

An approach of ovarian reserve test



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Objective

To review the literature regarding diminished ovarian reserve, the screening techniques that are currently available or under investigation and the appropriate application in clinical practice

Summary



- Introduction
- Objective
- Concept
- Age
- FSH
- LH and Estradiol
- The Citrate clomiphene test
- Inhibin
- Antral follicles count
- Ovarian volume
- Discussion
- Conclusion
- Recommendations for screening

Concept



The ability of a woman to conceive in the absence of specific pathophysiologic changes in her reproductive system determined by her reproductive potential.Scott 1995

This capacity declines with age



Physiological reasons.

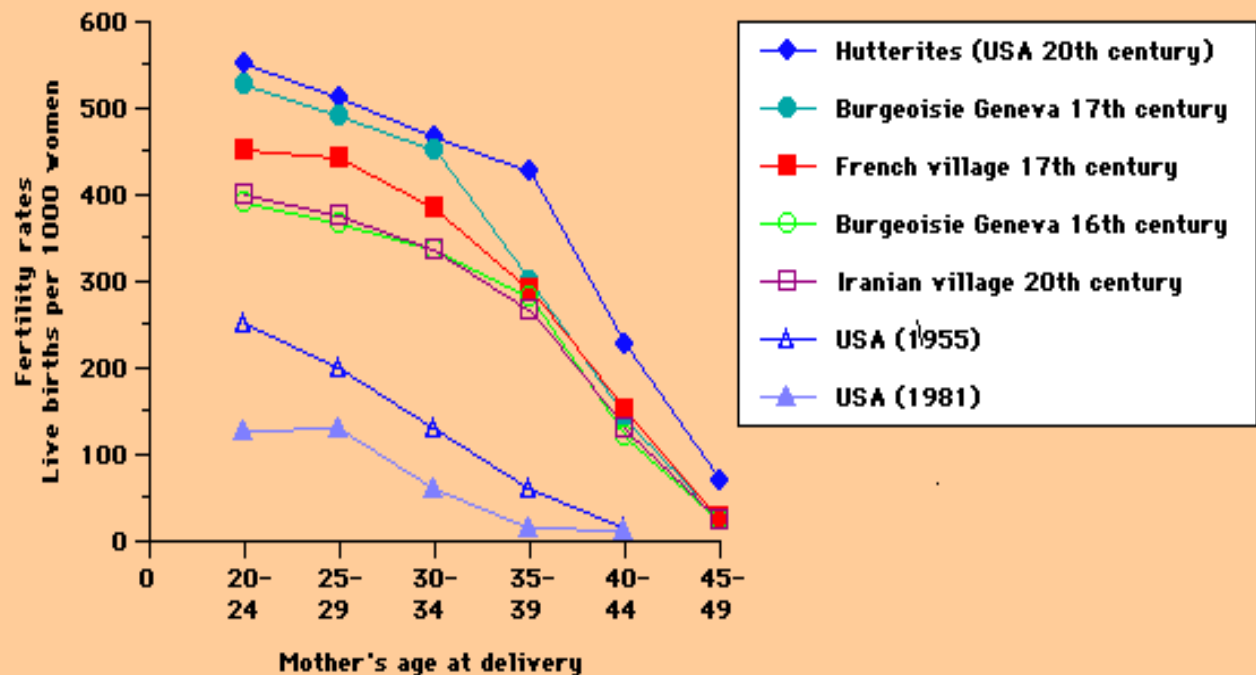
Exponentially declines in the number of follicles.

Inhibin ?

E2 ?

FSH ?

Age



Fertility rate in women declines with age Fertility rates in different groups of women from the 16th to the 20th centuries. The fertility rate declined with age in all the groups. (Redrawn from Maroulis, GB, Seminars Reprod Endocrinol 1991; 9:165.

Age



- . Age-dependent decline in pregnancy and livebirth rates.

Pearlstone 1992, Toner 1993, Magarelli1996.

Age

Table (1) Basal FSH and ovulation in women ≥ 40

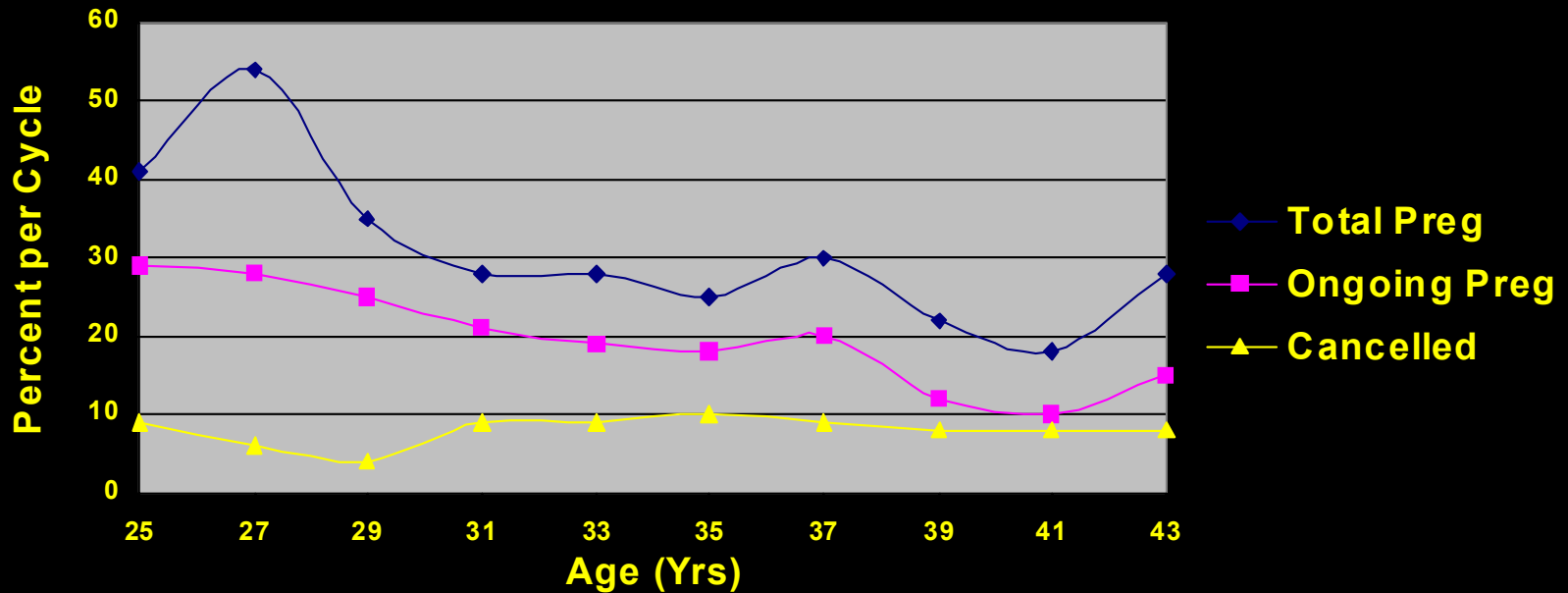
	AGE			
	<30	30 to 34	35 to 39	≥ 40
	(n=273cycles/73 women)	(n= 512 cycles/ 136 women)	(n=560 cycles/ women134)	(n=402 cycles/ 85 women)
PR (95% CI)*	13.6(9.5to 17.7)	9.6(7.0 to 12.2)	7.7(5.5 to 9.9)	3.5(1.7 to 5.3) ?
Livebirth rate (95% CI)*	11.4(7.6 to 5.2)	8.2 (5.8 to 10.6)	5.9 (3.9 to 7.9)	1.2(0.1 to 2.3) ?

* Percent per cycle

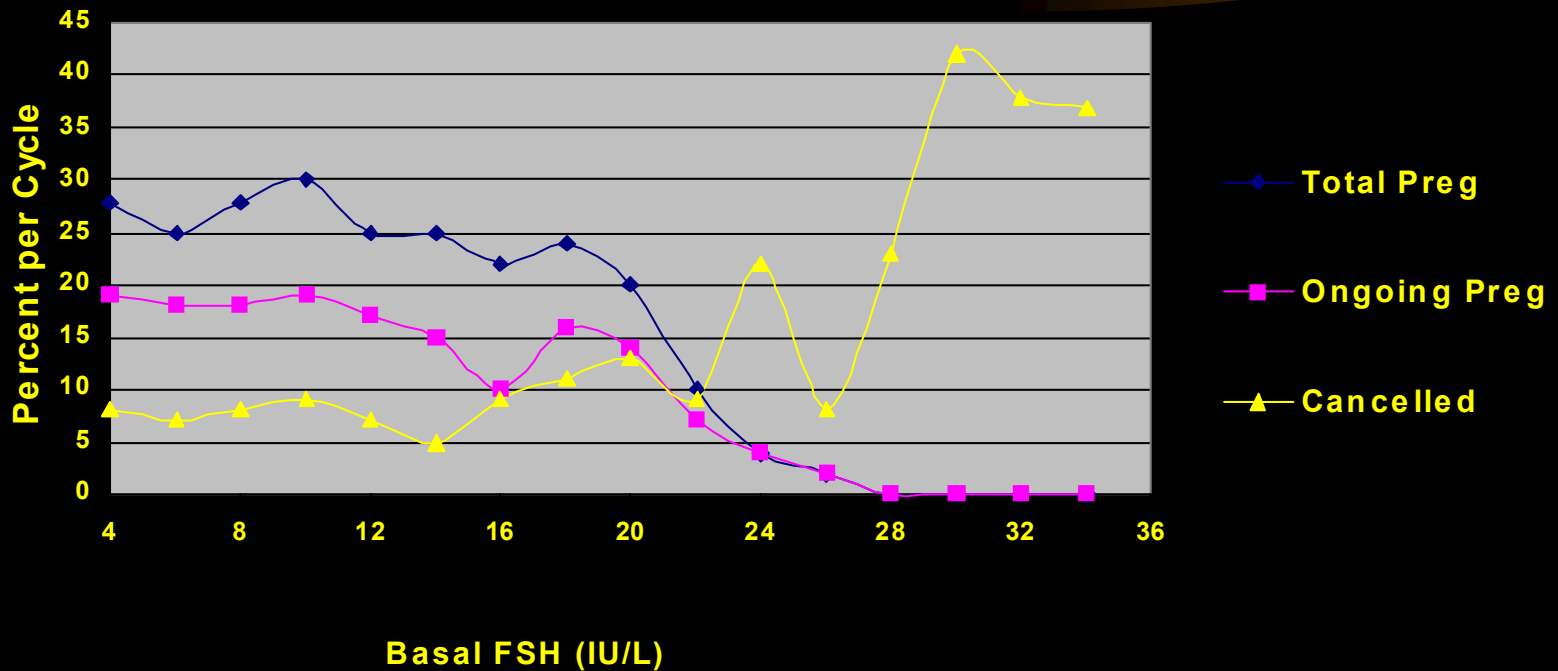
? P < 0.001 compared with all other age groups

Age

Pregnancy and cancellation rates in 1,478 IVF cycles divided by age
(adapted from Toner et al.)

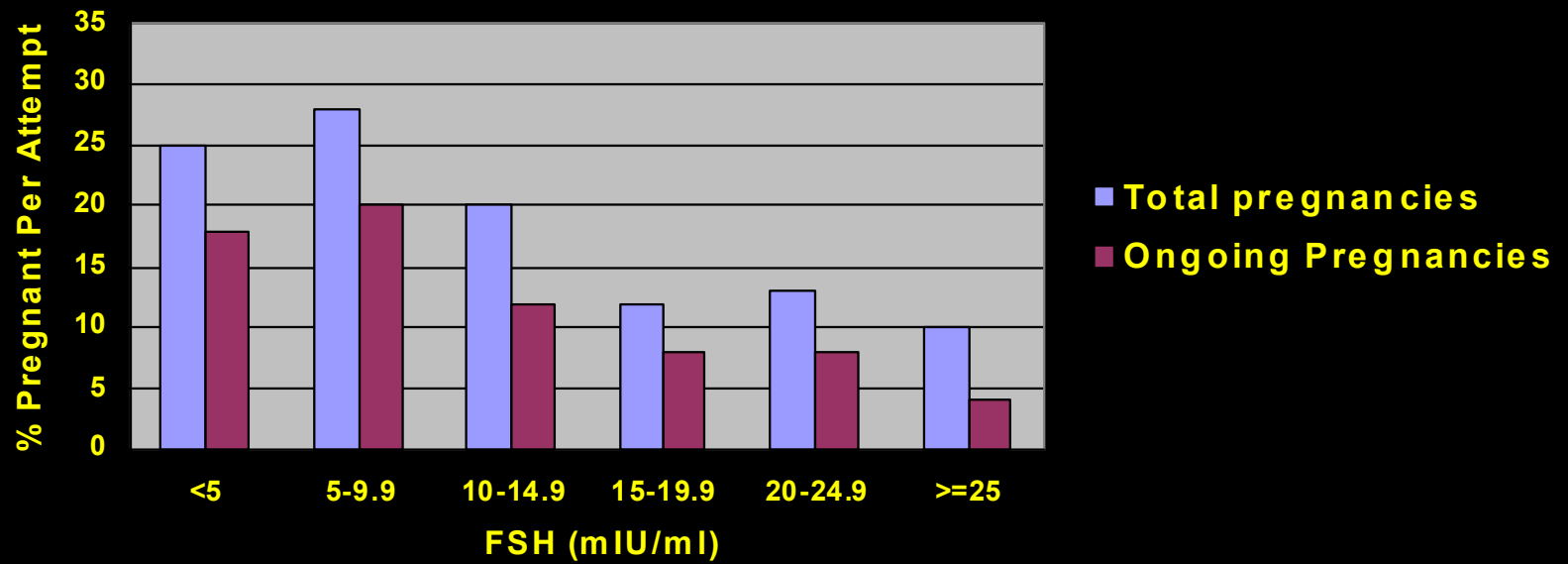


Pregnancy and cancellation rates in 1,478 IVF cycles divided by FSH (adapted from Toner et al.)



FSH

FSH



FSH

Based on these results, there are three distinct patient populations:

- **low (<15mIU/ml).**
- **moderate (15 to 24.9 mIU/ml).**
- **high (≥25mIU/ml)**

basal day 3 FSH concentrations are defined by their significantly different chances for conception and delivery

Pregnancy Rates With In Vitro Fertilization Based Day 3 FSH Concentrations

Basal FSH	No.	Pregnant	Ongoing	Miscarried
mlU/ml		No.(%)	No.(%)	No.(%)
<15	541	130(24.0)	92(17.0)	38(29.2)
15 to 24.9	161	22(13.6)	15(9.3)	7(31.8)
≥25	56	6(10.7)	2(3.6)	4(66.6)

Scott et al Fertil Steril Vol 51, No 4 April, 1989

Intercycle variability in basal FSH levels.

- <15 mIU/mL very low variation, mean value 2.6 ± 0.2 mIU/mL.
- Patients with elevated FSH levels, high variation mean value 7.4 ± 0.9 mIU/mL.

Intercycle variability in basal FSH levels.

- In the same study, there are patients with normal or intermediate range during one cycle and elevated in another.
- Maybe these patients needed to be monitored from cycle to cycle and then stimulated in the cycle when the FSH levels were normal.

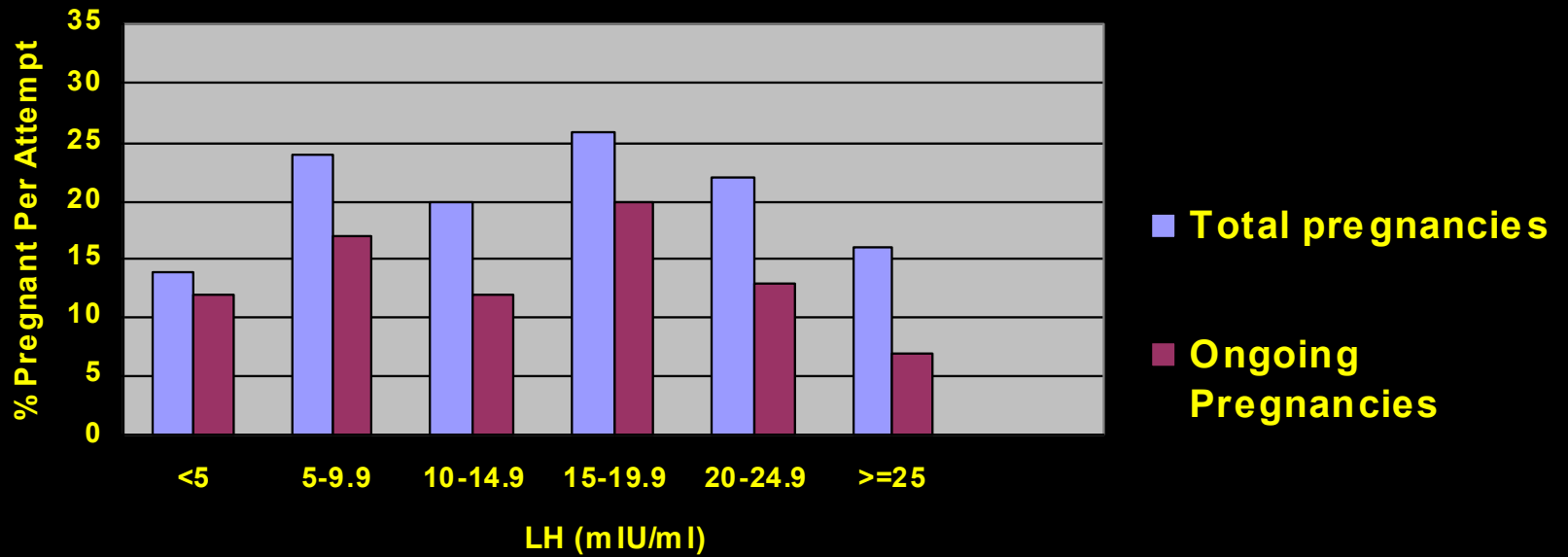
LH and E2

- Evaluation of basal E2 and LH and pregnancy rates revealed no consistent relationship.
- The individual analysis FSH, LH and E2 levels and pregnancy outcome

LH

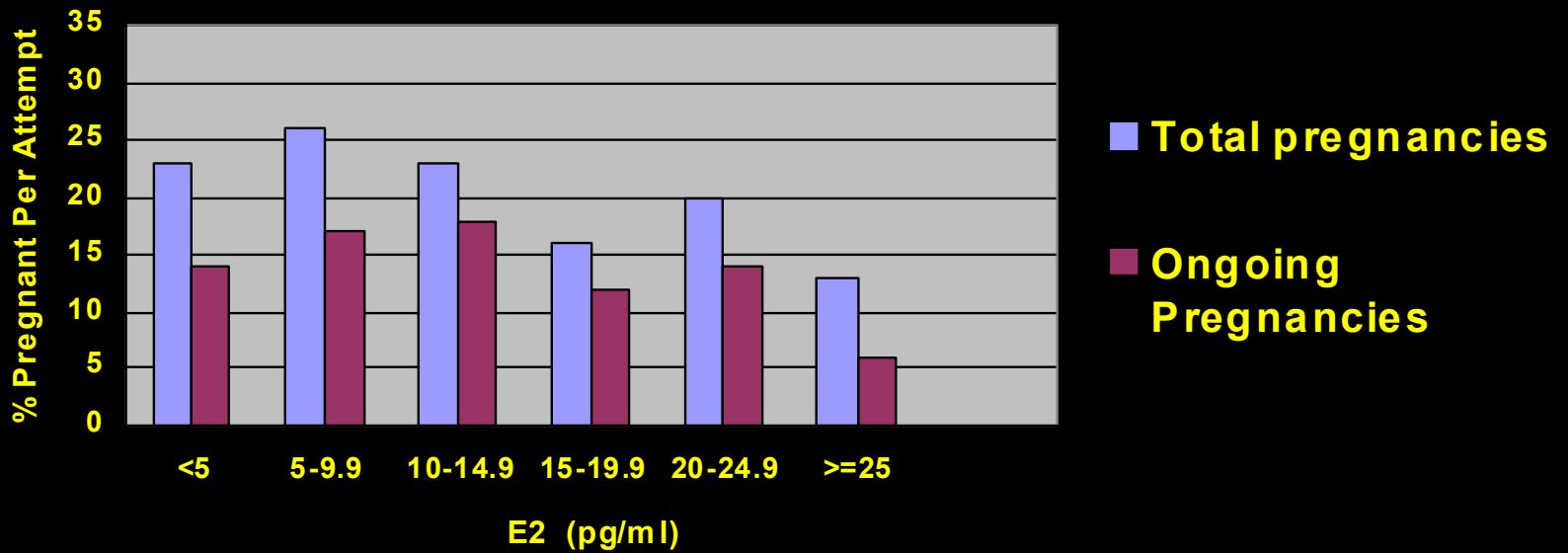


LH



E2

E2



The clomiphene citrate test.

- Measuring serum FSH concentrations on cycle day 3 (basal).
- Administration of 100 mg of clomiphene citrate on day 5 to 9.
- Measuring serum FSH concentrations on cycle day 10.

Hypothesis

In women with normal ovarian reserve , the overall increase in estradiol and inhibin production by developing follicles should be able to overcome the impact of clomiphene citrate on the hypothalamic-pituitary axis, and suppress FSH levels into the normal range (10 Day cycle).

Clomiphene citrate test

Predictive value.



- Predictive value of an abnormal test for failing to become pregnant was 100% Tanbo 1989, Loumayed 1990.
- Predictive value of an abnormal test for cycle cancellation was 85% (Tanbo 1989) and 31.2%(Loumayed 1990).

Scott, 1993.

- The authors studied 236 women from the general infertility population and found:
 - Abnormal clomiphene citrate test 10%.
 - Incidence of abnormal test rose with age.
 - Pregnancy rates in abnormal citrate clomiphene test was 9%.
 - Pregnancy rates in normal citrate clomiphene test was 43%.
 - Only 7 of the 23 patients with abnormal test had elevated day 3 FSH levels.

Clomiphene citrate test.



It is a test that unmask patients who might not be detected by basal FSH screening alone.

Inhibins

Inhibins are multifunctional molecules(Petraglia 1993):


- Involved in the control of the pituitary gonadotropin secretion, selective control of the secretion of follicle stimulating hormone (FSH) during the menstrual cycle.
- Ovarian follicular development.
- Placental function.
- Spermatogenesis.
- Inhibins are currently recognized as paracrine ovarian regulators and have multiple paracrine effects in the utero - placenta unit.

Sources



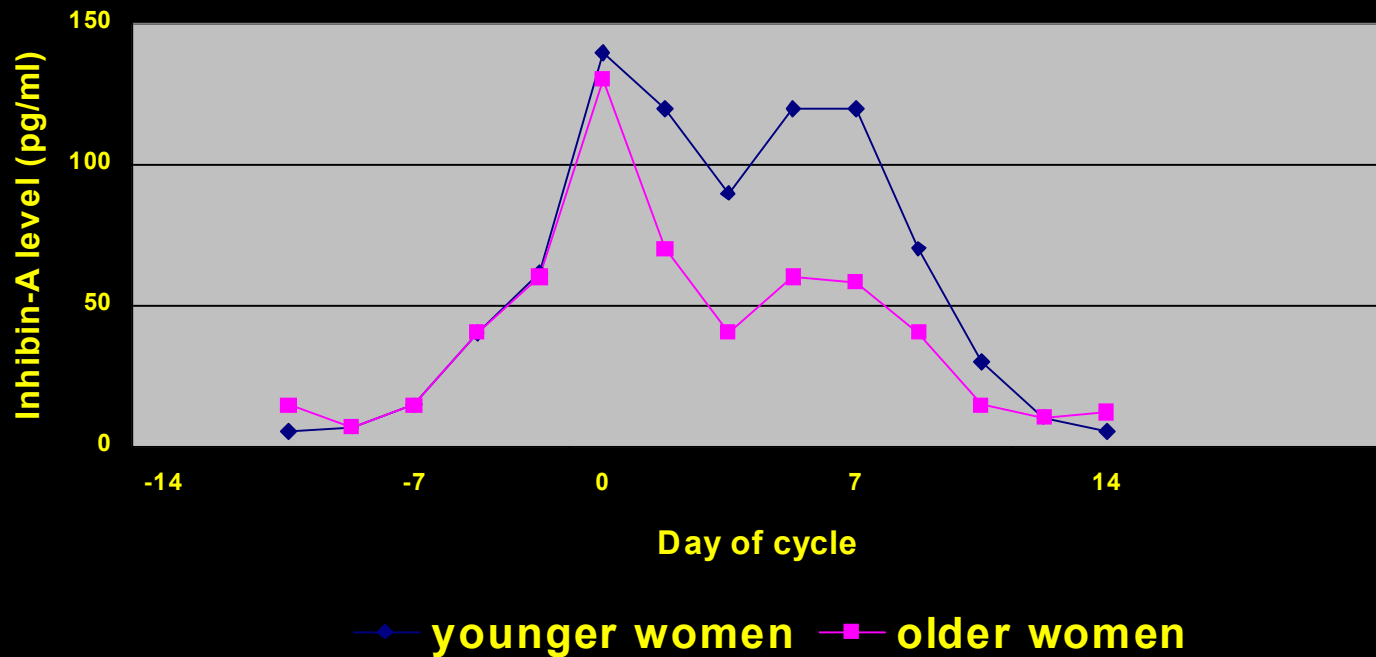
- Granulosa and theca cells (ovary).
- Sertoli cells (testis)
- Extragonadal tissues (bone, marrow, brain, pituitary, liver, adrenal).

Patterns




Inhibin A : circulating levels are low in the early state of the follicular phase and rise from late follicular phase after a short indentation coinciding with the LH peak.

Patterns of inhibin A



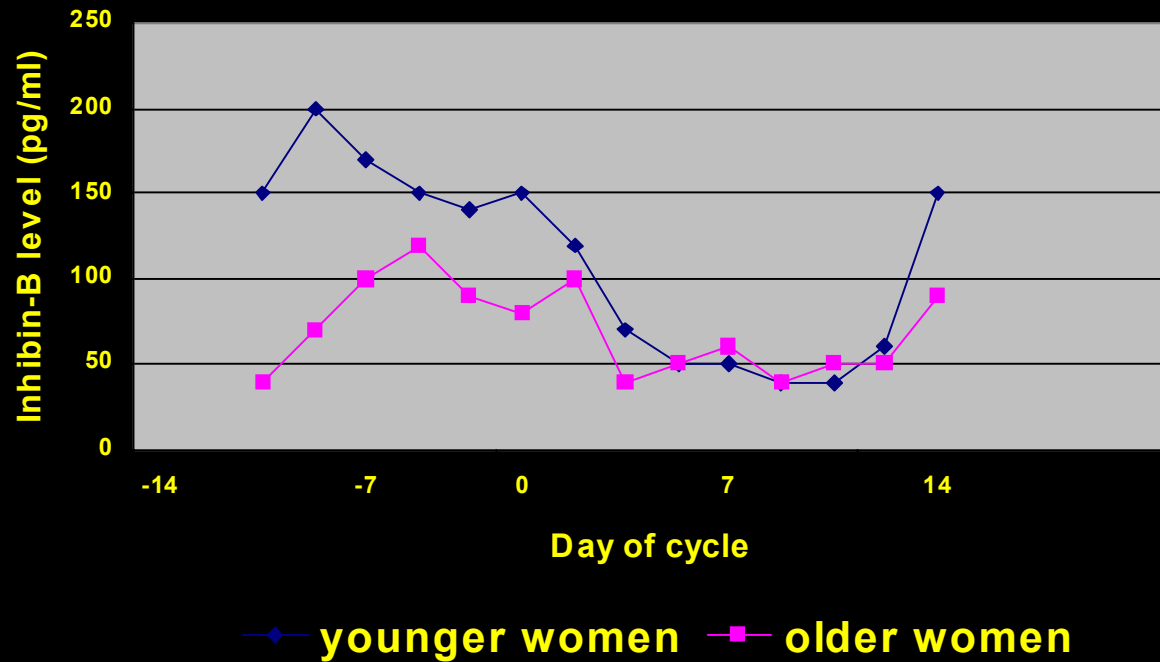
Patterns



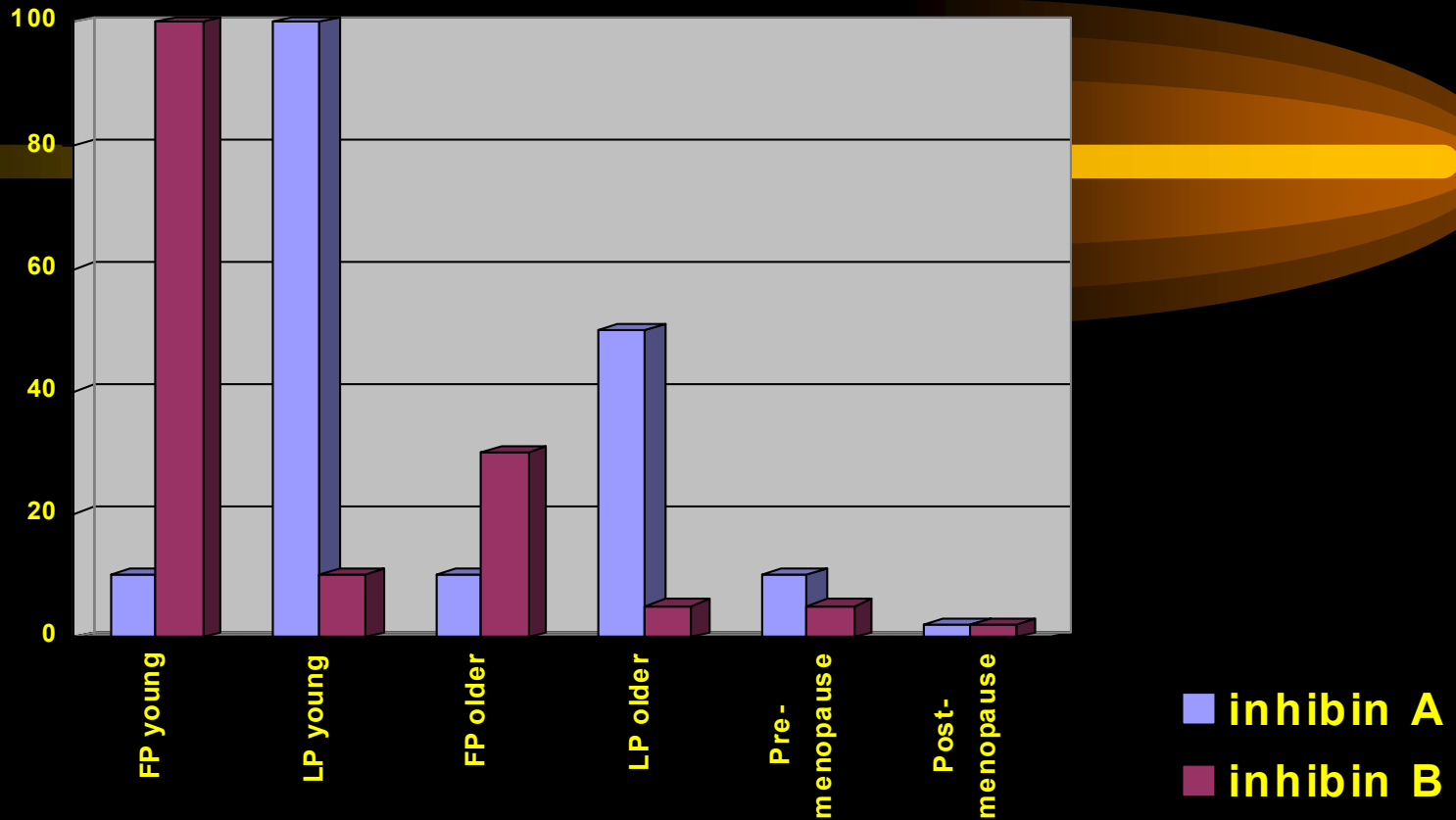
Inhibin B: rises sharply from the early follicular phase, with a peak following the FSH rise and progressive fall during the remainder of the follicular phase.

Another peak of it is observed two days after the midcycle peak followed by a rapid decrease during luteal involution

Patterns of inhibin B



Changes in serum levels of inhibin during menstrual cycle, reproductive aging, pre- and post menopause



Inhibin B

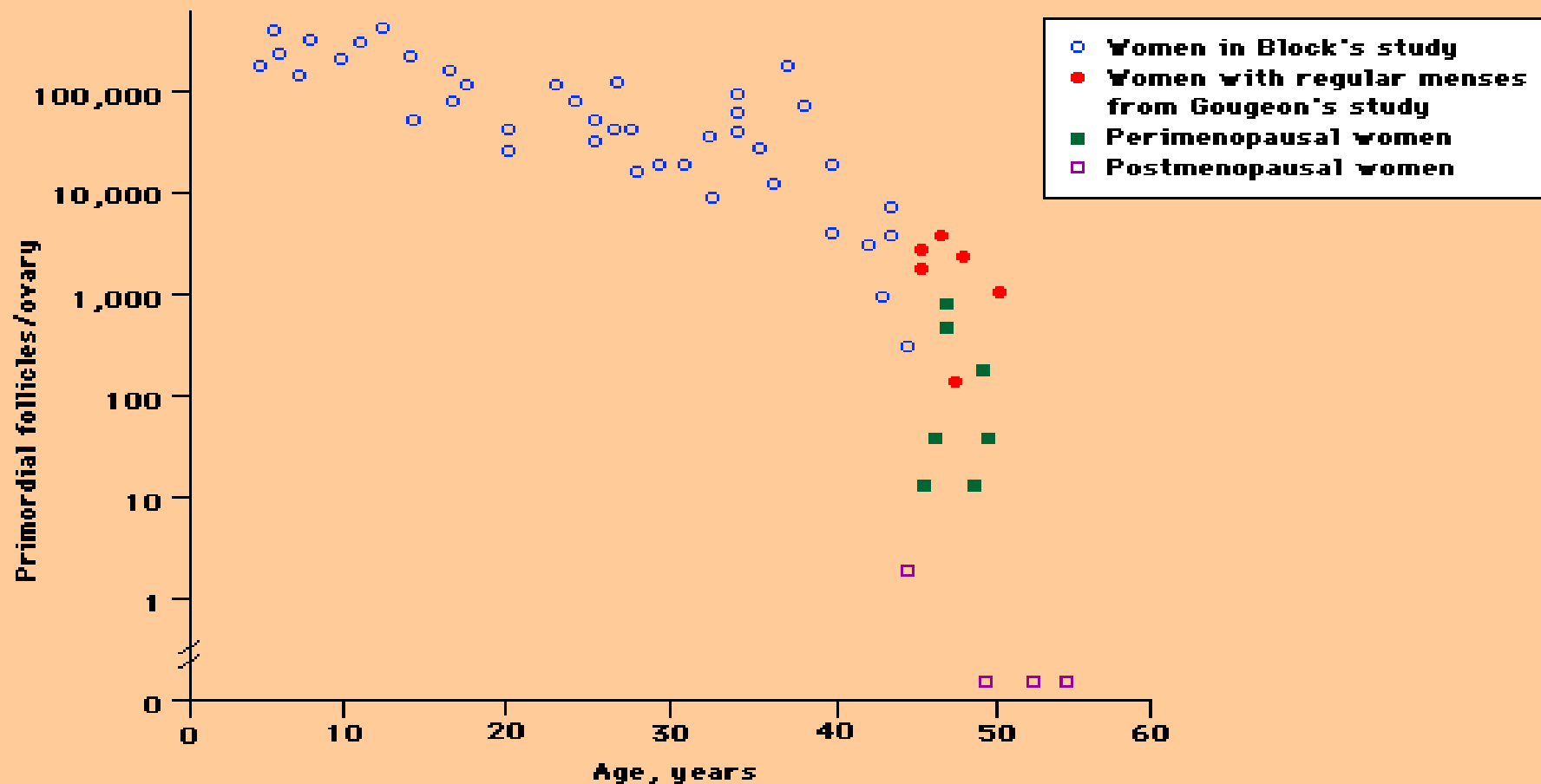
- Predicts ovarian reserve in older infertile women undergoing the citrate clomiphene test (CCT):
 - Abnormal CCT? ?Inhibin 3DayB ?3dayFSH
E2 levels normal
- Inhibin B day 3 decreases before a rise in the day 3 FSH.
- Early indicator of ovarian function??

*Antral follicle count by
transvaginal ultrasonography.*



- Decrease in the quality of oocytes.
- Gradual reduction in the number of primordial follicles.

Declining follicle number with age



Declining follicle number with age A comparison of the relationship between age and primordial follicle number in Block's study of 44 girls and women aged 7 to 44 years with that of Gougeon's study of women aged 45 to 55 years. Follicle depletion appears to accelerate in the decade preceding menopause. (Data from Block, E, *Acta Anat* 1952; 14:108 and Gougeon, A, *Contraception Fertile Sexual* 1984; 12:527.)

Antral follicle count by transvaginal ultrasonography.

- The number of primordial follicles appears to be correlated with the number of growing follicles(Gougeon, 1984).
- The decline in primordial follicle reserve leads to a decrease in size of the antral follicle cohort (Schefer, 1999)
- manifests as a reduction in the number of dominant follicles developing in response to high doses of exogenous gonadotropins.(Jacobs, 1990)

Antral follicle count by transvaginal ultrasonography.

Parameter	No. of antral follicles		P value
	≤ 3	> 3	
Mean age (y) (±SD)	36.8 ± 2.9	36.3 ± 3.8	< 0.0001
Mean day FSH levels (mIU/mL) (±SD)	12.7 ± 8.5	7.1 ± 5.6	< 0.0001
No. of pregnancies per attempt (%)	0/76 (0)	21/57 (36.8)	< 0.0005
No. of ongoing pregnancies per attempt (%)	0/76 (0)	15/57 (26.3)	< 0.01

Antral follicle count by transvaginal ultrasonography.

- Overall conception rate was higher for those with 4 follicles than for those with < 3 follicles (Chang, 1998).
- There is a relationship between follicle count, age < 40 years, serum day 3 FSH levels of < 10 mIU/mL. (Pache 1990.)

Ovarian volume

- Ovarian volume progressively decreases with age.
- The ovarian volume:
 - Formula prolate ellipse:
 - $0.523 \times \text{length} \times \text{width} \times \text{thickness}$.

Ovarian volume by decade of life

Decade	Mean Volume(cm ³)	Standard deviation	No. Of ovaries	95% confidence interval (cm ³)
1	1.7	1.4	19	0.2-4.9
2	7.8	4.4	83	1.7-18.5
3	10.2	6.2	308	2.6-23.1
4	9.5	5.4	358	2.6-20.9
5	9.0	5.8	206	2.1-20.9
6	6.2	3.6	57	2.1-20.9
7	6.0	3.8	44	1.0-15.0

Adapted from Cohen et al Radiology 1990; 177:189-192.

Ovarian volume and pregnancies rates

Ovarian volume mL	No. Of subjects	Age	Cancellation %	Clinical PR per initiate cycle %
Volume of smallest ovary				
<3	18	34.8	22	28
3 to 9	144	33.4	14	35
>9	26	32.7	0	46
Total ovarian volume				
<8.6	29	33.6	21	31
8.6 to 22.2	133	33.4	13	34

Syrop 1995

Discussion

Age related changes in sexual hormones during the intervening years probably because of the decline in oocyte quality and reduced number of follicles followed by a decrease in inhibin concentration and its loss would explain the elevated FSH with age despite the normal plasma E2 concentrations.

Discussion

- In any attempt to study variations in fecundity as a function of a woman's age two major problems are encountered:
 - the need to separate the influence of the woman's age from associated variables such as the pattern of coitus and the age of the husband.
 - the variable under study - the age of the woman - can itself result in bias, since time introduces a type of selection⁶⁶.

Discussion



- FSH
 - The intercycle variability of basal FSH has been reported.
 - There is a variation in FSH and E2 levels among laboratories despite the use of similar assay techniques.

Discussion

- **Clomiphene Citrate test.**
 - **Abnormal:** revealed PRs uniformly poor independent of patient's age.
 - **Normal:** with increased age, it revealed a significant diminution in pregnancy rates.
- The importance of considering patient's age even when CCT result are normal.

Discussion

- Antral follicle count and ovarian volume
 - Repeated cycle-cycle measurements of antral follicular count and ovarian volume revealed only moderate agreement.
 - A plausible explanation could be that the size of the follicle cohort varies among different cycles.

Conclusion



- Age is a determining factor for fertility.
- Elevated Day 3 FSH levels are highly predictive of diminished ovarian reserve.
 - The test is simple, inexpensive and routinely available.

Conclusion

- An abnormal CCT has excellent predictive value for diminished ovarian reserve.
 - It is quite specific
 - It is 2 to 3 times more sensitive than basal FSH.
 - The literature does not contain enough data to recommend omission of day 3 FSH.

Conclusion



- Transvaginal ultrasound is an easy method to complement other predictive factors of ovarian responsiveness.

Recommendations for screening.

Scott 1995

- All infertile woman over the age of 30 should be screened because ovarian reserve begins to diminish approximately at that time.
- Younger women with unexplained infertility should be screening because an abnormal test may approach 50% of these patients