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Hormonal Markers of Ovarian Reserve

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What is Ovarian Reserve?

The pool (number) of antral follicles in the ovaries that are capable of growing in the presence of gonadotrophins.

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Markers of Ovarian Reserve

Classical Markers

Basal FSH/LH (day 2/3)

Oestradiol

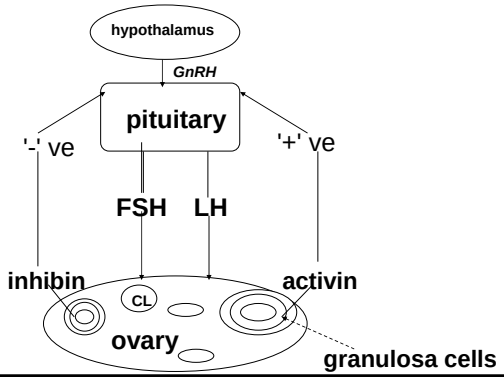
New Markers
Inhibin B
Anti Mullerian hormone (AMH)
Antral Follicle count

Dynamic tests
Clomiphene citrate challenge test
GnRH-analogue stimulation test
Ovarian Stimulation test

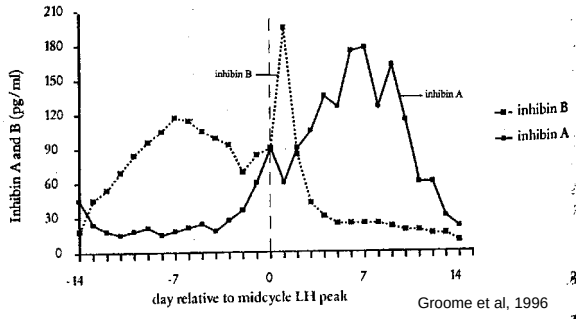
Inhibins

- Inhibins are heterodimeric glycoproteins with dissimilar subunits linked by disulphide bonds.

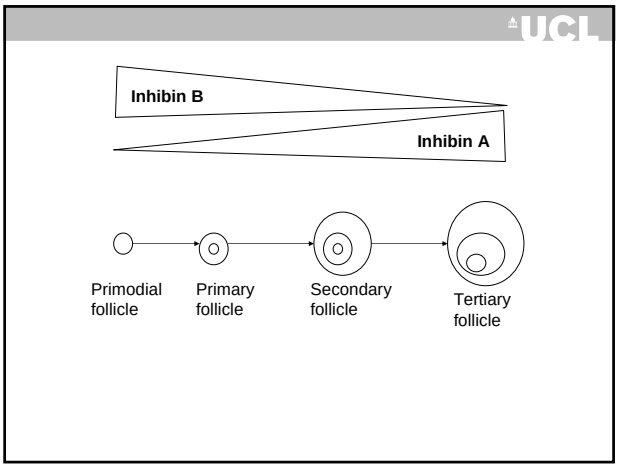
Endocrine role of inhibin in women



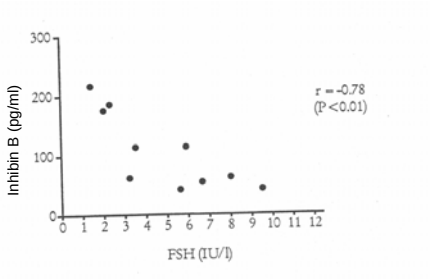
Inhibin A and B in the Menstrual cycle



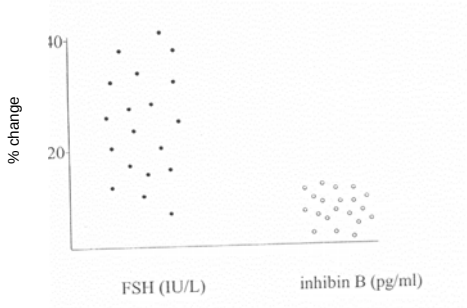
Groome et al, 1996



Relationship between day 5 inhibin B and FSH in fertile women



Inter cycle variation in fertility patients



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Anti Mullerian Hormone

- AMH is a homodimeric glycoprotein linked by disulphide bonds.
- A member of TGF-β family
- Causes regression of the Mullerian ducts during male fetal development
- In females, AMH is produced by granulosa cells of ovarian follicles
- Hormonal control of AMH secretion is unclear

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AMH

Possible Functions ?

- AMH may affect the transition of primodial follicles into growing follicles
- AMH may be involved in the recruitment of FSH sensitive follicles in the early antral stage

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Are AMH and inhibin B useful in predicting ovarian response to gonadotrophin stimulation?

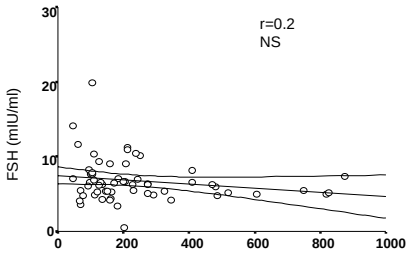
Ovarian Stimulation test

- Retrospective study using samples from 70 patients who had IVF treatment
- Basal blood sample collected on day 3
- Patients were given 300IU/l Gonal F (recombinant FSH) on day 3
- Blood sample was taken on day 4: a day after FSH stimulation

Measurements
Serum FSH, E2, inhibin B and AMH
Antral follicle count

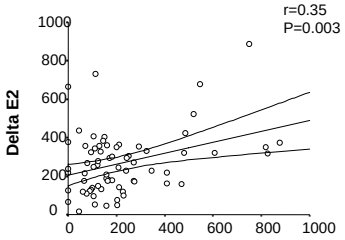
Muttukrishna et al 2005 (BJOG, 112:1384-1390)

Day 3 FSH vs number of eggs collected



Eggs collected x1000/number of ampoules of FSH

Delta E2 (day 4-day 3) vs number of eggs collected



Eggs collected x1000/number of ampoules of FSH

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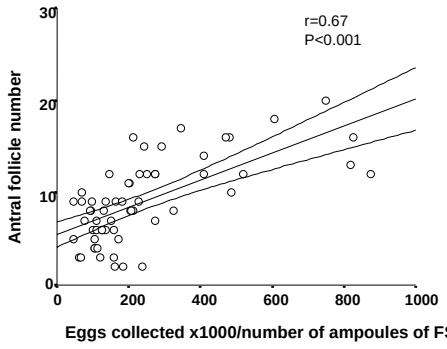
Antral follicle count vs number of eggs collected



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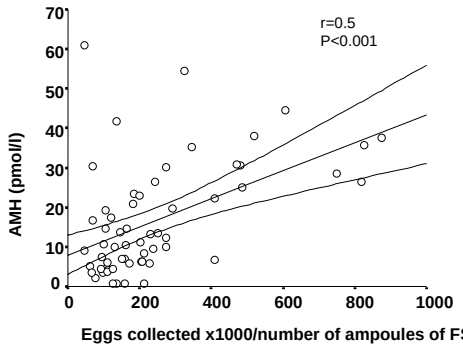
Day 3 AMH vs number of eggs collected



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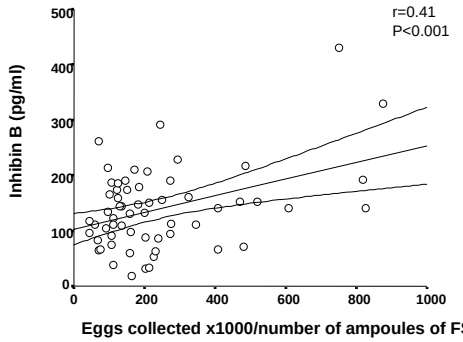
Day 3 inhibin B vs number of eggs collected



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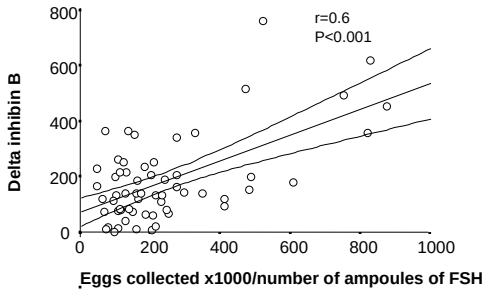
Delta inhibin B (day 4-day 3) vs number of eggs collected



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Efficacy of Combined Markers

Markers vs eggs collected/amp FSH	Regression co-efficient	Significance
Day 3 FSH + delta E2	0.37	P<0.01
Day 3 FSH + delta E2 + AFC (antral follicle count)	0.7	P<0.001
Day 3 FSH + Delta E2 + AFC + delta inhibin B	**0.8**	**P<0.001**
Day 3 FSH + delta E2 + AFC + AMH	0.73	P<0.001
AFC + delta inhibin B	0.78	P<0.001
AFC + day 3 AMH	**0.7**	**P<0.001**
AFC+ delta inhibin B+ day 3 AMH	0.78	P<0.001

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Conclusion 1

•Antral follicle count is the best single marker of ovarian reserve (r=0.67, P<0.001)
Problem: It is subjective

•The best combined markers of ovarian reserve in OST are, AFC + basal FSH + delta E2 + delta inhibin B (r=0.8, P<0.001)

•The best combined basal markers are, AFC + AMH (r=0.7, P<0.001)

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Predicting Poor Ovarian response

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Prospective study: 69 patients recruited

Blood samples: day 5/6 of an untreated menstrual cycle

Hormones measured: FSH, inhibin B and AMH

Outcome: Response to a subsequent gonadotrophin stimulation cycle

Muttukrishna et al, 2004 (BJOG, 111:1248-1253)

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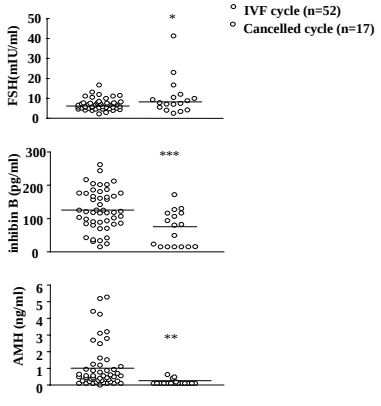
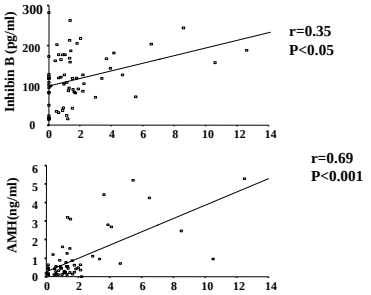


Predicting Poor Ovarian response



(Number of eggs collected x1000)/units of gonadotrophins used for stimulation

Conclusion

AMH is the best single marker to predict poor response in gonadotrophin stimulation

Recent reviews on the new markers……..

•Verhagen et al, 2008 (Human Reproduction update 14:95:100)

Reviewed 11 studies and concluded that poor response was predicted but not pregnancy rate. Sensitivity of prediction of Poor response:39-97% and specificity:50-96%.

Conclusion: Multivariate models were similar to AFC in predicting ovarian response.

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What other factors affect Ovarian reserve?

Environment ?

•Adult Migrant Banglasdeshi's in London have lower levels of salivary progesterone levels compared to white controls living in the same area (Nunez et al, 2007)

Ongoing prospective study

•Adult migrant women from Bangladesh, White controls and Sendentees living in Bangladesh

•Age 35-55 years

•Blood sample taken day 5/6

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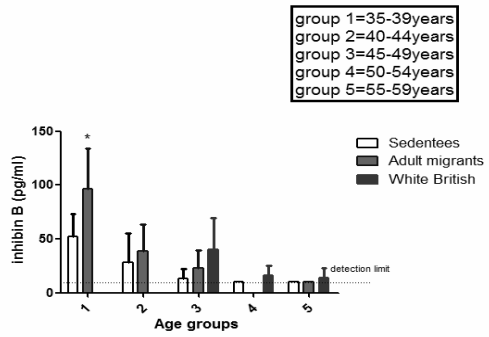

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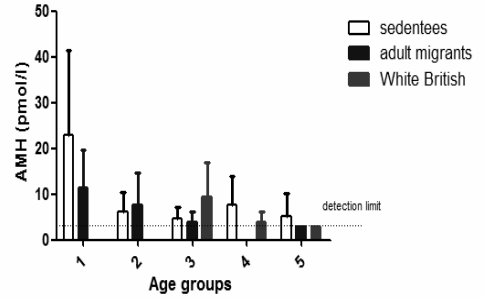

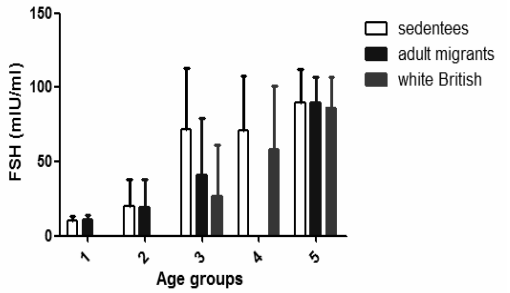

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