA FETE

1. Accelerare viteza de crestere

2. Telarha, peri 10 ani. Depinde de etnicitate, uneori intai e adrenarha. Si poate debuta mai devreme la afro-americani

3. Adrenarha

4. Viteza max de crestere 9cm/an. Apoi apare decelerarea vitezei prin inchiderea cartilajelor. In aceasta faza:

5. Menarha - in jur de 12 ani. Dupa 5 ani, devin toate ovulatorii.

Talia influentata genetic (ex SHOX din regiunile autozomale ale crz sexuali), hormonal (estrogeni, hh ty, GH).

PUBERTATE PRECOCE

inainte de 8 ani

Posibile complicatii - neo san, neo endometru, obezitate, boli CV, comportament sexual precoce

Cauze:

|  |  |
| --- | --- |
| Pubertate precoce centrala completa | Idiopatice  Leziuni CNS - hamartoame, glioame/astrocitoame de nn optic, craniofaringioame, hidrocefalie, postiradiere SNC, neurofibromatoza,  genetic - KISS 1, MKRN3  Hipoty  Dupa trt pt CAH |
| Pubertate precoce periferica izosexuala la fete | Telarha prematura  Menarha prematura  McCune Albright  Iatrogen  Chiste ovariene functionale  Tumori ovariene functionale. Tumori SR secr de E2  Peutz-Jagers |
| Pubertate precoce perferica heterosexuala la fete | Adrenarha prematura  CAH  tumori SR/ ovariene secretante de androgeni  Iatrogenic |

PUBERTATE PRECOCE CENTRALA

Hamartoame = malf congenitale hipoytalamus care contin neuroni secretori. Actioneaza ca un hipotalamus miniatural.

Mutatii activatoare pe KISS1 sau KISS1receptor.

Diagnostic

- clinic - semne de pubertate, viteza de crestere

- varsta osoasa

- eco pelvin/ testicular

- test la agonist de GnRH. diphereline 100mcg/m2 sc, max 100 mcg. Recoltare de LH (+FSH) la 40 minute. (+E2/TST la 24 ore). Test + valoare LH>4 mUI. Dar dc bazal > 1,1 (0,3 pe testele noi) dc pozitiv si nu e nevoie de test. Dc E2 e ff mare - frecvent tumori ovariene, SR.

Tratament - analog de GnRH. NU obligatoriu la orice copil. Pana la 11ani ( protocol rom 9 ani)

Telarha prematura (izolate)

- debut de obicei inainte de 4 ani, cel mai frecvent inainte de2 ani, 50% cazuri regreseaza.

- examen clinic: talie, greutate, nevi, pete caffe au lait, neurofibroame, mase abdominale

- anamneza - posibilitatea de ingestie de hh f./m.

- varsta osoasa - dc e normala, e ok

- eventual dozare de E2/TST.

- reevaluare peste 6 luni, incl rgf.

dc are VO>2 DS sau crestere de VO, talie inalta,>1 semne de pubertate, trebuie evaluate pt pubertate precoce

!!!! menstra izolata --> tumori, corp strain, abuz sexual

! deficitul de GH mascheaza cresterea in inaltime si dezvoltarea mamara, persista VO >>. Atentie la fetele care au avut iradiere cerebrala pt diferite cauze

Analize: FSH, LH, TST/E2 la laboratoare specializate cu limita de detectie de 0,2 U/l pt FSH,LH. valori foarte mari de E2 sau TST trebuie sa caut ovarele sau suprarenala de tumori.

Eventual dozare de E2 saptamanal pt a obtine valorile reale, eventual evaluarea mucoasei vaginale si a dimensiunilor uterului.(latime >1,5 cm).

LH >=0,6 U/L bazal si >= 6 dupa stimulare --> pubertate.

In pseudopubertate precoce(PPP)=periferica, raspuns absent la test, in telarha/pubarha precoce raspuns diminuat.

In pubertate precoce centrala (CPP) raspuns pubertar cu crestere de LH, E2/TST.

Laboratory Criteria for Rapidly Progressive Complete Precocious Puberty

1. Sex hormone level pubertal (diurnal early)

1.1 Estrogen (girls, cyclical): E29 pg/mL, vaginal cornifi cation

1.2 Testosterone (boys): 20–1200 ng/dL

1.3 DHEAS normal for age height age

2. Sex hormone excess is sustained: • Bone age >height age > chronological age

3. LH and FSH pubertal

3.1 Sleep-associated LH rise initiates puberty •

3.2 Basal: LH.0.6 and FSH.2.0 IU/L or more (monoclonal RIA) •

3.3 Post-GnRH LH4.2 IU/L

4 Exclude: tumor, hypothyroidism, gonadotropin-independent precocity

PUBERTATE PRECOCE PERIFERICA

- chiste ovariene functionale - de obicei peste 8 mm. Uneori mutatii locale activatoare de GsAlpha

- tumori granuloase juvenile, tumori thecale - pot folosi drept markeri AMH, inhibina.

- sindr McCune Albright - osteodisplazie fibrochistica, pubertate prec centrala, pete cafe au lait - mutatie activatoare postzigotica Gs alpha

Tratament

- inhibitori aromatizare - testolactona

- SERM - tamoxifen

Pubarha /adrenarha prematura.

Cel mai frecvent cah nonclasic, dar poate fi si izolata.

PUBERTATE INTARZIATA

Fara telarha pana la13 ani, fara MN pana la 15/16 ani