
بسم الله النور

Clinical Insights into Precocious and Normal Puberty: From Experience to Learning

سناریوها

خانمی نگران مراجعه می کند و فرزندش را پشت در نگه می دارد و سعی می کند دور از چشم فرزندش مسائلی را با شما در میان بگذارد.

ببخشید خانم دکتر: من نگران بلوغ زودرس برای دخترم هستم. آمده ام تا جلوی بلوغش را بگیرم.

- ببخشید خانم دکتر: **من دوست ندارم** کودکم زود بلوغ بشود میخواهم جلوی بلوغش را بگیرید تا قدش بلند شود

- همکلاسی دخترم برای افزایش قد دخترش بلوغ را متوقف کرده است من هم آمده ام تا این مطلب را با شما در میان بگذارم

- ببخشید دکتر: من متوجه شدم که موهای زیر بغل و ناحیه زهار کودکم ظاهر شده است. من خیلی نگرانم و می خواهم بلوغ به تعویق بیفتد

مشکلات مادران:

من دوست ندارم

من میترسم

دوست دارم قد بلند بشه

دوستم گفته

و.....

- چه کاری باید کرد؟
- چه کاری نباید کرد؟

بعنوان والدین و کسانی که مسئول سلامت روح و جسم کودکان هستیم چکار کنیم؟

- کودکی را به کودکان برگردانیم
سالم زندگی کنیم
ویژگی هر دوره از زندگی را بپذیریم


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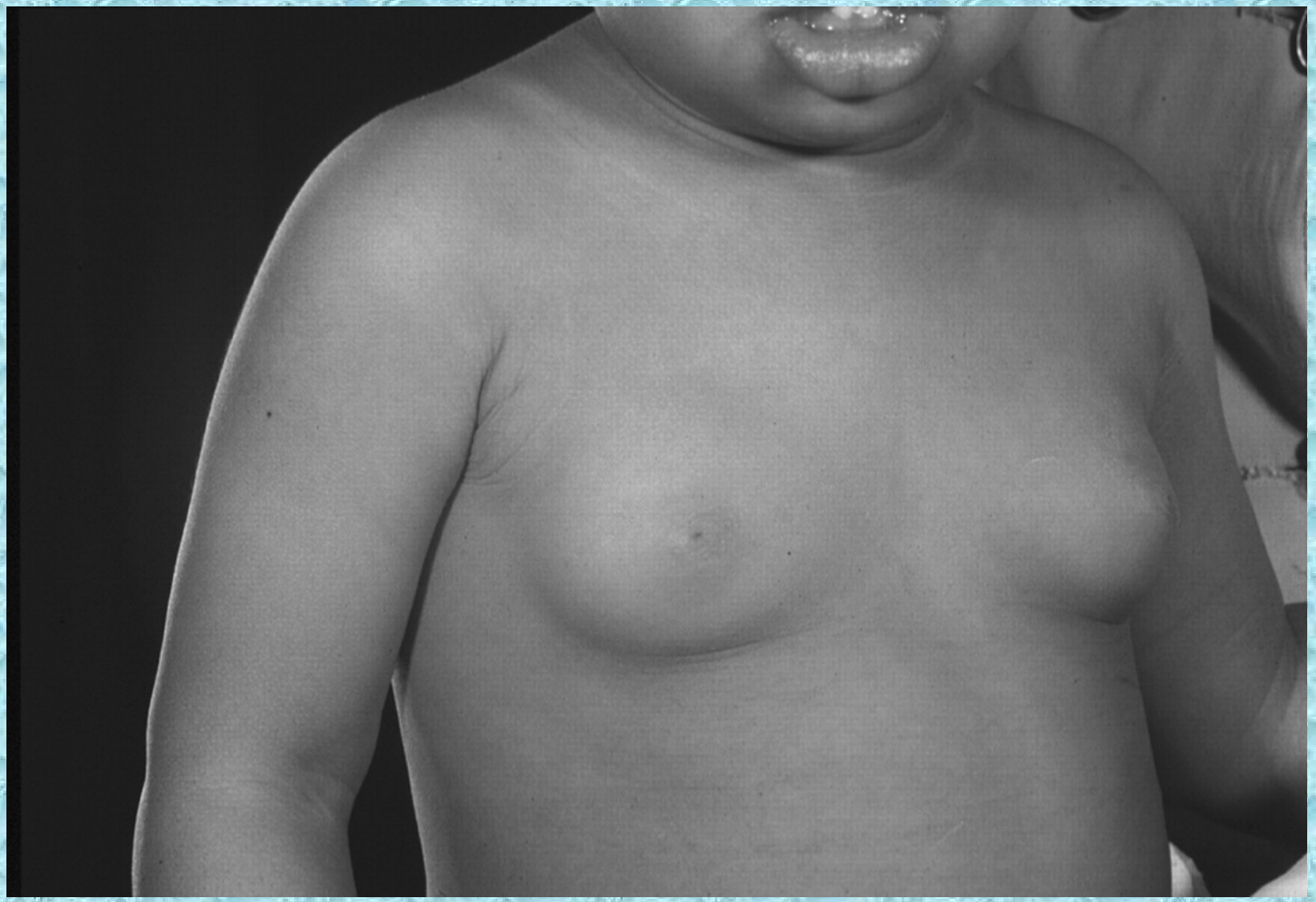
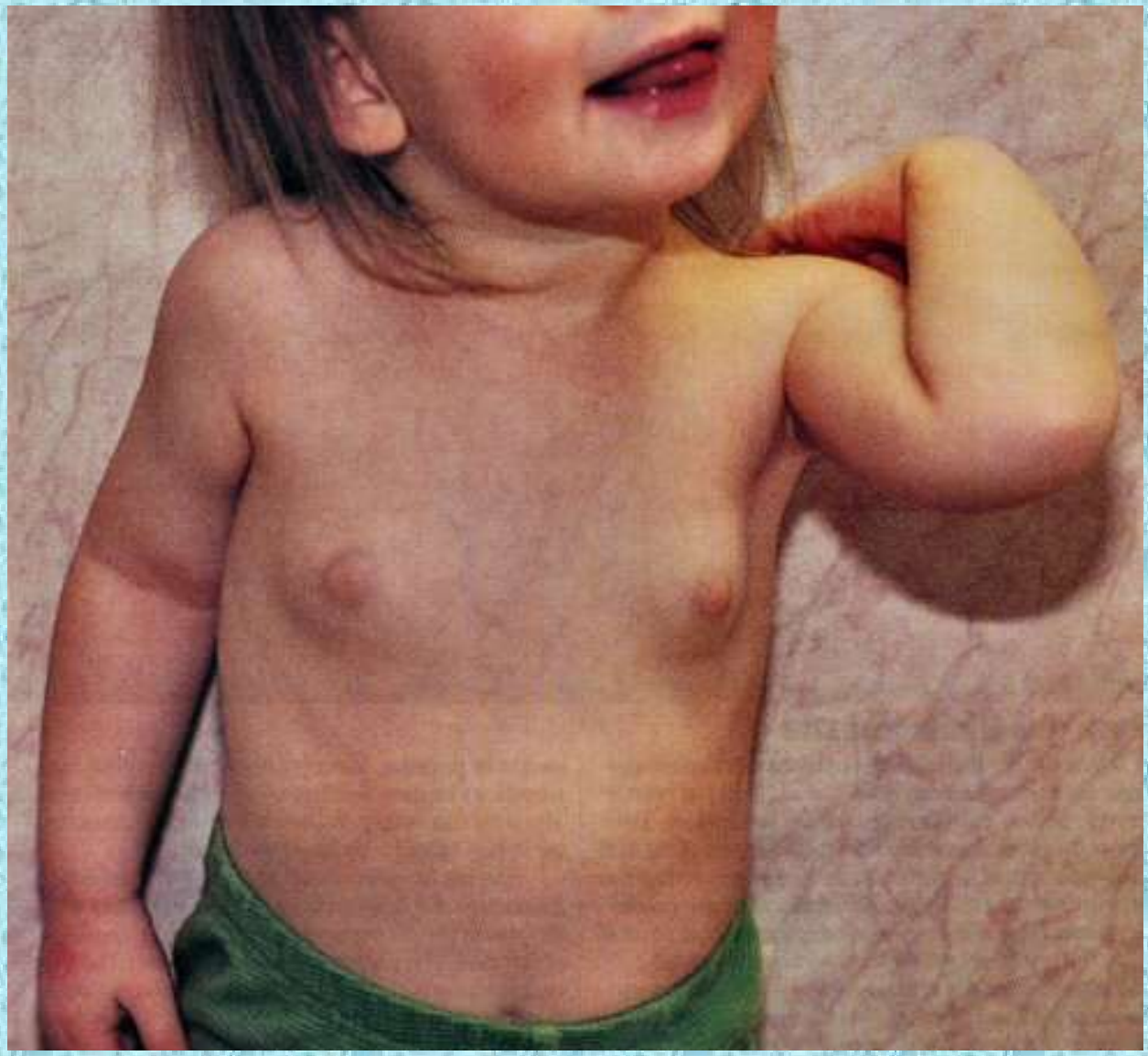
وحالا بلوغ ایجاد شده است:
چه کاری به صلاح است؟

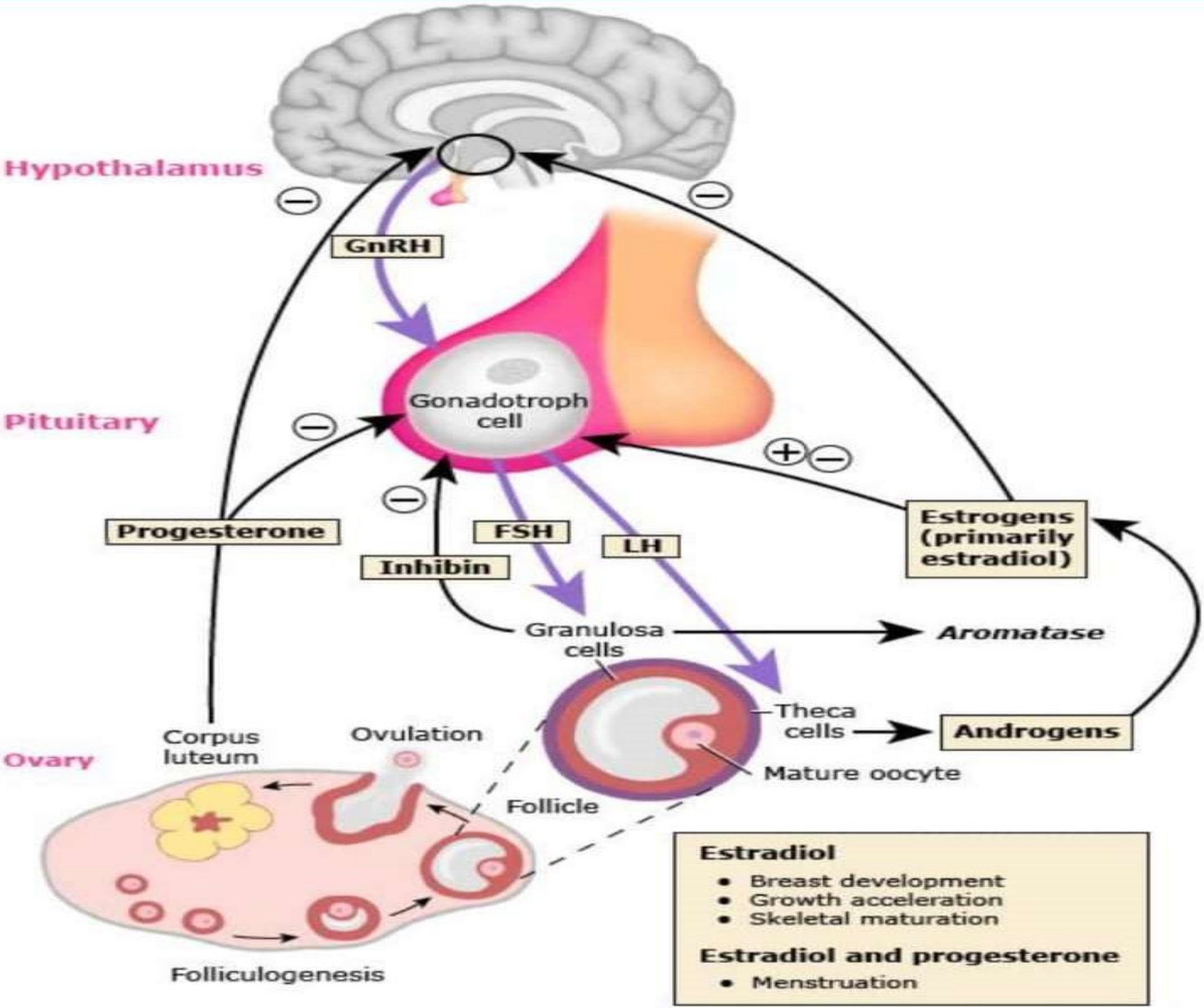




- بهترین مسیر، مسیر فیزیولوژیک است دخالتهای غلط را حذف کنیم.
- تغذیه خوب، تفریح سالم، روش و زندگی طبیعی

- چه کاری باید کرد؟
- چه کاری نباید کرد؟

Hypothalamic-pituitary-ovarian axis and puberty

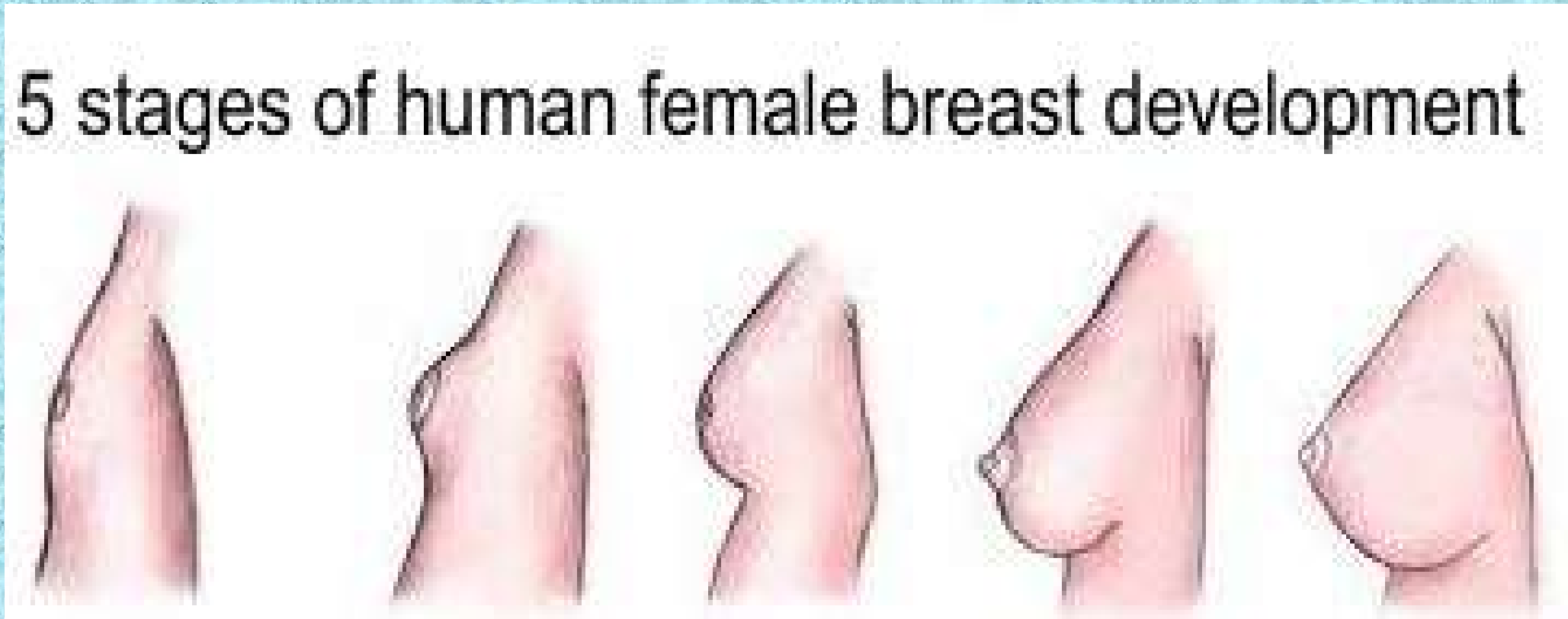


Normal developmental sequence

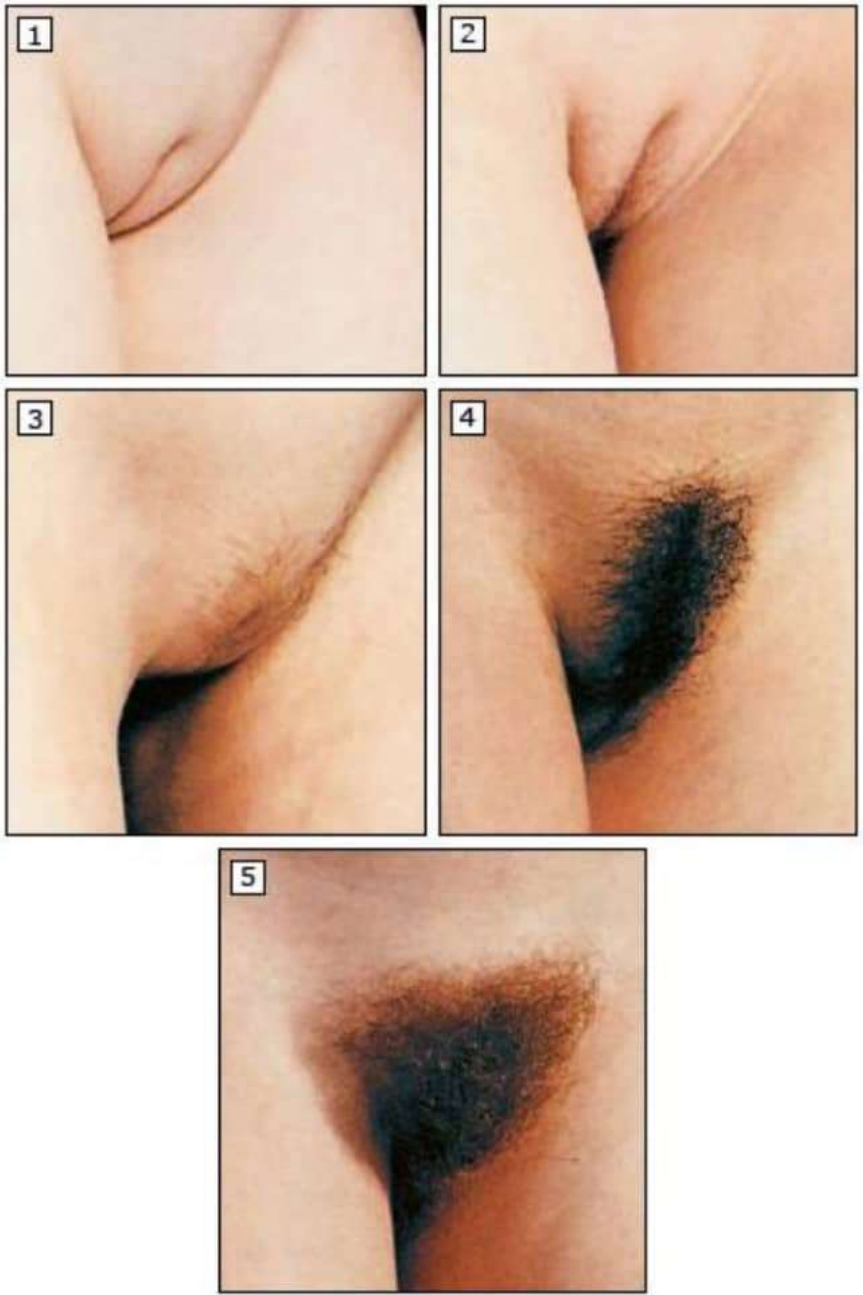
Tanner Staging of Breast Development

- **Stage I:** Preadolescent; elevation of papilla only
- **Stage II:** Breast bud; enlargement of areola (10-12.5yo)
- **Stage III:** Further enlargement and elevation of breast & areola no separation of contour (11-13.5yo)
- **Stage IV:** Projection of areola and papilla to form second mound (12-14yo)
- **Stage V:** Mature stage; projection of papilla due to recession of areola to general contour (13.5-17yo)

Pubertal stages in girls

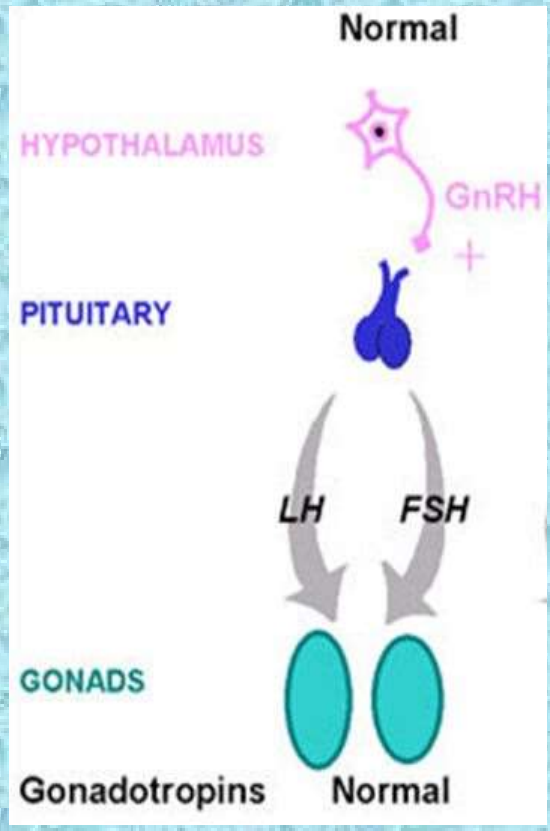


Sexual maturity rating (Tanner staging) of pubic hair development in girls



NORMAL PUBERTY

- **Gonadarche** is the activation of the gonads by the pituitary hormones FSH and luteinizing hormone LH.



Average age of onset:

١٠/٥ years in girls

١١/٥ years in boys

The study of pubertal stage and age of menarche in girls in Isfahan province, Iran

- **A total of ۱۳’۸۸۶ healthy girls were studied**.
- The median age for onset of
- Breast development ۹/۸۹ years
- **۹۵% CI: ۹/۷۷ - ۱۰/۰۲**
- For Menstruation ۱۲/۰۵ years
- **۹۵% CI: ۱۱/۸۸-۱۲/۲۱**
- ۳rd percentile for breast stage ۲ ۶/۸۵ years
- ۹۷th percentile for B۲ ۱۲/۹۴ years

- **BMC Pediatr ۲۰۲۵ Jan**

Adrenarche

- is the increase in production of androgens by the adrenal cortex. ٦-٨

Pubarche

- Pubic and axillary hair
- Apocrine sweat glands
- Acne

Precocious puberty

- Onset of secondary sexual characteristics before the age of ٨yr in girls and ٩yr in boys.

precocious puberty

- Girls **> boys ٥-١٠–fold**
- sporadic

Consequences of Untreated Precocious Puberty on Adult Height

- The increased rate of bone maturation results in early closure of the epiphyses→**stature is less than** it would have been otherwise.
- **Without treatment**, approximately ٣٠% of girls and an even larger percentage of boys achieve a **height less than the ٥th percentile as adults**

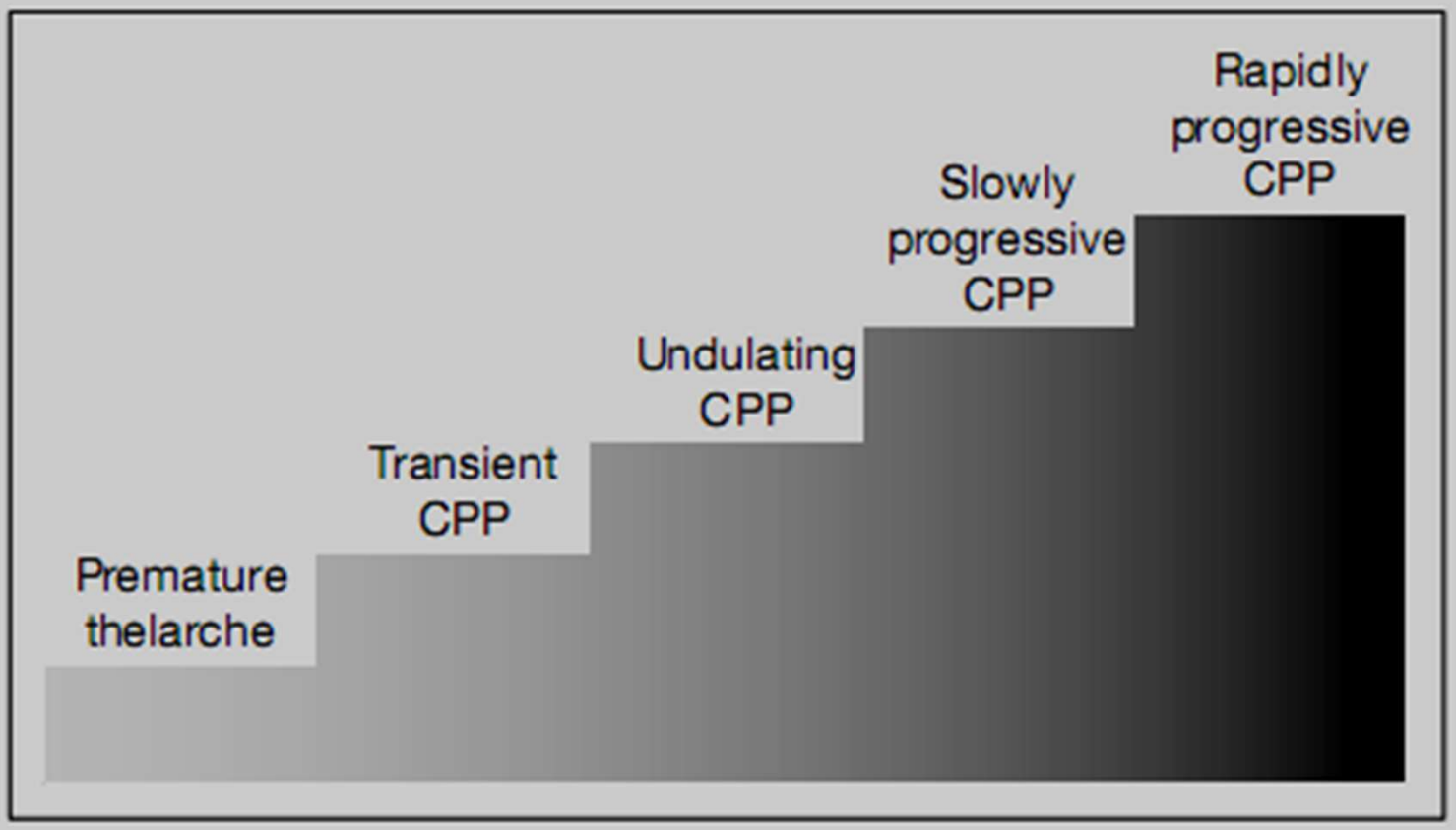


Fig. 2. Spectrum of precocious pubertal development.

slow pubertal progression

- ***Pubertal progression would be considered slow if there is no change in** stage of puberty during six or more months **.***

Who should be evaluated?

- Signs of secondary sexual development younger than the age **of eight (girls) or nine (boys) years**
- A rapid rate of linear growth and skeletal maturation
- Rapid Pubertal progression during **less than six months** of observation.

Table 5. Variability in Bone Age

Age in Months	Boys SD	Girls SD
12	2.1	2.7
18	2.7	3.4
24	4	4
30	5.4	4.8
36	6	5.6
42	6.6	5.5
48	7	7.2
54	7.8	8
60	8.4	8.6
66	9.1	8.9
72	9.3	9
84	10.1	8.3
96	10.8	8.8
108	11	9.3
120	11.4	10.8
132	10.5	12.3
144	10.4	14
156	11.1	14.6
168	12	12.6
180	14	11.2
192	15	15
204	15.4	15.4

The standard deviation calculation for each age category in the digital bone age atlas was based on the equation for the linear regression that best fit the variability of multiple samples at different ages.

Initial evaluation

- History
- Physical examination
- Bone age

History

- Timing of **pubertal onset** in patient
- Timing of pubertal onset in **his or her family**
- Linear growth acceleration
- Headaches, seizures
- Abdominal pain
- Previous history of CNS disease or trauma
- Exposure to exogenous sex steroids

Physical examination

- Height, weight , **height velocity**
- Funduscopic examination
- Dermatological exam
- Pubertal staging

Use of bone age in the assessment of children's pubery

- Differential diagnosis
- whether there may be an impact on final height

laboratory findings

- ***Increase Sex hormone concentrations.***

- Estradiol level exceeding **١٠- ٢٠ pg/ml** usually indicate puberty

laboratory findings

-
- **Blood sample should be take early morning**
- LH > ٠٫٢ to ٠٫٣ mIU/mL **means CPP**.

Confirmation of diagnosis

- **Basal serum FSH Have limited** diagnostic utility

Imaging

- ***Pelvic ultrasonography***

Pelvic USG findings supporting CPP in girls

- Uterus long diameter ٣٧-٤٠ mm
- Pear shaped uterus (F/C>٢:١)
- Ovarian volume >٢.٥ ml
- follicul number >٨, size > ٨mm

Normal puberty

Ovarian volume in ml	
Age	Volume (sd)
0 – 1 month	0.5 (0.4)
3 months	0.4 (0.1)
1	0.5 (0.2)
3	0.7 (0.4)
5	0.7 (0.5)
7	0.8 (0.6)
9	0.6 (0.4)
11	1.3 (1.0)
13	3.7 (2.1)
15	6.7 (4.8)

Indications for MRI

- ***Rapid breast development.***
- ***Estradiol >٣٠ pglmL.***
- ***Girls <٦ yr of age.***
- ***All boys***

Decision-Making Before Initiating Therapy in Precocious Puberty

- ***Need for longitudinal observation at the onset of sexual development, before treatment is considered***

  ٣- to ٦-month period

- It is often **difficult to decide** whether to treat or not to treat a child with sexual precocity

Height Prediction and Decision for Therapy

- ***If height prediction is above ۱۵۰ cm in girls and above ۱۶۰ cm in boys,***
- ***Therapy is probably not needed***

Decision to treat CPP

- Rapidly progressive precocious puberty
- very young girls at risk of early menarche**<٩years**
- ***Girls Breast development before ٨ years***
- ***Boys Testicular enlagement <٩years***
- ***Height velocity is considered accelerated if it is more than ٦ cm per year***

Decision to treat CPP

Psychosocial reasons with

- Behavioral disturbances
- Emotional immaturity
- Mental retardation
- specific personality patterns
- Menstrual hygiene in handicapped girls
- Social reasons

The effect of GnRHa on final height

- **GnRHa treatment can preserve growth potential by slowing bone age progression, resulting in short adult height,**
- **it cannot alter the genetic growth potential**

The effect of GnRHa on final height

- **GnRH agonists do not improve mean final height in girls over ٨ year's of age at start of treatment**
- final adult height may not improve in children aged >٩ years at initiation of therapy, possibly because of
- significant advancement of bone age at presentation

Ovarian Function After Therapy

- Ovarian function was not impaired

Case

- **٥-year-old girl** was brought by her mother with a **٦-month history of progressive breast development**.
  There was **no vaginal bleeding, no pubic or axillary hair**, and **no neurological symptoms**.
  There was **no history of drug intake** or **hypothyroidi**

Physical Examination

- **Weight:** ٢١ kg (٧٥th percentile)
- **Tanner staging:** P١, B٣
- **Skin:** No café-au-lait macules
- **Musculoskeletal:** No bony deformities
- **Neck:** No goiter
- **Neurological:** Deep tendon reflexes normal
- **Visual field and acuity:** Normal
- **Abdomen:** No palpable mass
- **Systemic examination:** Unremarkable

Hormonal profile

Test	Result	Normal Range	Interpretation
LH	۲٫۳ mIU/ml	< ۰٫۳	↑ Elevated
FSH	۳٫۹ mIU/ml	—	Mildly elevated
Estradiol	۷۸٫۴ pg/ml	< ۱۰-۲۰	↑ High
Prolactin	۲۱٫۲ ng/ml	۴٫۷–۲۳٫۳	Normal
Thyroid function test	Normal	—	Euthyroi

Pelvic Ultrasonography

- **Uterine length:** ۴٫۱ cm
- **Right ovarian volume:** ۳٫۰ ml
- **Left ovarian volume:** ۲٫۵ ml
- **Multiple follicles** seen bilaterally
- **Interpretation:** Findings consistent with **pubertal uterine and ovarian developmen**

MRI

- MRI was normal

What's your diagnosis

What is diagnosis ?

- idiopathic gonadotropin-dependent precocious puberty

Differential diagnosis

- **The premature breast development**
- puberty
- premature thelarche
- Drug intake
- **Air pollution**
- **Ovarian cysts**
- **Ovarian tumor**

premature thelarche

- premature thelarche during the first two years of life
- Nonprogressive and regresses spontaneously within ٦ **months to** ٦ **years** after the diagnosis.
- pubarche, menarche, and enlargement of uterus are absent
- Normal growth velocity
- No advancement **in bone age**

Discussion

- According to clinical and laboratory findings premature thelarche was excluded

Management Plan

Which of the following?

- **Observation Phase**
- Confirmed diagnosis of **Central Precocious Puberty**
- Short **٣–٦ month observation period** may be considered initially
  → to assess **rate of progression** of pubertal signs and **growth velocity**
- To treat

Why did we decided to treatment?

Indication of treatment in the index child was Based on

- **uterine size**
- **Hormone levels**
- **Advanced bone age**
- **Breast size**
- **Psychosocial distress** due to early puberty

.

Therapeutic Goals

- **Arrest further pubertal progression**
- **Delay epiphyseal closure** → preserve adult height potential
- **Reduce psychological stress** associated with early pubert

Specific Treatment

- GnRH Analog Therapy **(Depot preparation)**
- Continuous administration causes **downregulation of pituitary GnRH receptors**, suppressing LH & FSH secretion

Monitoring During Therapy

- **Clinical:** Tanner staging, height velocity every ٣–٦ months
- **Biochemical:** LH, FSH, Estradiol suppression
- **Radiologic:** Bone age annually
- **Psychological:** Assess emotional well-being

Duration & Follow-Up

- Continue until **appropriate pubertal age** (~١١ years in girls)
- After discontinuation, **normal puberty resumes**
- **Ovarian function is not impaired**

Prognosis

- **final adult height improves** if treated early
- **Favorable psychosocial outcome**
- No long-term adverse effects on **fertility or gonadal functio**

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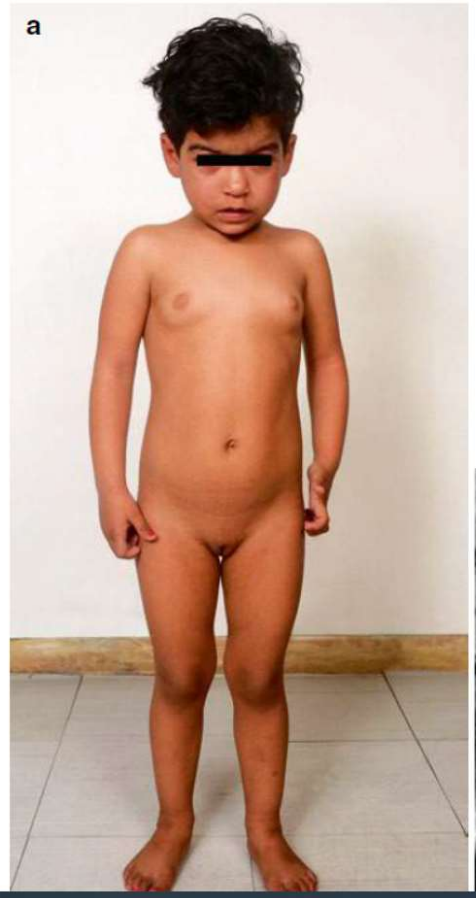

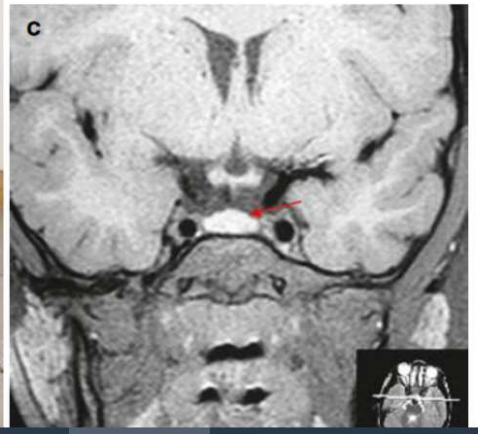

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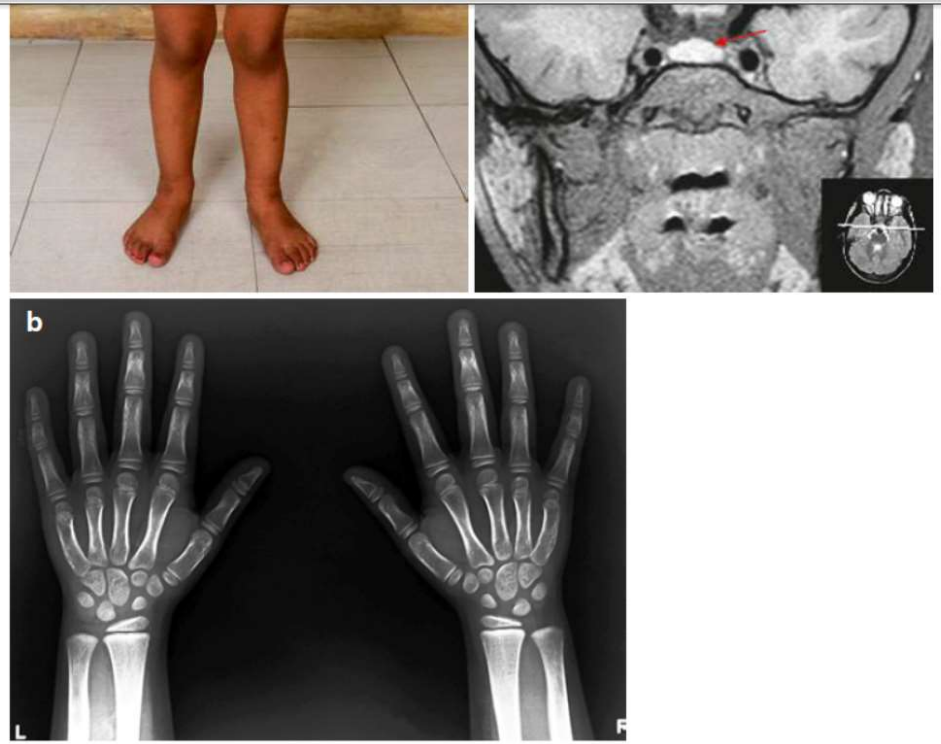
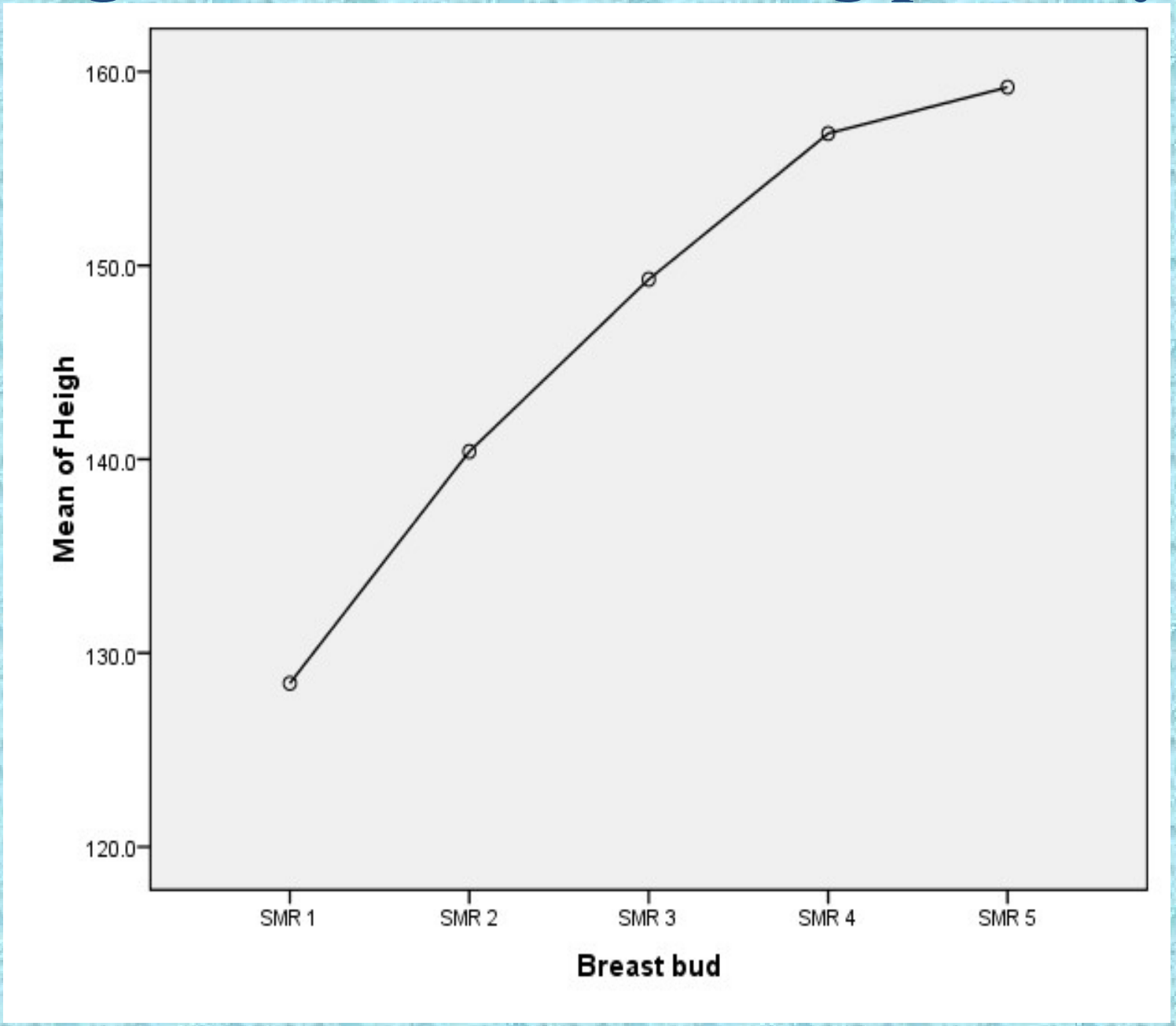


Fig. 6.1 (a) A 3-year-old child presented with thelarche (B_3), (b) X-ray of wrist showing bone age of 7 years, (c) CEMRI sella showing convex upper border of the pituitary (*red arrow*) suggestive of GDPP

Case

- .دختری ۸ سال و ۵ ماهه به‌دلیل بروز علائم بلوغ زودرس توسط والدین مراجعه کرده است.
- در معاینه بالینی، **پستان‌ها در مرحله IIتانر** (Tanner stage II breast development)و **موهای پوبیک نیز در مرحله IIتانر** مشاهده می‌شود.
- **قد و وزن بیمار در صدک پنجاهم منحنی رشد** قرار دارد.
مادر از شروع زودرس علائم بلوغ و احتمال **بلوغ زودرس مرکزی** نگران است
- **در معاینه فیزیکی نکته مثبت دیگری ندارد ر بررسی‌های انجام شده هم مشکلی نبوده است**
- **تصمیم ؟**

Height attainment during puberty



Do not do anything

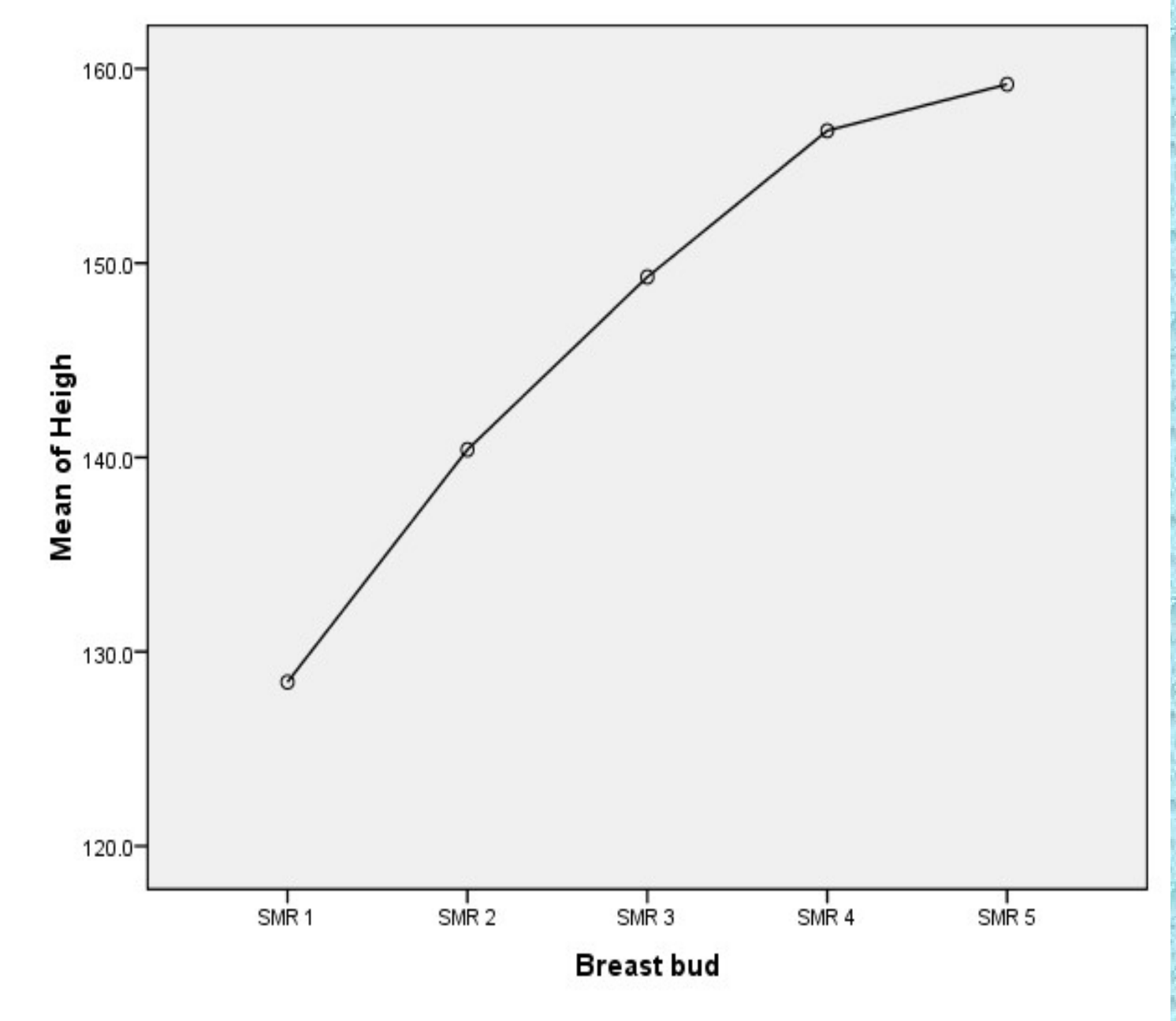
Case

- ١٠-year-old girl was referred with her mother to the pediatric endocrinology clinic with concerns of **precocious puberty**.
- Her parents expressed concern about her **growth pattern and potential final height**.
- There were **no remarkable findings** in the past medical, drug, or family history.
- On physical examination, **breast development was consistent with Tanner stage II**, and **no menarche** had occurred.
  Her **height was ١٤٥ cm**, corresponding to approximately the **٥٠th percentile for age**.

Case

- **What is your suggestion to do as paraclinical Work-Up?**
- **What do you recommend to her family?**

Height attainment during puberty



Do not do anything

Case

- An ۱۱/۵ y/o girl referred to the clinic due to the first episode of menstruation.
- Breast is in tanner stage of ۴.
- Height : ۱۴۲ cm
- Parents concerned about her height

Do you recommend to start any treatment to stop puberty?

Do not do anything

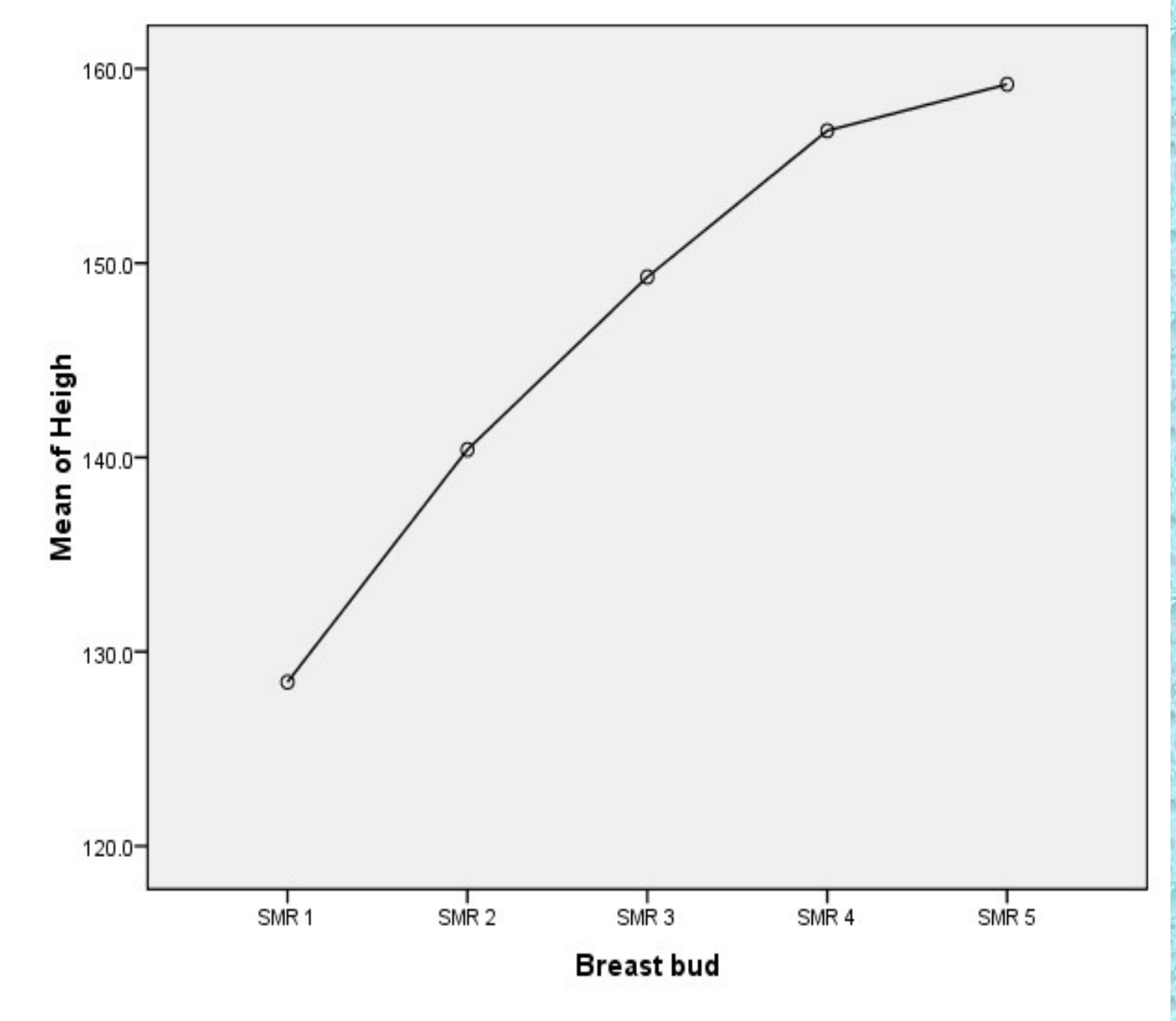
Case

- **Growth after menarche : ١ – ١٠ cm**
- Do not do anything

Case

- دختر ۹ساله ای به شما مراجعه کرده است.در معاینه برست وی در **مرحله ۲ تانر است**
- **.قد** وی ۱۴۰ سانتیمتر است.مادر وی نگران شروع بلوغ و قد ش میباشد.
- ۱- توصیه شما به مادر بیمار چیست؟
- ۲-در صورت سیر طبیعی بلوغ چند سانتی متر به قد وی اضافه میشود؟
- چه ازمایشاتی ارسال می کنید

Height attainment during puberty



Case

- با توجه به سن بیمار شروع بلوغ زودرس نمی باشد.
- حدود ۱۷-۲۵ سانتیمتر.

Case

- دختر ۸/۵ ساله ای به شما مراجعه کرده است.او تا کنون ۳ بار عادت ماهیانه شده است .پستانها در مرحله ۵ تانر است.قد وی روی منحنی ۷۵ پرسنتایل است در سونوگرافی حجم رحم ۸سی سی و ابعاد ان ۶۵*۲۳*۳۰
- میلی متر

Case

- -تشخیص بیمار چیست؟
- یک اقدام پاراکلینیک مهم در مورد این بیمار چیست؟
- ۳-درمان بیمار فوق چیست؟

جواب:

- *Precocious puberty*
- *Brain MRI*
- *Gn RH agonist(Dipherelin) in case of family agreement*

Case

- **A ١٠ y/o female brought to clinic to delaying her menstruation for improvement of height.**
- **Breast is in tanner stage ٢.**
- **Height is ١٢٠ cm**
- Mother's height ١٥٦ cm
- father' height ١٧٦ cm
- Bone age: ٨

:2–20 Yr	5th		10th		25th		9 in 45 5th		75		90		95	
2	79.6 10.27	(31.4) (22.6)	80.9 10.64	(31.9) (23.4)	83.0 11.31	(32.7) (24.9)	85.4 12.13	(33.6) (26.7)	87.7 13.08	(34.5) (28.8)	89.9 14.04	(35.4) (30.9)	91.1 14.60	(35.9) (32.3)
2 1/5	84.2 10.99	(33.1) (24.2)	85.5 11.38	(33.7) (25.0)	87.8 12.12	(34.6) (26.7)	90.3 13.04	(35.6) (28.7)	92.9 14.12	(36.6) (31.1)	95.2 15.24	(37.5) (33.5)	96.6 15.99	(38.0) (35.2)
3	87.8 11.66	(34.6) (25.6)	89.2 12.09	(35.1) (26.6)	91.6 12.90	(36.0) (28.4)	94.2 13.94	(37.1) (30.7)	96.9 15.16	(38.1) (33.4)	99.3 16.47	(39.1) (36.2)	100.8 17.36	(39.7) (38.2)
3 1/5	91.0 12.35	(35.8) (27.2)	92.4 12.83	(36.4) (28.2)	94.9 13.72	(37.3) (30.2)	97.6 14.88	(38.4) (32.7)	100.5 16.27	(39.6) (35.8)	103.1 17.78	(40.6) (39.1)	104.6 18.83	(41.2) (41.4)
4	94.0 13.09	(37.0) (28.8)	95.6 13.61	(37.6) (29.9)	98.1 14.59	(38.6) (32.1)	101.0 15.88	(39.8) (34.9)	104.0 17.44	(41.0) (38.4)	106.8 19.17	(42.0) (42.2)	108.4 20.39	(42.7) (44.9)
4 1/5	97.2 13.88	(38.3) (30.5)	98.7 14.44	(38.9) (31.8)	101.4 15.51	(39.9) (34.1)	104.5 16.93	(41.1) (37.2)	107.6 18.67	(42.4) (41.1)	110.5 20.63	(43.5) (45.4)	112.2 22.04	(44.2) (48.5)
5	100.4 14.71	(39.5) (32.4)	102.0 15.32	(40.2) (33.7)	104.8 16.47	(41.3) (36.2)	108.0 18.02	(42.5) (39.7)	111.2 19.95	(43.8) (43.9)	114.3 22.15	(45.0) (48.7)	116.1 23.75	(45.7) (52.3)
5 1/5	103.6 15.56	(40.8) (34.2)	105.3 16.22	(41.5) (35.7)	108.2 17.47	(42.6) (38.4)	111.5 19.16	(43.9) (42.1)	114.9 21.28	(45.2) (46.8)	118.1 23.72	(46.5) (52.2)	120.0 25.53	(47.3) (56.2)
6	106.8 16.44	(42.1) (36.2)	108.6 17.14	(42.8) (37.7)	111.6 18.50	(43.9) (40.7)	115.0 20.34	(45.3) (44.7)	118.6 22.66	(46.7) (49.9)	121.9 25.37	(48.0) (55.8)	123.9 27.39	(48.8) (60.3)
6 1/5	110.0 17.32	(43.3) (38.1)	111.8 18.09	(44.0) (39.8)	114.9 19.56	(45.2) (43.0)	118.4 21.57	(46.6) (47.4)	122.1 24.12	(48.1) (53.1)	125.6 27.11	(49.4) (59.7)	127.7 29.36	(50.3) (64.6)
7	113.1 18.23	(44.5) (40.1)	114.9 19.06	(45.2) (41.9)	118.1 20.67	(46.5) (45.5)	121.8 22.87	(47.9) (50.3)	125.6 25.68	(49.4) (56.5)	129.1 28.98	(50.8) (63.8)	131.3 31.47	(51.7) (69.2)
7 1/5	115.9 19.16	(45.6) (42.2)	117.8 20.08	(46.4) (44.2)	121.1 21.84	(47.7) (48.1)	124.9 24.26	(49.2) (53.4)	128.8 27.35	(50.7) (60.2)	132.5 31.00	(52.2) (68.2)	134.7 33.75	(53.0) (74.3)
8	118.5 20.15	(46.7) (44.3)	120.5 21.15	(47.5) (46.5)	123.9 23.09	(48.8) (50.8)	127.8 25.76	(50.3) (56.7)	131.9 29.17	(51.9) (64.2)	135.6 33.19	(53.4) (73.0)	137.9 36.23	(54.3) (79.7)
8 1/5	121.0 21.19	(47.6) (46.6)	123.0 22.30	(48.4) (49.1)	126.5 24.44	(49.8) (53.8)	130.6 27.38	(51.4) (60.2)	134.7 31.15	(53.0) (68.5)	138.5 35.58	(54.5) (78.3)	140.9 38.92	(55.5) (85.6)
9	123.2 22.32	(48.5) (49.1)	125.3 23.54	(49.3) (51.8)	129.0 25.90	(50.8) (57.0)	133.1 29.14	(52.4) (64.1)	137.4 33.29	(54.1) (73.2)	141.4 38.17	(55.7) (84.0)	143.8 41.82	(56.6) (92.0)
9 1/5	125.3 23.54	(49.3) (51.8)	127.6 24.88	(50.2) (54.7)	131.3 27.48	(51.7) (60.5)	135.6 31.04	(53.4) (68.3)	140.1 35.60	(55.1) (78.3)	144.1 40.93	(56.7) (90.1)	146.6 44.92	(57.7) (98.8)
9 2/5	127.5 24.87	(50.2) (54.7)	129.8 26.33	(51.1) (57.9)	133.7 29.17	(52.6) (64.2)	138.2 33.06	(54.4) (72.7)	142.8 38.04	(56.2) (83.7)	147.0 43.85	(57.9) (96.5)	149.6 48.18	(58.9) (106.0)

- ۵th = ۱۲۷
- ۵۰th=۱۳۸
- SD=۵/۵ cm
- Zscore = ۱۳۸-۱۲۰=۱۸
- ۱۸÷ ۵/۵= ۳/۲
- **HT SDS= - ۳/۲**

	Girls			Boys		
	Retard	average	advance	Retard	average	advance
9-3	0.851	0.836	0.800	0.794	0.761	0.728
9-6	0.858	0.844	0.809	0.800	0.769	0.734
9-9	0.866	0.853	0.819	0.807	0.777	0.741
10-0	0.874	0.862	0.828	0.812	0.784	0.747
10-3	0.884	0.874	0.841	0.816	0.791	0.753
10-6	0.896	0.884	0.856	0.819	0.795	0.758
10-9	0.907	0.896	0.870	0.821	0.800	0.763
11-0	0.918	0.906	0.883	0.823	0.804	0.767
11-3	0.922	0.910	0.887	0.827	0.812	0.776
11-6	0.926	0.914	0.891	0.832	0.818	0.786
11-9	0.929	0.918	0.897	0.839	0.827	0.800
12-0	0.932	0.922	0.901	0.845	0.834	0.809
12-3	0.942	0.932	0.913	0.852	0.843	0.818
12-6	0.949	0.941	0.924	0.860	0.853	0.828
12-9	0.957	0.950	0.935	0.869	0.863	0.839
13-0	0.964	0.958	0.945	0.880	0.876	0.850
13-3	0.971	0.967	0.955		0.890	0.863
13-6	0.977	0.974	0.963		0.902	0.875

What is the prediction of final height ?

Do you prescribe GnRh agonist to this girl ?

TABLE 23-1 -- PREDICTION OF ADULT STATURE

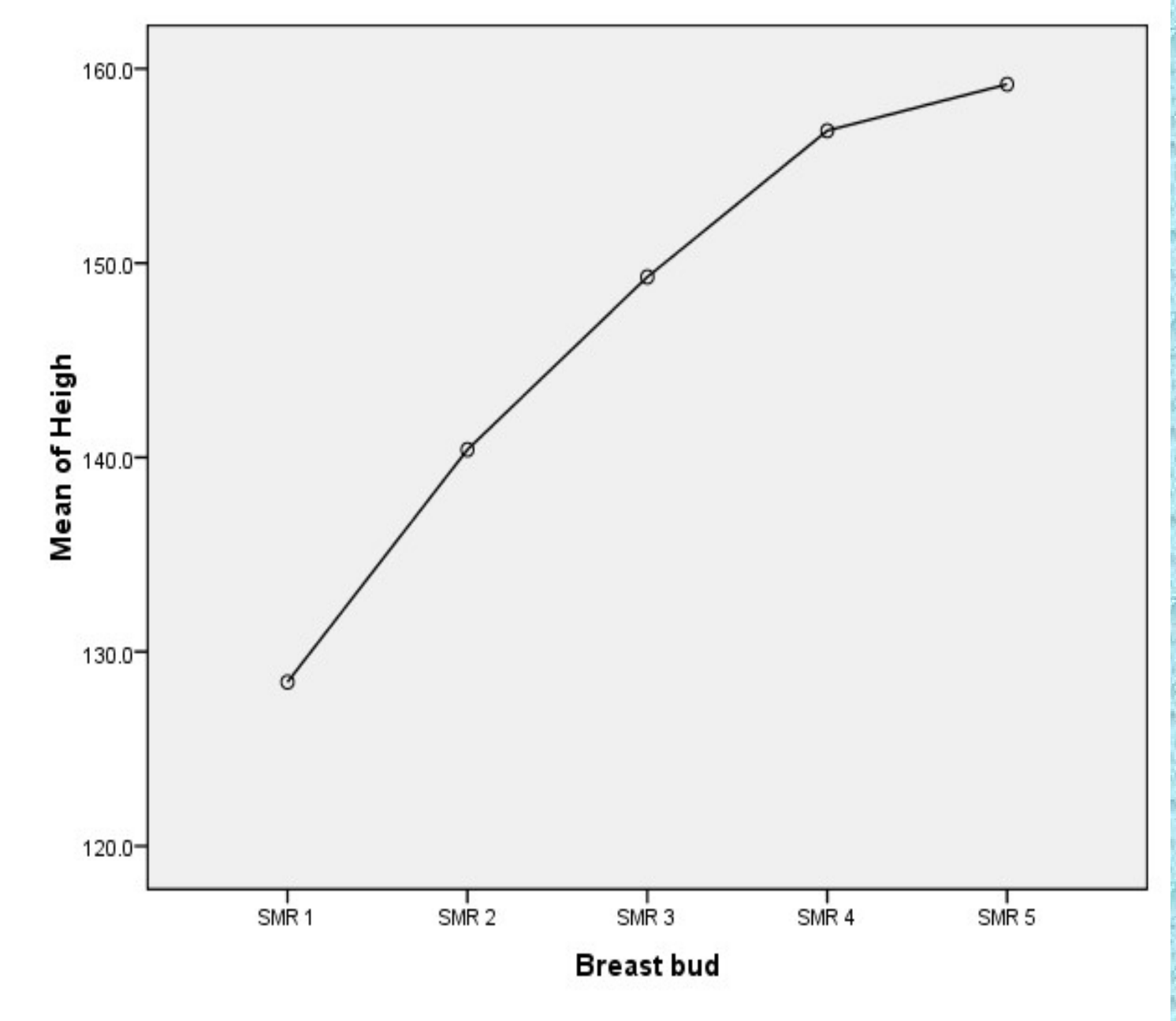
	Fraction of Adult Height Attained at Each Bone Age					
	Girls			Boys		
Bone Age (yr-mo)	Retarded	Average*	Advanced	Retarded	Average*	Advanced
6-0	0.733	0.720		0.680		
6-3	0.742	0.729		0.690		
6-6	0.751	0.738		0.700		
6-9	0.763	0.751		0.709		
7-0	0.770	0.757	0.712	0.718	0.695	0.670
7-3	0.779	0.765	0.722	0.728	0.702	0.676
7-6	0.788	0.772	0.732	0.738	0.709	0.683
7-9	0.797	0.782	0.742	0.747	0.716	0.689
8-0	0.804	0.790	0.750	0.756	0.723	0.696
8-3	0.813	0.801	0.760	0.765	0.731	0.703
8-6	0.823	0.810	0.771	0.773	0.739	0.709
8-9	0.836	0.821	0.784	0.779	0.746	0.715
9-0	0.841	0.827	0.790	0.786	0.752	0.720
9-3	0.851	0.836	0.800	0.794	0.761	0.728

- PAH= ۱۲۰ ÷ ۰/۸۰۴
- **PAH= ۱۴۹**

- Target height
- ۱۵۶+۱۷۶=۳۳۲
- ۳۳۲ ÷ ۲= ۱۶۶
- ۱۶۶-۶٫۵= ۱۵۹٫۵± ۱۰
- Target height= ۱۴۹-۱۶۹

- No necessery GnRh agonist
- Recommend GH therapy

Height attainment during puberty




Thank you for your Attention