

# PUBERTY BLOCKERS:

WHY, WHAT, WHEN, ALTERNATIVES,  
AND POTENTIAL PITFALLS

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# DISCLOSURES

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I have no financial disclosures.

I will be speaking about off-label therapies.



# OBJECTIVES

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- Purpose of using puberty blockers in gender non-conforming children
- When to use puberty blockers
- How to use GnRH agonists
- Options available
- Alternatives
- Avoiding pitfalls



# WHY USE PUBERTY BLOCKERS?

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- Prevents development of further secondary sexual characteristics
- Reversible\*
- Considered safe
- Extensive experience in children with precocious puberty
- Gives the patient (and family) time to explore their gender identity
- Reduction in level of distress/anxiety
- Recommended by WPATH

# WPATH 8

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Statement 7.11

**We recommend health care professionals provide information to gender diverse children and their families/caregivers as the child approaches puberty about potential gender-affirming medical interventions, the effects of these treatments on future fertility, and options for fertility preservation.**

# WPATH 8

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Statement 12.1

**We recommend health care professionals begin pubertal hormone suppression in eligible\* transgender and gender diverse adolescents only after they first exhibit physical changes of puberty (Tanner stage 2).**

Statement 12.2

**We recommend health care professionals use GnRH agonists to suppress endogenous sex hormones in eligible\* transgender and gender diverse people for whom puberty blocking is indicated.**

# WPATH 8

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Statement 12.1

**We recommend health care professionals begin pubertal hormone suppression in eligible\* transgender and gender diverse adolescents only after they first exhibit physical changes of puberty (Tanner stage 2).**

**OK, so when to start?**

Statement 12.2

**We recommend health care professionals use GnRH agonists to suppress endogenous sex hormones in eligible\* transgender and gender diverse people for whom puberty blocking is indicated.**

# PUBERTAL TIMING

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**DFAB:** < 8 yo is precocious 10 is average  
**DMAB:** < 9 yo is precocious 11 is average

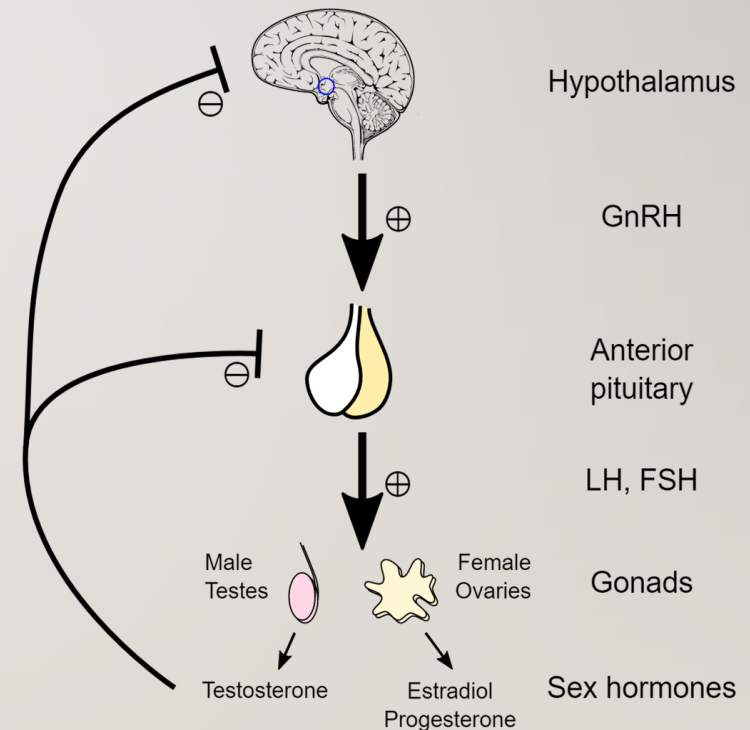
90% of DFAB who start puberty < 8 (but > 6) is benign

90% of DMAB who start puberty < 9 is **PATHOLOGIC**

Any **DMAB** who has signs of puberty < age 9 should be referred to Endocrinology for evaluation of Precocious Puberty.

# NORMAL PUBERTY

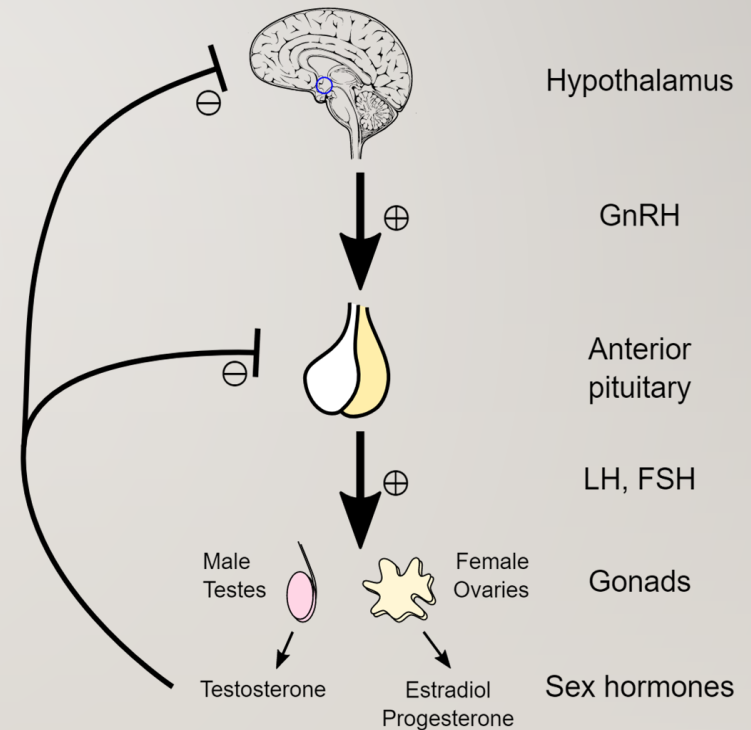
- Hypothalamic-pituitary-gonadal (HPG) axis is quiescent for most of childhood
  - Hypothalamic activation in late childhood
  - LH/FSH pulses increase in amplitude and frequency
  - Testes/Ovaries produce gonadal hormones
  - Once physical signs are present, true puberty is well underway



# NORMAL PUBERTY

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- First detectable signs of puberty:
  - DFAB: breast development  
(**thelarche**)
  - DMAB: testicular enlargement
  - **NOT pubic hair!!!**



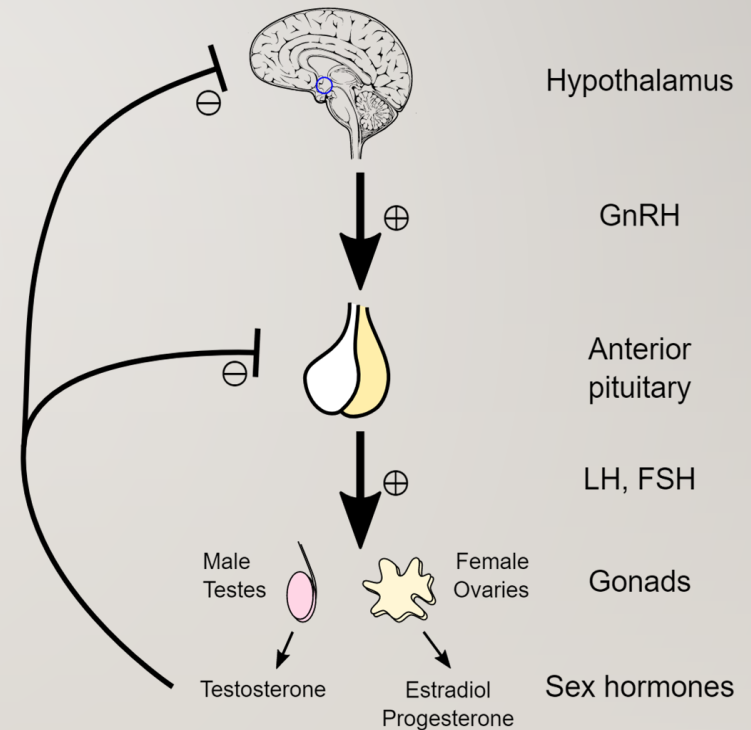
# NORMAL PUBERTY

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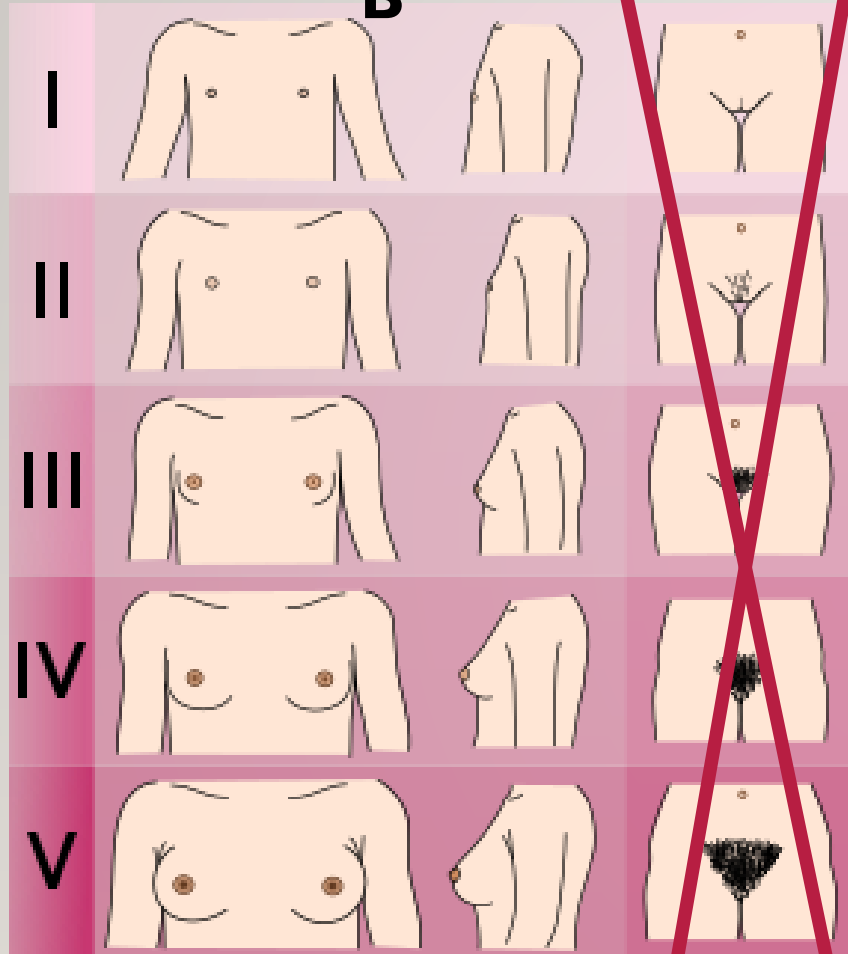
- DFAB: breast development  
(**thelarche**)
- DMAB: testicular enlargement
- **NOT pubic hair!!!**



**Adrenarche** = maturational increase in androgens made by adrenals - effects on skin, apocrine glands, pubic/axillary hair



# DFA B



# DMAB



≥ 3 cc

# EARLY THELARCHE IS EXTREMELY COMMON BUT IS NOT TRUE PUBERTY

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- The majority of cases of premature thelarche are idiopathic.
- Unsuppressed hypothalamic-pituitary-gonadal axis in the early years of life
- “Overactivation” of HPA in early childhood secondary to altered sensitivity to steroids of the hypothalamic receptors controlling sexual maturation
- Increased circulating free estradiol
- Increased sensitivity of breast tissue to estrogens
- Exposure to exogenous estrogens
- Exposure to pseudo-estrogens
  
- **Basal LH < 0.3 mIU/ml**
- **Low Serum Estradiol level**

# MAKING INSURERS HAPPY\*

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I am seeing more demands for supporting evidence and specific verbiage:

1. Physical Exam – Tanner Stage 2 must be documented

**AND**

2. Labs:

- a. Serum LH > 0.3 mIU/ml
- b. Elevated sex steroids

**AND**

- I. Verbiage to be included:

- b. Why is the therapy needed
- c. All risks have been discussed
- d. Impact on future fertility has been discussed
- e. Consent obtained

\* - sarcasm

# POTENTIAL RISKS OF GnRH AGONISTS

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1. Impaired linear growth
2. Negative impact on bone health
3. Impact on fertility
4. Menopausal symptoms
5. Cost

# POTENTIAL RISKS

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1. Impaired linear growth
2. Impact on bone health
- 3. Impact on fertility**
4. Menopausal symptoms
5. Cost

DMAB patients who start a GnRH agonist at Tanner stage 2 and then progress to estrogen therapy will have impaired fertility because the testes will not have matured. If fertility is desired, the patient would have to progress through puberty in order to produce viable gametes.

# POTENTIAL RISKS

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1. Impaired linear growth
2. Impact on bone health
3. Impact on fertility
4. **Menopausal symptoms**
5. Cost

Patients who have already progressed to Tanner Stage 4/5 may experience intolerable menopausal symptoms on a GnRH agonist.

So everyone has agreed that it is time to start Puberty Blockade.

**Now what?**



# GnRH AGONISTS

## Leuprolide acetate

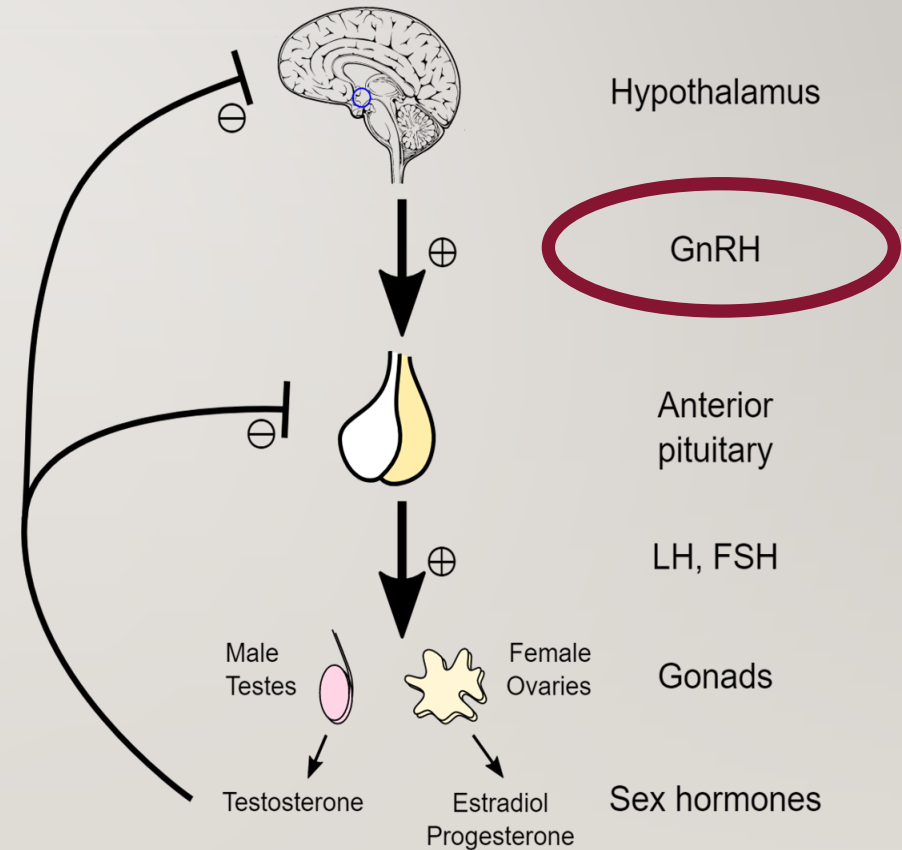
- Lupron Ped Depot
- Lupron Depot
- Eligard
- Fensolvi

## Histrelin acetate

- Supprelin LA
- Vantas

## Triptorelin

- Triptodur



	<b>Age Group</b>	<b>FDA indication</b>	<b>route</b>	<b>Freq</b>	<b>\$/yr</b>
Lupron Depot-Ped	Ped	CPP	IM	Q 3 mo	
Lupron Depot-Ped	Ped	CPP	IM	Q 6 mo	
Lupron Depot	Adult	Prostate CA	IM	Q 3 mo	
Fensolvi	Ped	CPP	SubQ	Q 6 mo	
Supprelin LA	Ped	CPP	implant	Q 12 mo	
Vantas	Adult	Prostate CA	implant	Q 12 mo	
Triptodur	Ped	CPP	IM	Q 6 mo	

	Age Group	FDA indication	route	Freq	\$/yr
Lupron Depot-Ped	Ped	CPP	IM	Q 3 mo	52,000
Lupron Depot-Ped	Ped	CPP	IM	Q 6 mo	52,000
Lupron Depot	Adult	Prostate CA	IM	Q 3 mo	2,000
Fensolvi	Ped	CPP	SubQ	Q 6 mo	55,000
Supprelin LA	Ped	CPP	implant	Q 12 mo*	51,000
Vantas	Adult	Prostate CA	implant	Q 12 mo*	5,100
Triptodur	Ped	CPP	IM	Q 6 mo	44,000

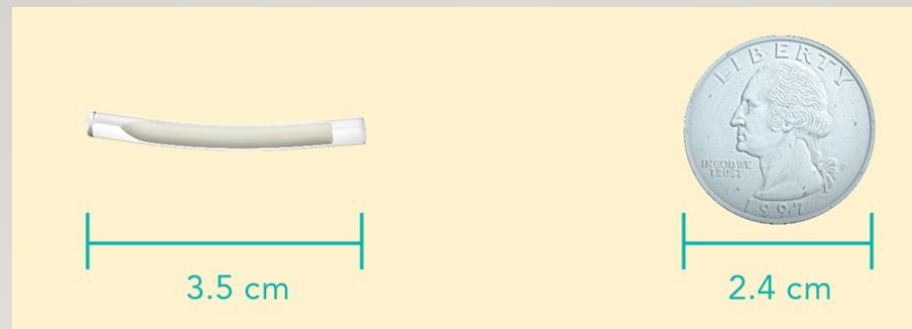
\* May be active up to 2-3 years in some cases.



# OTHER ISSUES

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- Must be mixed and used **QUICKLY** – turns into gel over time
- Classed as a chemotherapeutic agent
  - May not be administered by a pregnant person
  - Gown/glove/mask
- Note that after initial injection DFAB patients may have **transient bleeding**
- LH will **not** be suppressed quickly – check in 3-6 months
- Physical signs of puberty should be arrested, and there may be some regression of breast tissue.



## The SUPPRELIN® LA Implantation Kit<sup>1</sup>

SUPPRELIN® LA is supplied in a corrugated shipping carton that contains 2 inner cartons: a small one for the vial containing the SUPPRELIN® LA implant, which is shipped with a cold pack inside a polystyrene cooler that must be refrigerated upon arrival, and a larger one comprising the Implantation Kit, which must not be refrigerated, for use during insertion or removal of SUPPRELIN® LA. The SUPPRELIN® LA Implantation Kit includes all the necessary components for the insertion and removal of the implant (sterile gloves not included).



# IMPLANT ISSUES

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- Insertion requires training
- Painful
- Will leave a small scar
- Young patients may require sedation
- Removal can be problematic, especially the longer the implant is in place
- Expense

What if a GnRH Agonist  
is not an option?



# ALTERNATIVES TO GnRH AGONISTS

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Statement 12.3

**We suggest health care professionals prescribe progestins (oral or injectable depot) for pubertal suspension in eligible\* transgender and gender diverse youth when GnRH agonists are not available or are cost prohibitive.**

Statement 6.7

**We recommend providers consider prescribing menstrual suppression agents for adolescents experiencing gender incongruence who may not desire testosterone therapy, who desire but have not yet begun testosterone therapy, or in conjunction with testosterone therapy for breakthrough bleeding.**

# ALTERNATIVES TO GnRH AGONISTS

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**DFAB** patients who are already menstruating may be better treated with menstrual suppression to reduce the anxiety caused by vaginal bleeding while avoiding the menopausal effects of a GnRH agonist.

For **DMAB** patients in whom a GnRH agonist is not an option:

- Spironolactone 100 mg BID  
PLUS
- Norethindrone 5-10 mg QD
- Titrate the serum total testosterone to  $\leq 50$  ng/dl  
OR
- 5- $\alpha$  reductase inhibitors
- True androgen blockers

# SPIRO PLUS NORETHINDRONE

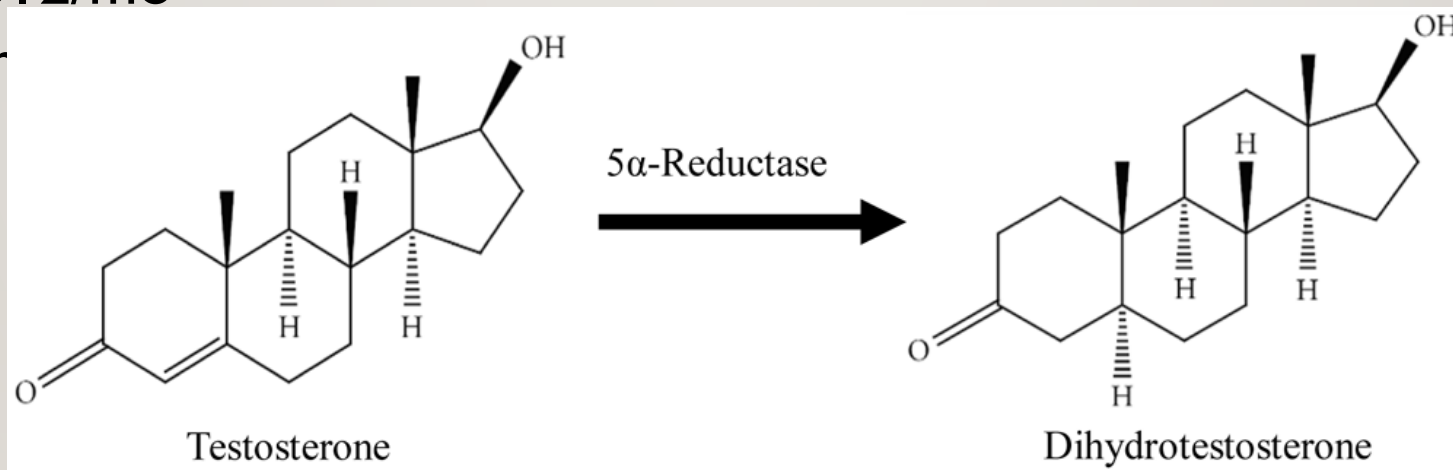
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- Low Cost
- Generally well tolerated
- Serum levels of testosterone can be measured
- Dose of norethindrone can be adjusted to achieve desired T level
- Progestins can worsen depression
- Spironolactone
  - Monitor electrolytes
  - Mild diuretic
- Doses may be reduced as Estradiol is added/increased

# 5- $\alpha$ REDUCTASE INHIBITORS

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- Finasteride            5 mg/d  
    \$ 8/mo
- Dutasteride            0.5 mg/d  
    \$12/mo
- Serum



# TRUE ANDROGEN BLOCKERS

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- Bicalutamide            50 mg/d                            \$ 24/mo  
    Bicalutamide blocks the ability of DHT to bind to the androgen receptor.  
    Serum testosterone levels unchanged
- Cyproterone acetate – NOT FDA approved for use in US, liver toxicity

# ISSUES

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- Serum Testosterone levels cannot be used to assess effectiveness of therapy.
- Monitor effectiveness with symptoms
- Ask about spontaneous erections
- Less known about the blocker Bicalutamide
- Dutasteride seems to be more effective than Finasteride.

# RECAP

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- As the patient approaches the age of puberty, monitor closely.
- Recognize that early thelarche is extremely common, but often is ~~is~~ not actual puberty.
- Pubic hair      Puberty
- If puberty is precocious refer to Endocrine.
- Start pubertal blockade at Tanner Stage 2, if possible.
- Discuss risks, including potential loss of fertility.
- Appreciate side effects and cost of GnRH agonists.