Ovarian function in classic galactosemia:

a research update from the Fridovich-Keil lab

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*no conflicts of interest to disclose

In this breakout session…

· What we <u>know</u> and what we <u>don't</u> know about ovarian function in classic galactosemia.

   <u>new data shed light on</u>:
   · timing: when does the "problem" first begin? Is it consistent or does it wax and wane?
   · biomarkers: what can we learn from AMH and FSH at different points in a girl's life?
   · predictors of outcome?

Want to hear more about clinical practice and options relating to puberty and fertility for girls and women with classic galactosemia?

 Saturday 11:15am-12:15pm:

   <u>POI and fertility in galactosemia</u>, with
   • Dr. Jen Badik (a pediatric endocrinologist) and
   • Dr. Jessica Spencer (a fertility specialist)

What do we know?

• >80% of girls and women with classic galactosemia experience premature ovarian insufficiency (POI).

• For some girls the defect is PRIMARY, meaning they need exogenous hormones to enter or complete puberty.

• For other girls and women the defect is SECONDARY, meaning they achieve spontaneous puberty, but then stop cycling before age 40, sometimes before age 20.

What do we NOT know?

• For those GG girls and women who will experience POI, at what age do their ovaries become functionally different?

• Is the difference permanent or does it wax and wane?

• What factors distinguish the 10-20% who demonstrate apparently normal ovarian function as young women from the >80% who do not?
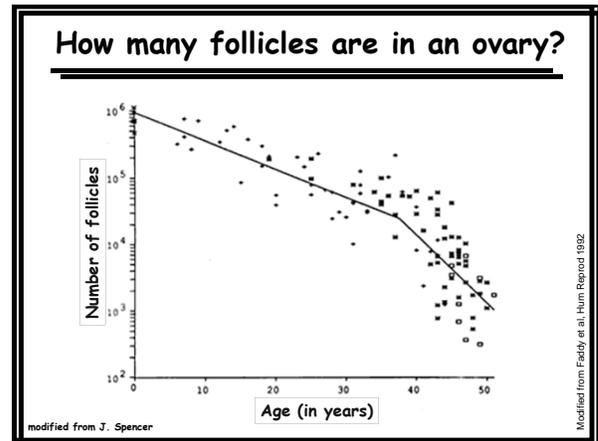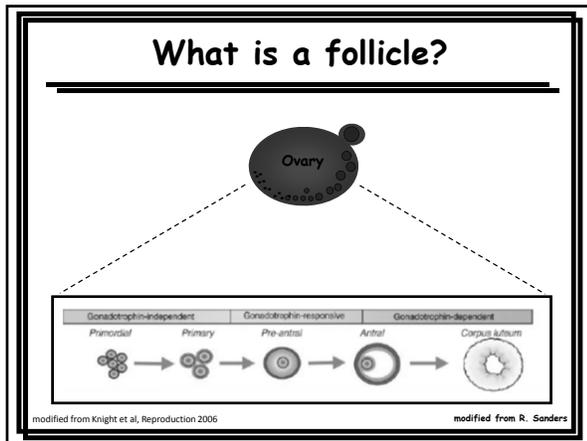
• Mechanism?

How Healthy Ovaries Work
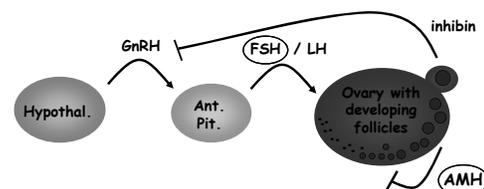
Hypothalamic-pituitary-ovarian (HPO) axis

| birth to ~18 months | active |
| 18 months to peripuberty | inactive |
| peripuberty and beyond | active |

modified from R. Sanders

What is a follicle?

modified from Knight et al, Reproduction 2006

modified from R. Sanders

How many follicles are in an ovary?

modified from J. Spencer

Modified from Faddy et al, Hum Reprod 1992

How can we assess ovarian status NONINVASIVELY?

- monitor relevant hormone levels in the blood (e.g. estradiol, FSH, AMH)

- ultrasound to measure ovarian size and to count the antral follicles (big enough to see by ultrasound)

Follicle Stimulating Hormone (FSH)

www.medscape.com
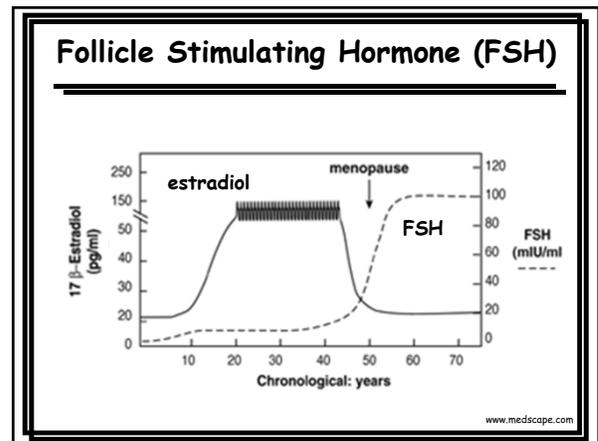
Anti-Müllerian Hormone (AMH)
(*aka* Müllerian Inhibiting Substance, MIS)

♂
- expressed at VERY HIGH levels in prenatal and postnatal boys
- prevents development of female "plumbing"

♀
- expressed in primary, preantral, and early antral follicles
- serum levels are relatively high in young girls and women, and decline over time as a woman approaches menopause

Serum anti-Müllerian Hormone (AMH, pmol/L) in 926 healthy infants, girls, and women in Denmark

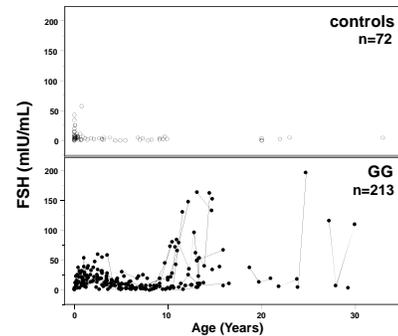Hagen et al. JCEM 2010
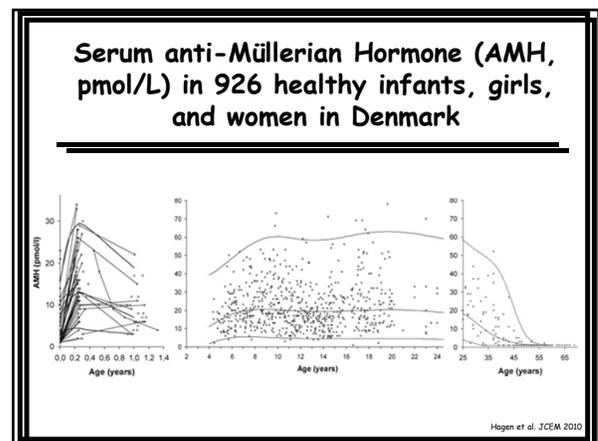
FSH vs. AMH

FSH
- Unreliable in very young girls
- Varies through the menstrual cycle
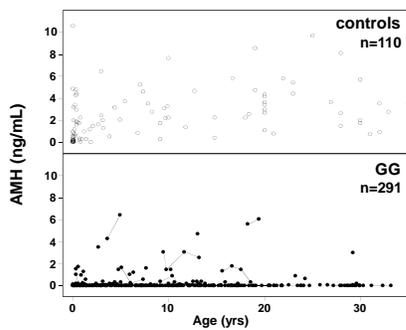- Varies in response to hormone therapy

AMH
- Reliable at all ages beyond about 2 months
- Unaffected by menstrual cycle
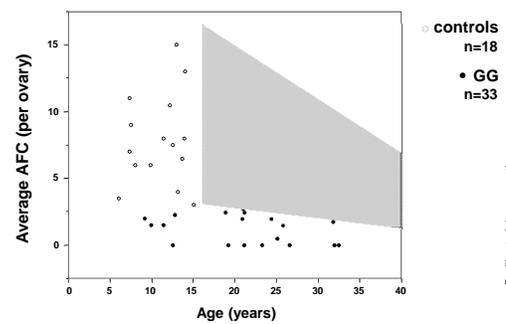- Unaffected by hormone therapy

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FSH in GGs and controls

Spencer, Badik, et al. in preparation

AMH in GGs and controls

Spencer, Badik, et al. in preparation

Antral follicle count by age

Spencer, Badik, et al. in preparation

So... what have we seen?

- >80% of GG girls have unusually low AMH, even as infants
- AMH levels in the low range tend to stay low; AMH levels in the normal range sometimes stay normal and sometimes decrease
- the HPO axis seems to remain active in some GG girls much longer than in controls (e.g. elevated FSH in a 4 year old)
- antral follicle counts (and ovarian volumes) in most GG girls are unusually low

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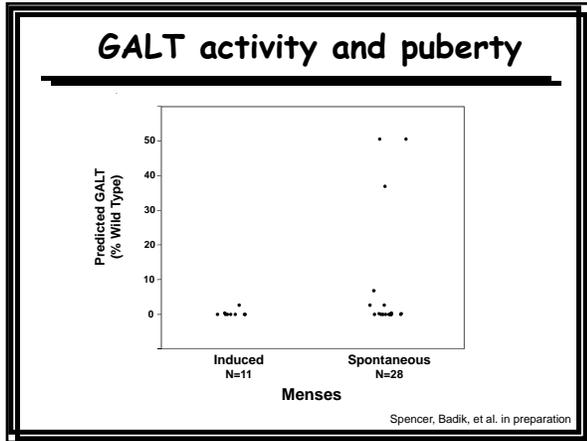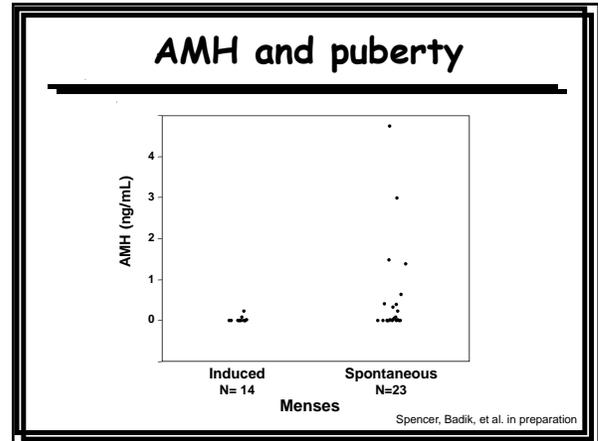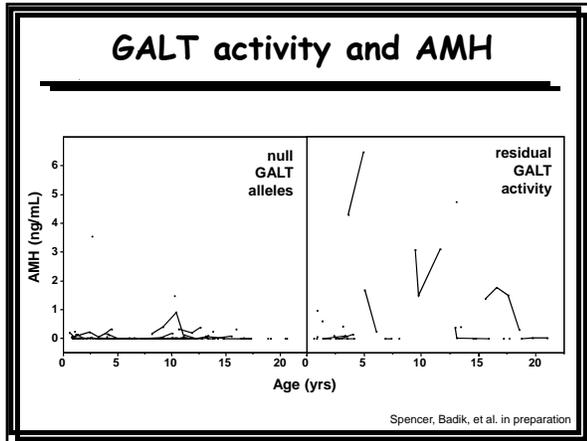## Is predicted residual GALT activity a predictor of outcome?

Some GALT alleles with residual activity detected in yeast		Some GALT alleles with no residual activity detected in yeast	
S135L	L195P	Q188R	R204X
D136H	P183T	F171S	Q206R
D98N	A78T	D98H	R148P
D197G	Y209C	M142K	5kb del

Gleason et al. in preparation

GALT activity and AMH

Spencer, Badik, et al. in preparation

AMH and puberty

Spencer, Badik, et al. in preparation

GALT activity and puberty

Spencer, Badik, et al. in preparation

What does this tell us about mechanism, and what does it mean for girls and women with classic galactosemia?

Thanks to you all for your attention, to the many wonderful volunteers who made this work possible, to NIH for funding this project, and to the outstanding colleagues who did the work.