

Puberty and Fertility

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*no conflicts of interest to report

Part One **PUBERTY!**

Normal Female Puberty

- Every girl goes through puberty at her own rate.
- This rate is determined by many factors including genetics, diet, and activity.
- Some girls will have puberty very young
 - before age 8
- Other girls will have puberty much older
 - after age 15

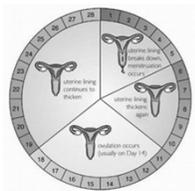
Normal Female Puberty

- Most girls will have breast development starting between age 8 and 12 years



Normal Female Puberty

- Most girls will have their first period between age 10 and 14 years.



What about girls with Galactosemia?

- Not all girls with galactosemia will have spontaneous puberty
- Some girls with galactosemia will start developing breasts on time, but will not get a period on their own
- Some girls with galactosemia will not be able to develop breasts on their own



Should I Worry?

- If your daughter is 13 years old and does not have breasts starting or is 15 years old and has not had her period she should be evaluated



- Some doctors will evaluate girls with galactosemia for the possibility that they will need help with puberty as early as 11 or 12 years

Will it Hurt?

- The evaluation typically has 2 parts:
 - Bone Age
 - Blood Draw

Bone Age



- A bone age is an x-ray of your left hand
- **It does not hurt**
- It tells your doctor how old your body *THINKS* it is
- Most girls will not have puberty until their bones age is 11-12 years

Blood Work



- Your doctor will test hormone levels
 - FSH and LH (signals from the brain to the ovary that it is time for action)
 - Estradiol (female sex hormone- produced by the ovary in response to signals from the brain)
 - AMH* (tells your doctor if you are likely to be able to ovulate)
- If your FSH level is very high and your estradiol level is very low it is unlikely that you will be able to have puberty without help

*AMH is a newer test and is not currently standard of care. It may not be ordered by your doctor.

What is the Treatment?

- There are many different treatment options available.
- Every endocrine doctor will have their own favorite way to induce puberty in their patients with ovarian dysfunction.



“Physiologic Replacement”



- A dosing regimen that mimics biologic puberty
- Usually started when bone age is at least 12 years
- Start with a low dose matrix patch (such as Vivelle Dot) at night only
- Slowly increase dose and duration of patch every 6 months
- After 2-3 years of Estrogen Only (earlier if breakthrough bleeding)- add Progestin (such as Prometrium) for 12 days of the month.

Davenport, M. Approach to the Patient with TS. J Clin Endocrinol Metab, April 2010, 95(4):1487-1495



What about Birth Control Pills?



- Once you are having a cycle you can consider switching to a birth control pill
- These are easier because you only have to take 1 pill every day and you don't have to remember to change a patch or count days of progestin
- However- many OCPs contain lactose so you will need to discuss with your provider

Do I have to have a period?

- There is no evidence that you **MUST** have a period every month to be healthy
- **HOWEVER-** if you have low estrogen levels (which many girls/women with galactosemia do) you may be at risk for
 - Heart Disease
 - Poor Bone Health
- Talk to your health care provider about what is best for you!



Resources

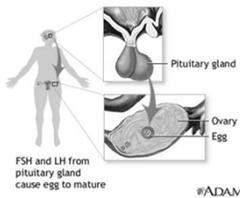
- Find-an-Endocrinologist: www.hormone.org or call 1-800-HORMONE (1-800-467-6663)
- http://www.hormone.org/Resources/upload/FS_MWH_Amenorrhea_EN-6-12.pdf

Part Two

FERTILITY AND PREGNANCY

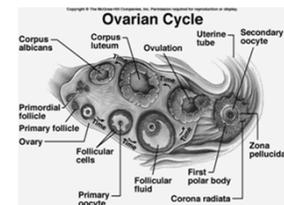
Measuring ovarian reserve

- FSH
 - Made by the brain, it controls the ovaries.
 - **Not reliable test if done when on hormones
 - High levels mean the ovary is not responding to the signal
 - Normal <8
 - Diminished ovarian reserve 9-40 but still getting periods
 - Early menopause >40 with no periods



Measuring ovarian reserve

- AMH (anti-Mullerian hormone)
 - Made by the cells around the developing egg in the ovary
 - **Can do test while on hormones
 - Higher levels = higher numbers of eggs in the Ovary
 - Normal AMH levels in a young woman under 30: ~1-8
 - <0.14 or "undetectable" means very low egg count, but some women may still have regular periods despite having low AMH levels.



Measuring ovarian reserve

- Antral follicle count (AFC)



- Normal follicle count in young women:
~10-20 total

Fertility

- The probability of pregnancy occurring naturally is much lower in classic galactosemia
 - Women stop ovulating regularly or altogether (essentially run out of eggs in the ovary – have *diminished ovarian reserve* or *primary ovarian insufficiency*)
 - Hormone replacement will give anyone regular periods but doesn't enhance fertility or change her egg count

Fertility

- What are the chances of getting pregnant naturally?
 - If having regular periods on her own with normal FSH and AMH: *should be similar to the average woman her age*
 - If having regular periods on her own but FSH and/or AMH are abnormal: *time she can conceive may be shorter, at risk for early menopause.*
 - Having no periods on her own with a high FSH: *probably about 5-8% lifetime chance*

Preserving fertility

- As a baby/child:
 - No known intervention available.
 - Removing an ovary early is highly experimental and not advisable unless part of a research protocol.
 - If her AMH and FSH are normal, she *may* be able to preserve eggs after puberty/adolescence (however, if her testing is normal, she may be one of the few with normal future fertility anyway)

Preserving fertility

- As a young adult:
 - Limited options if she already has profound diminished ovarian reserve
 - If she has normal to relatively normal ovarian reserve, she *could* opt to do "oocyte cryopreservation" to set aside eggs until she is ready to conceive (however, she may have normal fertility if her testing is completely normal).

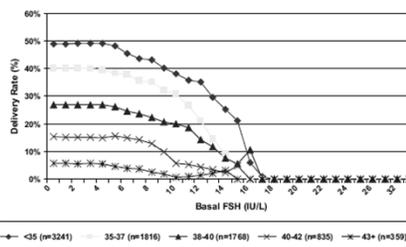
Oocyte cryopreservation (Egg freezing)

- Performed the same way a woman does in vitro fertilization:
 - Injectable hormones are given for 2-3 weeks to stimulate multiple eggs to develop
 - The eggs are then retrieved using a long needle through the vagina guided by ultrasound (under light anesthesia)
- No guarantee that it will result in a pregnancy
 - Largely depends on the number of eggs retrieved (which may be very low in a woman with classic galactosemia)
- Still considered experimental by the American Society of Reproductive Medicine (ASRM)
- Expensive (~\$10k), rarely covered by insurance

Why doesn't IVF work when the egg count is low?

- IVF relies on a woman's ability to make lots of eggs (ideally 10-20 at a time)
- Not all eggs will fertilize, not all fertilized eggs will divide into good quality embryos, not all embryos will implant and become a pregnancy
- Women with high FSH levels, make less eggs and have lower chances of pregnancy with IVF

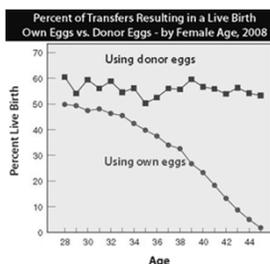
Influence of Age and FSH on IVF



Source: Threshold values for FSH screening in IVF. Fertil Steril 2008.

Egg donation

- The uterus appears to be normal in classic galactosemia
- Egg donors can be anonymous or someone you know (ideally <35)
- Very effective
- Costly ~\$18-25k



Hormone replacement while trying to conceive

- There are many options but my preference is:
 - Estradiol patch
 - Lower risk of blood clots than oral estrogen or birth control pills
 - Prometrium
 - Very similar to the progesterone a woman makes when she ovulates naturally
- Safe to conceive on if it does happen naturally

Hormone replacement when pregnancy is not desired

- Oral contraceptives are effective hormone replacement therapy but *not necessarily* effective birth control in women with high FSH levels
- Better options:
 - Oral contraceptives + Condoms
 - Mirena IUD

Resources

- www.rachelswell.org (POI support)
- www.cdc.gov/art (IVF clinics and their success rates, egg donation)