Puberty in Turner Syndrome

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Case presentation

- J.C. is a 10 year old girl who was diagnosed with Turner Syndrome at age 8 when she had a growth deceleration
- She has a karyotype of 45,X
- She is on growth hormone and overall doing well
- At the visit today, she says that many of her friends in class have started having “body changes”. She and her parents want to know what to expect for J.C.

Case presentation

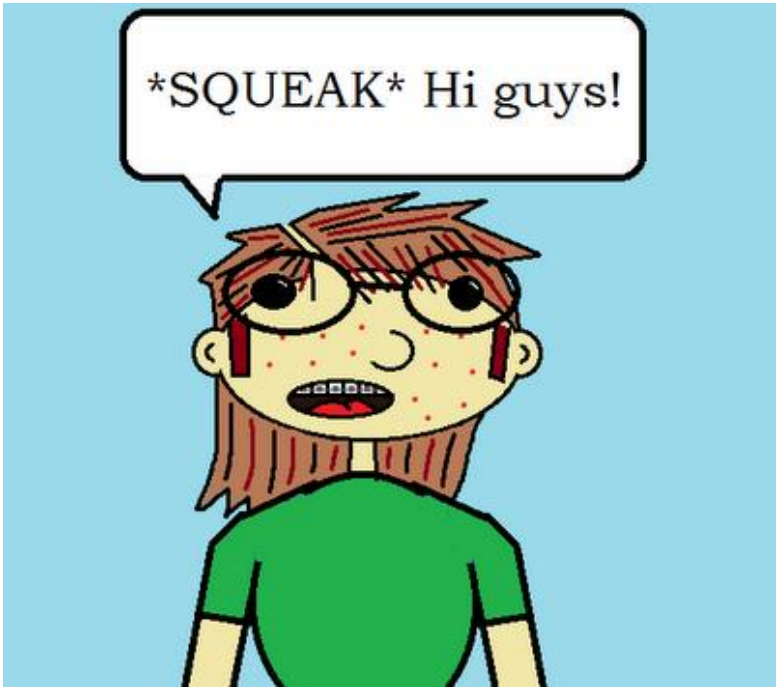
- On examination J.C. looks very well
- She is at the 1 % ile for height on the standard growth charts and 80 % ile on Turner Syndrome specific growth charts
- She is Tanner stage I for breast development and early Tanner stage II for pubic hair development
- The rest of her examination is normal

Talk outline

- Definition of puberty and its stages
- Expected normal onset and tempo of puberty
- What do we know about puberty in Turner Syndrome?
- Evaluation of ovarian function
- Treatment options for pubertal induction
  - Established tests and treatments
  - New directions for evaluation and referral

Definition of puberty

- Most of us think of "puberty" as that "awkward period" in our childhood
  - Acne
  - Body odor
  - Breast development
  - Menarche
  - Voice cracking
  - Growth spurts

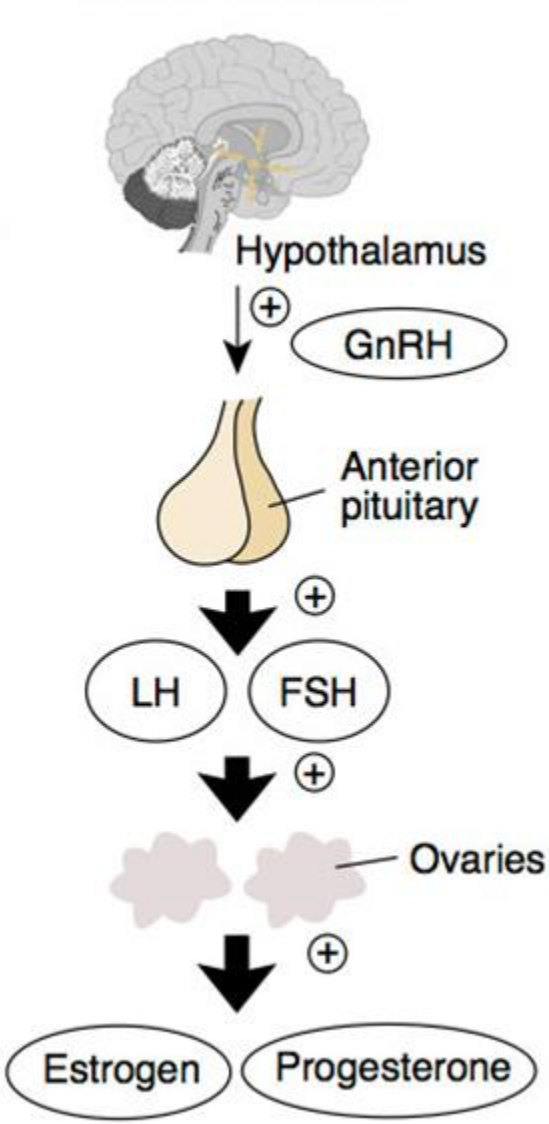


Medical definition of puberty

Hormones from the hypothalamus begin to signal the pituitary to produce 2 hormones
- Follicle stimulating hormone (FSH)
- Luteinizing hormone (LH)

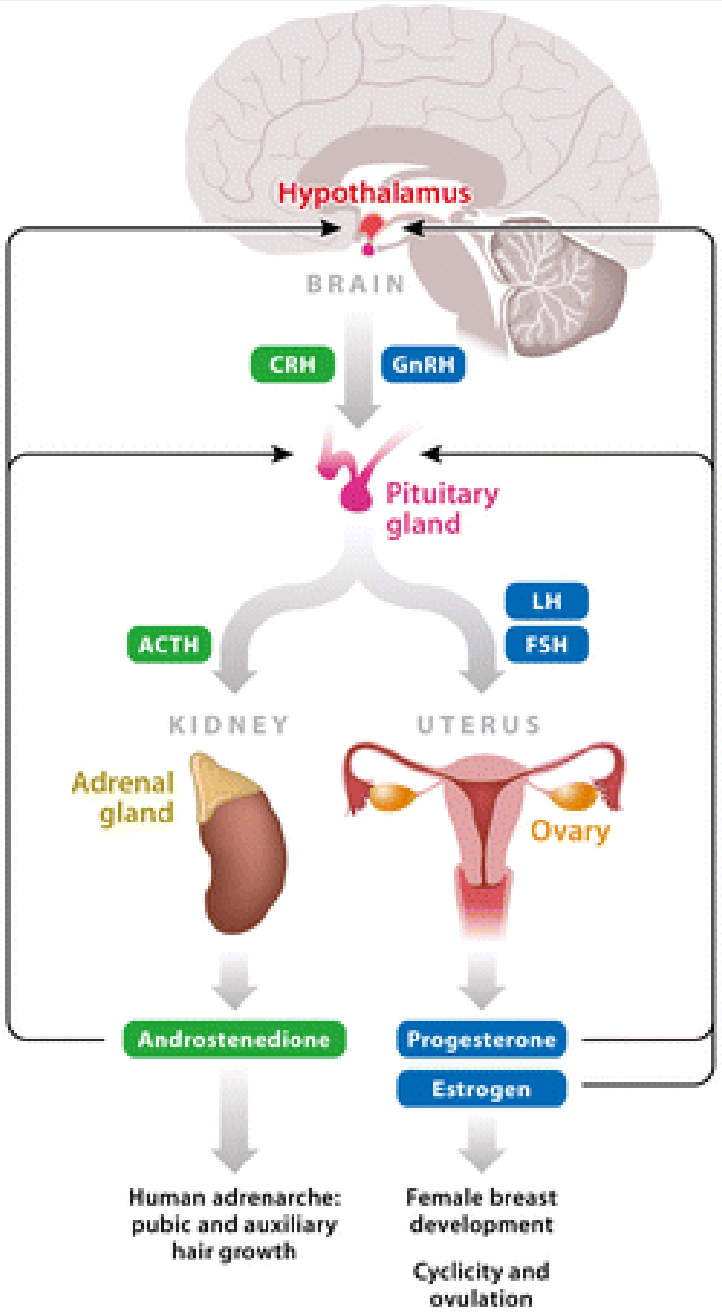
These hormones signal the ovaries to produce 2 other hormones
- Estrogen
- Progesterone

This hormonal pathway results in breast development, increased uterine thickness, and eventually menses

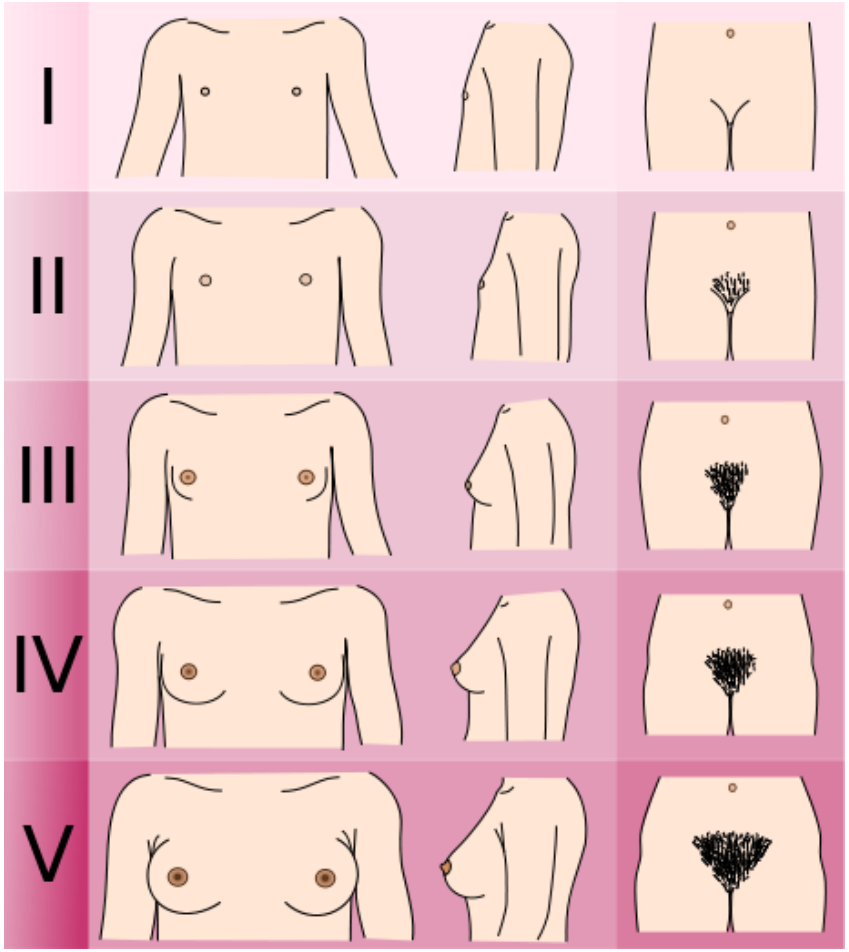


Puberty and adrenarche

- Adrenarche is the start of hormone signaling by the adrenal gland
- Adrenarche starts around the same time as central puberty, but the two are independent and can happen separately from each other



Tanner stages for breast and pubic hair development



Timing of puberty: Onset

- Expected onset of central puberty (breast development) in girls is AFTER age 8 years
  - Range: 8-13 years
  - Average: 9 years
- There is a debate as to whether this applies to certain ethnic populations, and if the age should be lowered to 6 ½ or 7 years in these groups
  - Not formally accepted by medical societies

Timing of adrenarche: Onset

- Expected onset of adrenarche (pubic hair development) in girls is AFTER age 9 years
  - Range: 9-13 years
  - Average: 10 years

Progression of changes in puberty and adrenarche

General rules:

One Tanner stage change
every 6-9 months

Average time from initial breast budding to menarche: 2-3 years

What constitutes delayed puberty?

- No signs of breast development by age 14 years
- No menarche by age 16 years
- Delayed progression from one Tanner stage to another
  - May be a normal variant

Puberty in Turner Syndrome

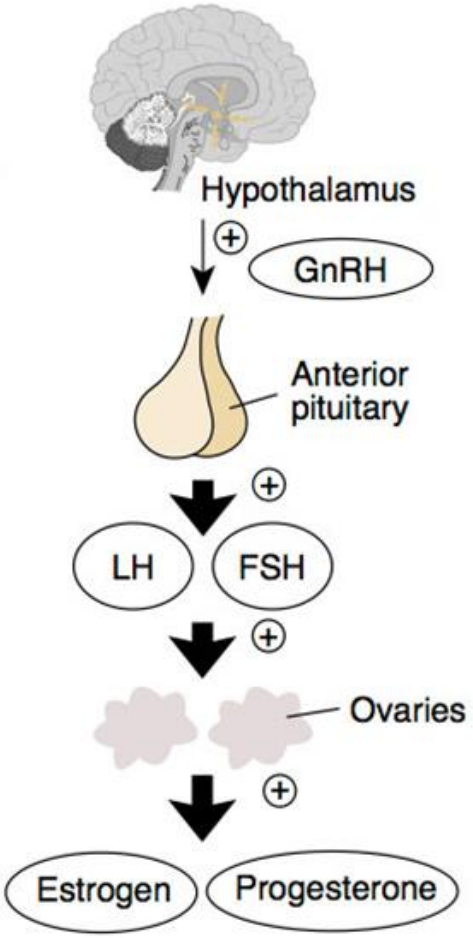
- The lack of 2 completely normal X chromosomes leads to accelerated follicle loss
- Without viable follicles, the ovary is unable to produce estrogen and progesterone
- The majority of girls with Turner Syndrome have premature ovarian failure (POF)

Puberty in Turner Syndrome

- Approximately 30% of girls with Turner Syndrome have spontaneous pubertal development
- 2-5% have spontaneous menarche prior to ovarian failure
- Girls with a 45,X karyotype are least likely to have either spontaneous puberty or menarche

Evaluation of puberty

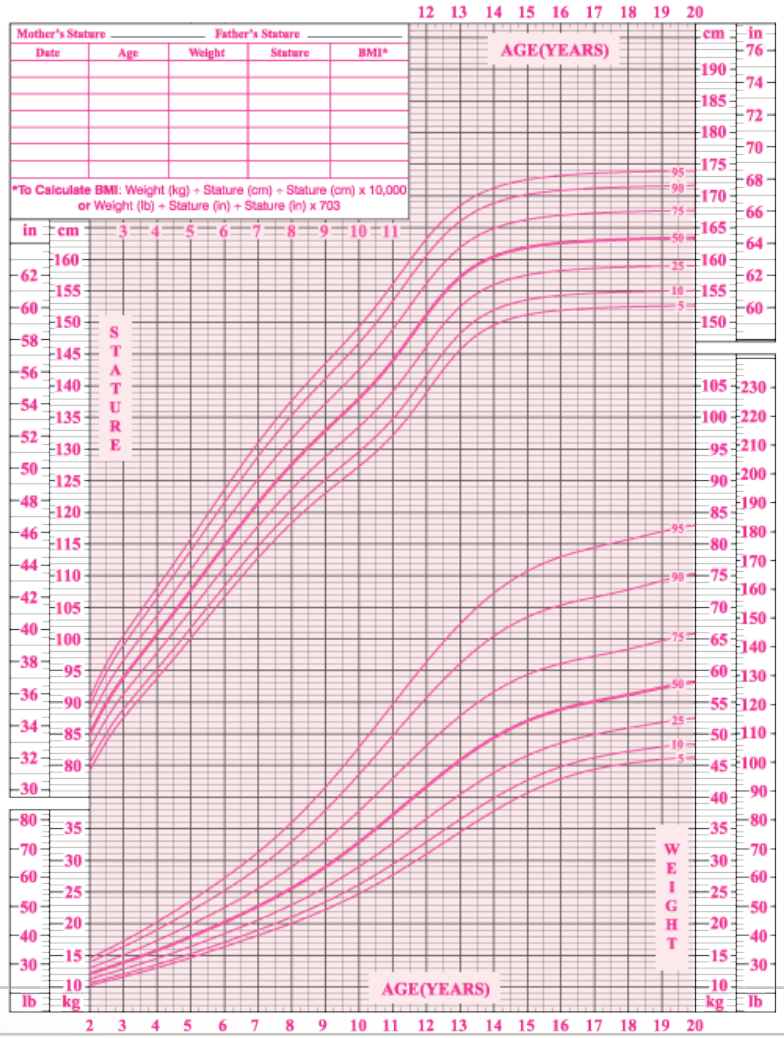
- At age 10 years, we routinely obtain levels of FSH, LH, and estradiol
- High FSH and LH levels are a sign of ovarian insufficiency

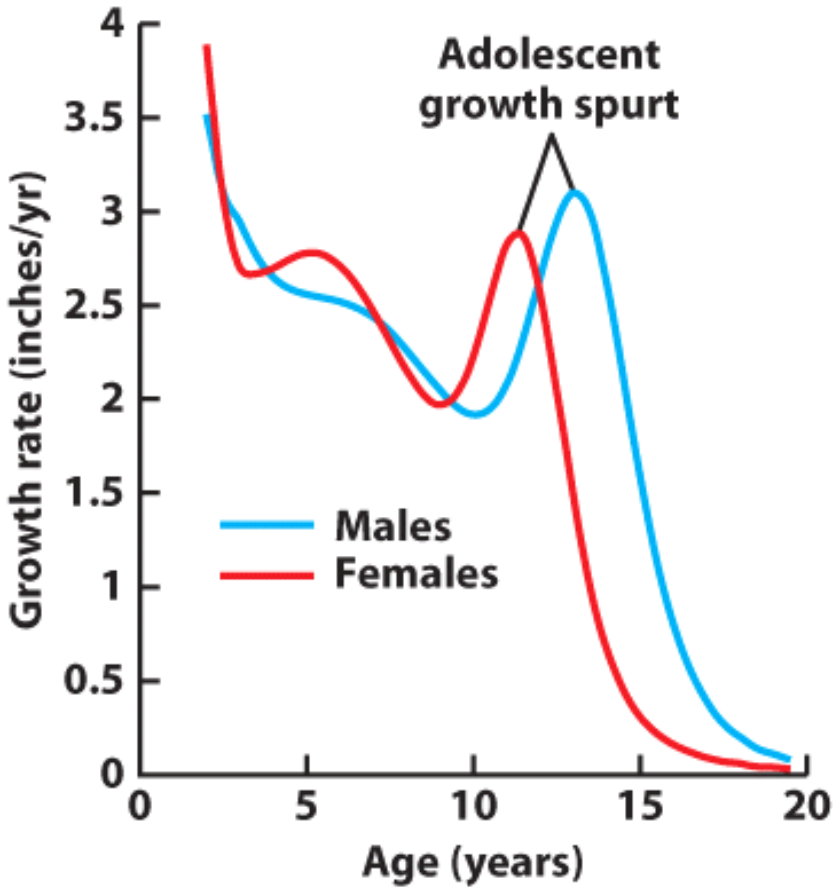


Why start screening at age 10?

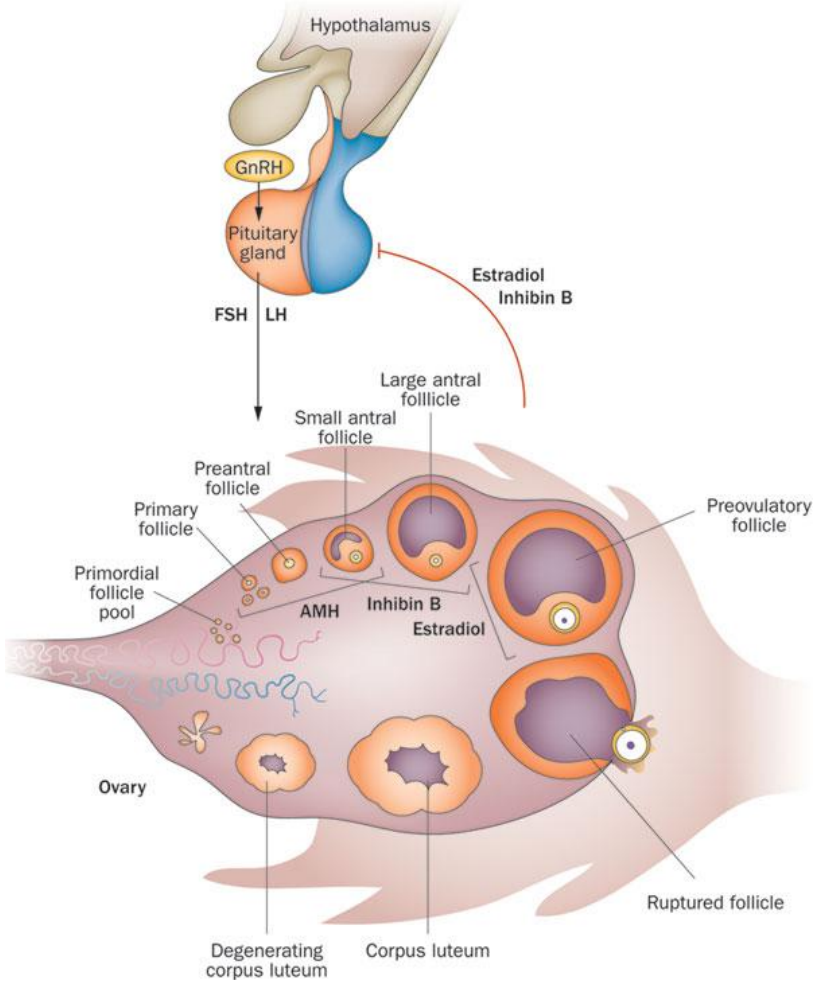
- The hormonal axis responsible for puberty is primed and mature by this age
  - Testing too early may show us low FSH and LH levels and falsely reassure us
  - Testing too late will result in missing the optimal window for the benefits of hormone replacement therapy

Pubertal effects on growth





Anti-mullerian hormone (AMH)



AMH levels may be helpful in evaluating ovarian reserve

- AMH levels correlate well with FSH and LH levels
  - High FSH and LH levels are associated with lower AMH levels
- AMH levels correlate well with clinical findings
  - Higher AMH levels are seen in girls with spontaneous puberty and menarche
- AMH levels may be helpful in evaluating ovarian reserve in pre-pubertal ages

AMH levels in Turner Syndrome

Table II Detailed characterization of observed karyotypes and AMH levels.

Categories	Subcategories	*n* (%)	Measurable AMH [*n* (%)]	OR[2] (95% CI[2])	AMH [ng/ml (median/range)]
45,X		136 (50.4)	14 (10.3)	1 (reference)	0.53 (0.12–2.10)
45,X/46,XX		22 (8.1)	17 (77.3)	37.0 (11.2–122.3)	2.26 (0.24–6.37)
Others		112 (41.5)	28 (25)	3.4 (1.6–7.2)	1.06 (0.04–7.78)
	46,X,i(Xq)	40 (14.8)	5 (12.5)		
	46,X,i(Xp)	4 (1.5)	0		
	46,X,del(X)	15 (5.6)	8 (53.3)		
	46,X,r(X)	13 (4.8)	2 (15.4)		
	45,X/47,XXX	19 (7.0)	8 (42.1)		
	45,X/46,XY	9 (3.3)	2 (22.2)		
	'others'[1]	12 (4.4)	3 (25)		

Human Reproduction, Vol.28, No.7 pp. 1899–1907, 2013

Should we be measuring AMH levels routinely?

- In select cases there may be utility (i.e. decisions for fertility treatment)
- In most cases there is little to additional information to be gained from these levels at this time

Diagnosing Primary Ovarian Failure

- Lack of pubertal development after age 10 years
- Elevated FSH and LH levels
  - FSH > 40 mIU/mL
  - LH > 20 mIU/mL

Treating ovarian failure

- Goals of treatment:
  - Provide optimal timing of puberty with respect to growth potential
  - Induce secondary sexual characteristics at psychosocially appropriate time
  - Optimize bone mineral density

Appropriate age of initiation of HRT

- Begin estrogen replacement therapy at approximately 11-12 years of age
  - This age allows for maximizing growth potential
- Low dose estrogen with slow titration will result in menarche at approximately age 13-14 years
- Progesterone is added once menarche is attained

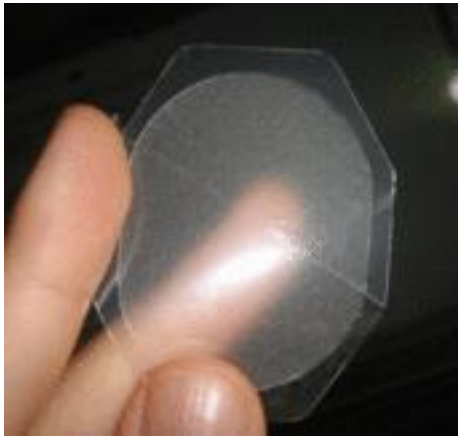
Estrogen sources

- Oral conjugated estrogens
  - Example: Premarin
- Source: Urine of pregnant mares
- Risks: Estrogens not typically made by humans are included
- Benefits: Available in multiple small doses, has been used for many years and is well tolerated and studied

The appearance of these tablets is a trademark of Wyeth-Ayerst Laboratories.

Estrogen sources

- Topical estrogens
  - Example: Climara, Vivelle Dot
- Risks: Site erythema, less well studied, has to be cut for small dosing (? Dose accuracy)
- Benefits: Easier regimen (1-2X / week), bypasses liver metabolism



Progesterone

- Added to the regimen once bleeding is noted with estrogen use
- Can be given as a pill for 10 days alongside a patch
- Can be given as part of an estrogen / progesterone combination pill (OCP's)
- Important for preventing unopposed estrogen action on breast and uterine tissues

Ultra-low dose estrogen in pre-pubertal girls with Turner Syndrome

- The theory here is that pre-pubertal girls without Turner Syndrome still produce some amount of estrogen, and it may be a consideration in Turner syndrome as well
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  - Concerns include early pubertal onset and loss of growth potential

- One large prospective study actually showed a height gain over those treated with GH alone

Ross J et al. E Engl J Med 364;13 March 31. 2011

Ultra-low dose estrogen in pre-pubertal girls with Turner Syndrome

- The other theory is that low-dose estrogen in pre-pubertal girl may improve nonverbal processing and memory
  - Ross, J et al. Neurology 2000
  - Ross J, et al. JCEM 1998
  -

Precocious puberty in Turner Syndrome

- Defined as onset of puberty before age 8 years (or rapid progression of puberty)
- Well documented in case reports
- Contrary to estrogen replacement, consideration can be given to medically stopping puberty
  - Height benefits
  - Psychosocial benefits

A (brief) word on fertility

- Young women with Turner Syndrome who have spontaneous puberty and menarche are still at risk for early ovarian failure and should be counseled properly
- Although previously not feasible, fertility specialists can now freeze just one egg if it is possible to harvest any follicles at all.
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Back to J.C.

- Laboratory data:
- FSH 22 mIU/mL
- LH 11 mIU/mL
- Estradiol < 10 pcg/mL
- What should we do?

Summary

- Puberty is a series of well defined stages controlled by connections between the hypothalamus, pituitary, and ovaries
- Spontaneous puberty can occur in Turner Syndrome
- More commonly, hormonal induction of puberty is required
- Treatment should be individualized for every girl
- Consideration of height and psychosocial benefits are critical in the decision-making process
- The likelihood of early ovarian failure should be discussed even with women who undergo spontaneous puberty and menarche for timely evaluation and intervention