

Ovarian Reserve, Female Age, and the Chance for Successful Pregnancy

James P. Toner, MD, PhD, Director, Donor Egg Program

Atlanta Center for Reproductive Medicine

100 Stone Forest Drive, suite 300

Woodstock, GA 30189 USA

(770) 928-2276

Jim.Toner@acrm.com

Summary

Both quantitative and qualitative factors regarding egg production are strong influences on IVF outcome. Markers of ovarian reserve such as basal FSH, CCCT, and antral follicle counts are good predictors of the quantity of eggs which can be induced to grow. However, the quality of those eggs seems better predicted by the age of the women. In women past age 40, current success rates are low overall, even in those who good ovarian reserve who make many eggs; at this age, quantity does not make up for quality. By contrast, young women with limited ovarian reserve can have good success rates despite their limited cohort of eggs, because the eggs themselves are of high potential; here quality matters more than quantity. The ramifications of these observations include the following: Diminished ovarian reserve should not be used as an exclusionary criterion in young women, because overall they still have satisfactory pregnancy rates, though their risk of cancellation is increased. In women past age 40, normal ovarian reserve testing is not reassuring because even reduced egg quality is likely to limit the opportunity for successful pregnancy no matter how many eggs are available.

Fifteen years ago Muasher and colleagues from the Norfolk IVF program reported that basal FSH levels predicted ovarian response and pregnancy outcome in IVF cycles [1]. Since then more than a hundred articles have sought to refine our understanding of the link between markers of “ovarian reserve” and pregnancy in ART. And while there have been important refinements to our original understanding of the concept of ovarian reserve, the essence of the initial message has only been confirmed in the numerous studies that followed. In this article we will consider the biological basis for the links among the markers of ovarian reserve, the reserve itself, and the pregnancy potential. We will also review the original and newer elements of this understanding.

Physiology of Ovarian Reserve

Women make all the eggs they will ever have before they are born. This supply begins to be depleted before birth, and continues until menopause, when the endowment is gone (Fig. 1). Most studies have suggested that the rate of egg loss is essentially constant over a women’s life span, although several reports have detected an accelerated rate of loss at around age 37 years on average. This means that at the beginning of every menstrual cycle, a relatively fixed proportion of all the remaining eggs becomes ‘recruitable,’ i.e., sensitive to gonadotropins. Given that the overall number of eggs in younger women is higher than at later years, the size of the ‘cohort’ of recruitable eggs in younger women is much larger.

As the size of the egg endowment decreases with age, certain predictable concomitants have been observed. These include physical manifestations, such as smaller ovaries and fewer antral follicles, but also hormonal events, such as elevations of basal FSH and

shorter follicular phases [2,3]. Morris [4] has confirmed that the number of visible antral follicles on ultrasound correlates with the actual number in the primordial follicle pool.

Another feature of follicle depletion relates to the expected pattern of FSH rise. While 'basal' (i.e., days 2 to 5 of the menstrual cycle) FSH fluctuates somewhat from cycle to cycle, we can distinguish 3 phases: 1. Up until the time when egg supply begins to become limited, basal FSH is never elevated. 2. Once menopause is well established, basal FSH is always elevated. 3. During the intermediate stage, FSH is sometimes elevated and sometimes normal (Fig. 2). During this phase, however, fecundity is reduced whether or not the FSH is elevated during a particular cycle or not. Several studies have demonstrated that the ovarian response and pregnancy rate in cycles with normal FSH is not normal if any prior cycle displayed an abnormal FSH.

Original understandings:

Many elements of the initial reports are still valid, including:

1. High age is limiting even with normal FSH. Original reports demonstrated lower pregnancy rates in women past 40 years of age, no matter their basal FSH level [5]. Even with today's treatments, successful pregnancies past age 42 are uncommon, and past 45 are rare.
2. High FSH is limiting even with normal age. The original reports saw a declining pregnancy rate as FSH rose above 20, and no ongoing pregnancies beyond an FSH of 25 IU/L [5,6]. While the assay has since changed and altered these cutoffs, there still tends to be a threshold above which declining performance (egg production and pregnancy rate) is detected, and a higher threshold above which egg production is quite limited, and almost no pregnancies have occurred.
3. Cutoffs for FSH depend on the lab test employed. Up through the early 1990's, most commercial assays reported FSH levels about twice as high as those now in wide use. Thus, whereas the cutoff of normal FSH was 20 IU/L in early reports, it is now more commonly about 10 IU/L. And whereas markedly abnormal ovarian reserve was formerly seen only above 25 IU/L, now that threshold occurs above about 15 IU/L. It is still best if clinics develop their own thresholds to define then end of the normal range, and the entry into the very abnormal range, for FSH and estradiol assays commonly employed for their patients.
4. The highest-ever FSH is the one most likely to be true. Several early reports demonstrated the futility of delaying treatments until a cycle with a normal FSH occurs. More recent studies have continued to affirm this effect [7,8]. Once an FSH elevation is observed, egg production capacity will be limited thereafter. This is to be expected, given the on-again, off-again nature of basal FSH elevations once egg numbers become critically short (as illustrated in Fig. 2).
5. Prediction of ovarian reserve is easier than predicting pregnancy. Basal FSH levels are better able to predict outcomes more closely related to ovarian function, such as cancellation ($R^2=77\%$), follicles aspirated ($R^2=35\%$), and oocytes retrieved ($R^2=21\%$) than more distal events such as pregnancy rate ($R^2=4\%$) [5,9].

Refined understandings:

1. High age and high FSH affect delivery rates but in different ways. FSH is the better predictor of the number of eggs that can be induced to grow by gonadotropin administration, and consequently cancellation rate [10-14]. Age, on the other hand, is the better predictor of embryo implantation and miscarriage rate [11,14-16]. Since prospects for delivery are affected by both quantitative and qualitative deficiencies in eggs, both age and FSH are important (Fig. 3).

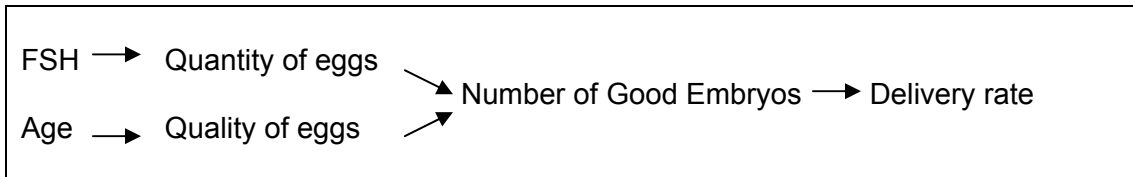


Figure 3.

Initial claims (by this author) that FSH was more predictive of outcome than age, and similar subsequent claims, reflects a lack of understanding that both ovarian reserve and age are important. The apparent strength of one over the other in any particular study has more to do with the operating range of FSH and age in the cases under study than in any underlying physiological principle.

Furthermore, at extremes of either age or FSH (e.g., age >45 years, FSH >20 IU/L), fertility is essentially nil [17-20]. In one large study of IVF patients, FSH >14.2 IU/L was associated with a very low pregnancy rate (2.7% and a high miscarriage rate (71.4%) which persisted even among women below age 35 years [21]. Annual reports of U.S. ART live born delivery rates in women over age 43 years are chronically under 3% per attempt. Clearly both factors are important predictors.

2. Young women with moderate elevations of FSH will make fewer eggs, and run a high risk of cycle cancellation, but if eggs are retrieved, they have reasonable chances for pregnancy. This 'protective' effect of young age was not seen in the original study (Toner 91), but has been seen repeatedly since [22-25].

For example, the van Rooij study [23] noted that in women under age 40 with elevated FSH, the risk for cancellation was high, but the pregnancy rate among those proceeding to transfer was good (Table I).

In another informative study [26], mild elevations of FSH predicted the need for more stimulation to get an acceptable ovarian response. Even with this adjustment, a lower response was in evidence, but enough eggs were produced to achieve a roughly equivalent transfer and pregnancy rate (Table II). However, as FSH became more elevated, pregnancy rates fell as stimulation adjustments were unable to compensate for diminished ovarian responsiveness.

It is also important to note that while FSH (and related endocrine or ultrasound markers) are the best available predictors of the quantity of eggs that can be produced, the actual number produced is more meaningful to outcome than the

prediction. Thus studies that focus on cycles in which only a few eggs are produced show low success rates even at young ages [27] (Table III).

The strength of the relation between basal hormone markers and ovarian reserve is enhanced with luteal estradiol administration [28].

The combined effect of age and FSH on ultimate delivery rate is illustrated in the following Figure 4. Note that women beyond age 42 are unlikely to deliver no matter what their basal FSH might be; this reflects the significant reduction in egg quality (i.e., implantation potential) which is nearly universally seen at this age independent of predicted or actual ovarian responsiveness. Also note that while younger women's success is heavily dependent on basal FSH, only when the FSH is markedly elevated (typically above 20 IU/L) will their chances as low as the women in their mid-forties.

3. Other markers of ovarian reserve:
 - a. An exaggerated FSH/LH ratio, even with normal FSH, is a sign of diminished ovarian reserve. In fact, the ratio of FSH/LH appears to be a clinically useful index, suggesting a PCO-like high response when LH exceeds FSH, to diminished ovarian reserve with FSH exceeds LH [29-31]. It is interesting to note that some PCO will develop regular cycles as their egg supply declines [32], as their FSH levels rise and their inhibin B levels fall.
 - b. Decreased early follicular phase inhibin B levels may occur before increases in FSH are observed [33].
 - c. Antral follicle count and ovarian volume are good predictors of ovarian reserve [34-37], and in some studies appear better than the usual endocrine markers. Cancellation rate and egg production are better predicted by these features than is pregnancy rate.
 - d. Increased day 3 estradiol has been associated with both diminished ovarian reserve and enhanced ovarian reserve (ala PCO). Those with diminished ovarian reserve display a high estradiol because of hurried folliculogenesis. Those with PCO can display a high estradiol as their many antral follicles each make a bit of estradiol. Interestingly, cancellation is increased with either low (<20 pg/mL) or high (>80 pg/mL) estradiol levels [38,39], but these levels did not predict pregnancy rate in those not canceled. The combined FSH and estradiol in screening for diminished ovarian reserve appears to be more sensitive than either test alone [40].
 - e. Provocative tests of ovarian reserve, such as EFFORT [41], GAST [42], and CCCT [43] are more sensitive indicators of ovarian reserve than basal tests. Among those reported the CCCT seems to best predict ovarian reserve [44,45]. In the CCCT, an abnormal day 10 appears to carry the same poor prognosis as does an abnormal day 3; the prognosis is even worse if both are abnormal [46].
 - f. Premature luteinization and a short follicular phase can be signs of diminished ovarian reserve [37,47,48].
4. Miscarriage risk is increased in those with diminished ovarian reserve [49-51].
5. Birth defect risks may be increased in those with diminished ovarian reserve [52].

6. Ovarian reserve effects in natural cycles. In a small study (n=129) of a general population of couples trying to conceive, FSH was not predictive of who became pregnant, or the fate of pregnancies [53]. Even in general subfertility population, one small study of women with an FSH>10 did not predict more time to pregnancy or fewer pregnancies or deliveries over a year's effort to conceive naturally [54]. In another similar study of 103 young couples (average age of 33.2) pregnancy in the first year of unassisted reproduction was influenced by the woman's age, but not basal FSH, estradiol, or the basal follicle count [55]. Insofar as natural cycles generally produce and release only 1 egg, and that markers of ovarian reserve are more predictive of egg production capacity than egg quality, this absence of effect in unstimulated cycles is not so surprising.
7. When an elevated FSH does not signal trouble. On occasion, an elevated FSH may not signal quantitative limitations in egg production capacity per se, such as in cases of familial twinning or in the presence of heterophilic antibodies to FSH (Lambalk 03). Further, while in many cases a rise in FSH signals both quantitative and qualitative reductions in eggs, after ovarian tissue loss (surgical extirpation for cysts, endometriomas, etc), one would expect only a quantitative reduction.

In summary, estimates of ovarian reserve have proved helpful in predicting pregnancy potential in ART, largely through their ability to predict the quantity of eggs which can be induced to grow. The quality of those eggs seems better predicted by the age of the women, and both factors are important. In women past age 40, current success rates are low overall, even in those who good ovarian reserve who make many eggs; at this age, quantity does not make up for quality. By contrast, young women with limited ovarian reserve can have good success rates despite their limited cohort of eggs, because the eggs themselves are of high potential; here quality matters more than quantity.

The ramifications of these observations include the following: Abnormal tests of ovarian reserve are the best predictors we have of egg production capacity, but are not perfect. Thus diminished ovarian reserve should not be used as an exclusionary criterion in young women, because overall they still have satisfactory pregnancy rates, though their risk of cancellation is increased. In women past age 40, normal ovarian reserve testing is not particularly reassuring because even reduced egg quality is likely to limit the opportunity for successful pregnancy even when many eggs are available.

References

1. Muasher SJ, Oehninger S. The value of basal and/or stimulated serum gonadotropin levels in prediction of stimulation response and in vitro fertilization outcome. *Fertil Steril* 1988; 50(2): 298-307.
2. Scheffer GJ, Broekmans FJM et al. Antral follicle counts by transvaginal ultrasonography are related to age in women with proven natural fertility. *Fertil Steril* 1999; 72(5): 845-51.
3. Erdem A, Erdem M, Biberoglu K, Hayit O, Arslan M, Gursoy R. Age-related changes in ovarian volume, antral follicle counts and basal FSH in women with normal reproductive health. *J Reprod Med* 2002; 47(10): 835-9.
4. Morris JL, Thyer AC, Soules MR, Klein NA. Antral follicle count by transvaginal ultrasound is reflective of the actual primordial follicle pool. *Fertil Steril* 2002; 78(1001): S3-4.

5. Toner JP, Philput CB, Jones GS, Muasher SJ. Basal follicle-stimulating hormone level is a better predictor of in vitro fertilization performance than age. *Fertil Steril* 1991; 55(4): 784-91.
6. Scott RT, Toner JP, Muasher SJ, Oehninger S, Robinson S, Rosenwaks Z. Follicle-stimulating hormone levels on cycle day 3 are predictive of in vitro fertilization outcome. *Fertil Steril*. 1989 Apr;51(4):651-4.
7. Pal L, Witt BR. Maximal historical FSH is a better predictor of cycle outcome than the baseline FSH for the IVF cycle. *Fertil Steril* 2002; 78(1001): S135.
8. Lass A, Gerrard A, abusheikha N, Akagbosu F, Brinsden P. IVF performance of women who have fluctuating early follicular FSH levels. *J Assist Reprod Genet* 2000; 17(10): 566-73.
9. Tinkanen H, Blauer M, Laippala P, Tuohimaa P, Kujansuu E. Prognostic factors in controlled ovarian hyperstimulation. *Fertil Steril* 1999; 72(5): 932-6.
10. Ghazeeri GS, Chuang A, Barker LJ, Ke RW, Kutteh WH. Elevated day 10 FSH is predictive of pregnancy loss in patients undergoing IVF. *Fertil Steril* 2001; 76(3, suppl 1): S209.
11. Akande VA, Fleming CF, Hunt LP, Keay SD, Jenkins JM. Biological versus chronological ageing of oocytes, distinguishable by raised FSH levels in relation to the success of IVF treatment. *Hum Reprod* 2002; 17(8): 2003-8.
12. Magarelli PC, Pearlstone AC, Buyalos RP. Discrimination between chronological and ovarian age in infertile women aged 35 years and older: predicting pregnancy using basal follicle stimulating hormone, age and number of ovulation induction/intra-uterine insemination cycles. *Hum Reprod* 1996; 11(6): 1214-9.
13. Poe-Zeigler R, Toner JP, Oehninger S, Muasher SJ: Basal FSH affects IVF pregnancy rates primarily by influencing oocyte numbers and not their quality. Abstract #O-014, Program Supplement p. S8, Amer Fertil Soc Ann Meeting, San Antonio, Texas, November 5-10, 1994 (oral presentation).
14. Sharif K, Elgendy M, Lashen H, Afnan M. Age and basal follicle stimulating hormone as predictors of in vitro fertilization outcome. *Br J Obstet Gynecol* 1998; 105(1): 107-12.
15. Chuang CC, Chen CD, Chao K-H, Chen S-U, Ho H-N, Yang Y-S. Age is a better predictor of pregnancy potential than basal follicle-stimulating hormone levels in women undergoing in vitro fertilization. *Fertil Steril* 2003; 79(1): 63-8.
16. Hull MG, Fleming CF, Hughes AO, McDermott A. The age-related decline in female fecundity: a quantitative controlled study of implanting capacity and survival of individual embryos after in vitro fertilization. *Fertil Steril* 1996; 65(4): 783-90.
17. Bancsi LFJMM, Huijs AM, den Ouden CT, Broekmans FJM, Looman CWN, Blankenstein MA, te Velde ER. Basal follicle-stimulating hormone levels are of limited value in predicting ongoing pregnancy rates after in vitro fertilization. *Fertil Steril* 2000; 73(3): 552-7.
18. Lass A, Croucher C, Duffy S, Dawson K, Margara R, Winston RML. One thousand initiated cycles of in vitro fertilization in women \geq 40 years of age. *Fertil Steril* 1998; 70(6): 1030-4.
19. Tummon IS, Hardy I, Lee M, Cardone VR, Seibel M, Summers M. Lifetime high day 2 FSH and diagnostic accuracy in IVF. *Fertil Steril* 2001; 76(3, suppl. 1): S232-3.
20. Bancsi LF, Broekmans FJ, Mol BW, Habbema JD, te Velde ER. Performance of basal follicle-stimulating hormone in the prediction of poor ovarian response and failure to become pregnant after in vitro fertilization: a meta-analysis. *Fertil Steril* 2003; 79(5): 1091-100.
21. Levi AJ, Raynault MF, Bergh PA, Drews MR, Miller BT, Scott RT Jr. Reproductive outcome in patients with diminished ovarian reserve. *Fertil Steril* 2001; 76(4): 666-9.

22. Pal L, Cohen H, Witt B. Pregnancy rates with IVF remain significant despite elevated maximal basal FSH levels in younger women. *Fertil Steril* 2002; 78(1001): S245.
23. van Rooij IAJ, Bancsi LFJMM, Broekmans FJM, Looman CWN, Habbema JDF, te Velde ER. Women older than 40 years of age and those with elevated follicle-stimulating hormone levels differ in poor response rate and embryo quality in in vitro fertilization. *Fertil Steril* 2003; 79(3): 482-8.
24. Hanoch J, Lavy Y, Holzer H, Hurwitz A, Simon A, Revel A, Laufer N. Young low responders protected from the untoward effects of reduced ovarian response. *Fertil Steril* 1998; 69(6): 1001-4.
25. Ulug U, Ben-Shlomo I, Turan E, Erden HF, Akman MA, Bahceci M. Conception rates following assisted reproduction in poor responder patients: a retrospective study in 300 consecutive cycles. *Reprod Biomed Online* 2003; 6(4): 439-43.
26. Hur K, Han K, Byun H, Yeum H, Choi S, Jun J. Mildly elevated basal FSH does not predict poor outcome of assisted reproductive technologies. *Fertil Steril* 2002; 78(1001): S249.
27. El-Toukhy T, Khalaf Y, Hart R, Taylor A, Braude P. Young age does not protect against the adverse effects of reduced ovarian reserve—an eight year study. *Hum Reprod* 2002; 17(6): 1519-24.
28. Fanchin R, Cunha-Filho J, Schonauer LM, Righini C, de Ziegler D, Frydman R. Luteal estradiol administration strengthens the relationship between day 3 follicle-stimulating hormone and inhibin B levels and ovarian follicular status. *Fertil Steril* 2003; 79(3): 585-9.
29. Kligman I, Rosenwaks Z. Differentiating clinical profiles: predicting good responders, poor responders, and hyperresponders. *Fertil Steril* 2001; 76(6): 1185-90.
30. Barroso G, Oehninger S, Monzo A, Kolm P, Gibbons WE, Muasher SJ. High LH:FSH ratio and low LH levels in basal cycle day 3: impact on follicular development and IVF outcome. *J Assist Reprod Genet* 2001; 18(9): 499-505.
31. Noci I, Maggi M, Fuzzi B, Biagiotti R, Ricci F, Marchionni M. Effects of low day 3 luteinizing hormone levels on in vitro fertilization treatment outcome. *Gynecol Endocrinol* 2000; 14(5): 321-6.
32. Elting MW, Kwee J, Korsen TJ, Rekers-Mombarg LT, Schoemaker J. Aging women with polycystic ovary syndrome who achieve regular menstrual cycles have a smaller follicle cohort than those who continue to have irregular cycles. *Fertil Steril* 2003; 79(5): 1154-60.
33. Seifer DB, Scott RT Jr, Bergh PA, Abrogast LK, Friedman CI, Mack CK et al. Women with declining ovarian reserve may demonstrate a decrease in day 3 serum inhibin B before a rise in day 3 follicle-stimulating hormone. *Fertil Steril* 1999; 72(1): 63-5.
34. Bancsi LFJMM, Broekmans FJM et al., Predictors of poor ovarian reserve in in vitro fertilization: a prospective study comparing basal markers of ovarian reserve. *Fertil Steril* 2002; 77(2): 328-36.
35. Pellicer A, Ardiles G, Neuspiller F, Remohi J, Simon C, Bonilla-Musoles F. Evaluation of the ovarian reserve in young low responders with normal basal levels of follicle-stimulating hormone using three-dimensional ultrasonography. *Fertil Steril* 1998; 70(4): 671-5.
36. Frattarelli JL, Lauria-Costab DF, Miller BT, Bergh PA, Scott RT Jr. Basal antral follicle number and mean ovarian diameter predict cycle cancellation and ovarian responsiveness in assisted reproductive technology cycles. *Fertil Steril* 2000; 74(3): 512-7.

37. Beckers NG, Macklon NS, Eijkemans MJ, Fauser BC. Women with regular menstrual cycles and a poor response to ovarian hyperstimulation for in vitro fertilization exhibit follicular phase characteristics suggestive of ovarian aging. *Fertil Steril*. 2002;78(2):291-7.
38. Phelps JY, Levine AS, Hickman TN, Zacur HA, Wallach EE, Hinton EL. Day 4 estradiol levels predict pregnancy success in women undergoing controlled ovarian hyperstimulation for IVF. *Fertil Steril* 1998; 69(6): 1015-9.
39. Frattarelli JL, Bergh PA, Drews MR, Sharara FI, Scott RT Jr. Evaluation of basal estradiol levels in assisted reproductive technology cycles. *Fertil Steril* 2000; 74(3): 518-24.
40. Ranieri DM, Quinn F, Makhoul A, Khadum I, Ghutmi W, McGarrigle H et al. Simultaneous evaluation of basal follicle-stimulating hormone and 17 β -estradiol response to gonadotropin-releasing hormone analogue stimulation: an improved predictor of ovarian reserve. *Fertil Steril* 1998; 70(2) 227-33.
41. Fanchin R, de Ziegler D, Olivennes F, Taieb J, Dzik A, Frydman R. Exogenous follicle stimulating hormone ovarian reserve test (EFORT): a simple and reliable screening test for detecting 'poor responders' in in-vitro fertilization. *Hum Reprod*. 1994 Sep;9(9):1607-11.
42. Winslow KL, Toner JP, Brzyski RG, Oehninger SC, Acosta AA, Muasher SJ. The gonadotropin-releasing hormone agonist stimulation test--a sensitive predictor of performance in the flare-up in vitro fertilization cycle. *Fertil Steril*. 1991 Oct;56(4):711-7.
43. Navot D, Rosenwaks Z, Margalioth EJ. Prognostic assessment of female fecundity. *Lancet*. 1987 Sep 19;2(8560):645-7.
44. Gulekli B, Bulbul Y, Onvural A, Yorukoglu K, Posaci C, Demir N, Erton O. Accuracy of ovarian reserve tests. *Hum Reprod* 1999; 14(1): 2822-6.
45. Bukman a, Heineman MJ. Ovarian reserve testing and the use of prognostic models in patients with subfertility. *Hum Reprod Update*. 2001; 7(6):581-90.
46. Yanushpolsky EH, Hurwitz S, Tikh E, Racowsky C. Predictive usefulness of cycle day 10 follicle-stimulating hormone level in a clomiphene citrate challenge test for in vitro fertilization outcome in women younger than 40 years of age. *Fertil Steril* 2003; 80(1): 111-5.
47. Younis JS, Matilsky M, Radin O, Ben-Ami M. Increased progesterone/estradiol ratio in the late follicular phase could be related to low ovarian reserve in in vitro fertilization-embryo transfer cycles with a long gonadotropin-releasing hormone agonist. *Fertil Steril* 2001; 76(2): 294-9.
48. Younis JS, Haddad S, Matilsky M, Ben-Ami M. Premature luteinization: could it be an early manifestation of low ovarian reserve. *Fertil Steril* 1998; 69(3): 461-5.
49. Hofmann GE, Houry J, Thie J. Recurrent pregnancy loss and diminished ovarian reserve. *Fertil Steril* 2000; 74(6): 1192-5.
50. Trout SW, Seifer DB. Do women with unexplained recurrent pregnancy loss have higher day 3 serum FSH and estradiol values? *Fertil Steril* 2000; 74(2): 335-7.
51. Nasser A, Mukherjee T, Grifo JA, Noyes N, Krey L, Cooperman AB. Elevated day 3 serum follicle-stimulating hormone and/or estradiol may predict fetal aneuploidy. *Fertil Steril* 1999; 71(4): 715-8.
52. van Montfrans J, van Hooff M, Martens F, van Vugt JMG, Lambalk N. Basal FSH concentrations as marker of ovarian aging are not related to pregnancy outcome in a general population of women over 30 years. *Fertil Steril* 2002; 78(1001): S223-4.
53. van Montfrans JM, Hoek A, van Hooff MHA, de Koning Ch, Tonch N, Lambalk CB. Predictive value of basal follicle-stimulating hormone concentrations in a general subfertility population. *Fertil Steril* 2000; 74(1): 97-103.

54. Broekmans F, van Rooy I, te Velde E. The predictive role of ovarian reserve tests in the normal population. *Fertil Steril* 2002; 78(1001): S217.
55. Lambalk CB. Value of elevated basal follicle-stimulating hormone levels and the differential diagnosis during the diagnostic subfertility work-up. *Fertil Steril* 2003; 79(3): 489-90.

Table I.

Comparison of outcomes in younger patients with diminished ovarian reserve to older patients with normal ovarian reserve [23]

	<40 years with FSH 15+	41+ years with FSH <15
N	36	50
% canceled	31%	8%
% embryos implanted	34%	11%
% clinically pregnant	40%	13%
% ongoing pregnant	25%	10%

Table II.

Influence of basal FSH on ovarian response and pregnancy outcomes.

	Basal FSH (IU/L)			
	<10	10-15	15-20	20+
# Amps	27.6	38.2		
Estradiol @ hCG	2391	1277		
# Eggs retrieved	13.1	6.5		
# Good embryos	2.9	2.5	2.1	1.7
Clinical pregnancy rate	24.6	23.4	13.6	5.7
Livebirth rate	19.6	18.2	13.6	2.9

Table III.

Poor outcomes at all ages in those with low ovarian reserve.

	<30 years	31-38 years	>38 years
Implantation Rate	13	9.6	9.8
Clinical Pregnancy Rate	11.8	10.2	10
Live Birth Rate	7.4	7.3	6.8

Legends

Figure 1. At birth, a woman has all the eggs she'll ever have, and steadily loses them thereafter, until none remain at menopause. As her age increases and the supply diminishes, fertility declines. This fall in fertility is often signaled by a rise in basal FSH levels.

Figure 2. The basal FSH level at the beginning of menstrual cycles can be divided into 3 phases. In the first phase, fertility is normal and FSH is always low. In the second phase, FSH is intermittently elevated and fertility is declining. In the last phase, FSH is always elevated and fertility is nil.

Figure 3. The chance for successful pregnancy outcome in IVF is influenced by both quantitative and qualitative factors regarding eggs. The quantitative aspect seems best predicted by various markers of ovarian reserve such as basal FSH. The qualitative aspect seems best predicted by maternal age, and is manifest in implantation rates.

Figure 4. Simultaneous consideration of age and FSH is important for understanding the chance for successful pregnancy in IVF (theoretical model). While high age (>42 years) is a significant impediment no matter the ovarian reserve, so too is high FSH (>20 in most labs) an intractable problem. Note that in young women, the success rate exceeds that for older women unless the FSH is extremely elevated. This supports the observation that in young women, even a few eggs can be sufficient; these women can and should be given the chance to try IVF as long as they are counseled regarding the increased risk of cancellation.

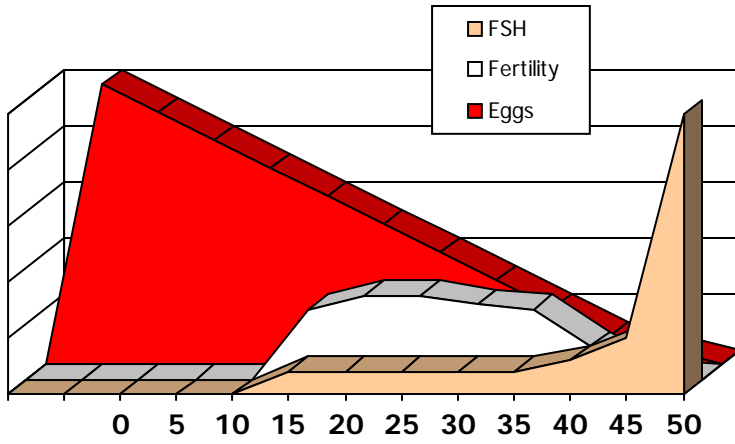


Figure 1.

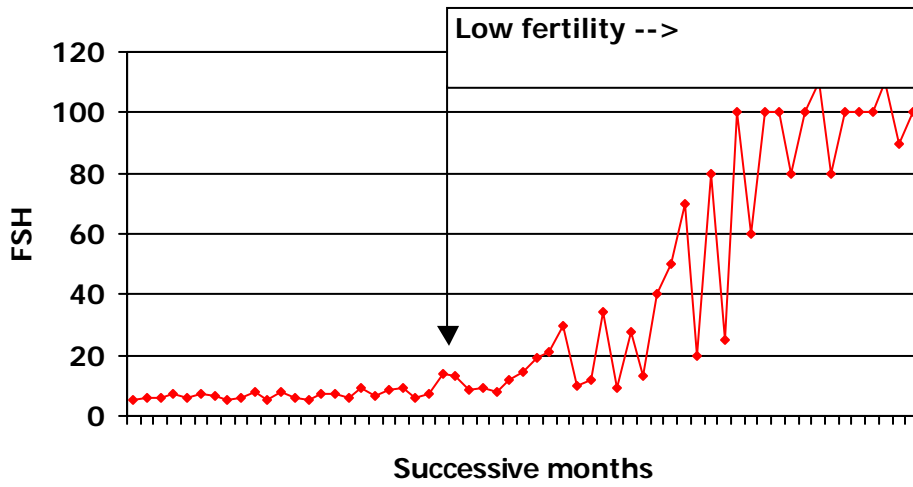


Figure 2.

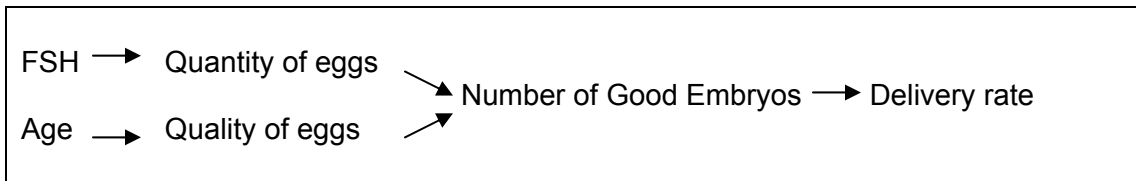


Figure 3.

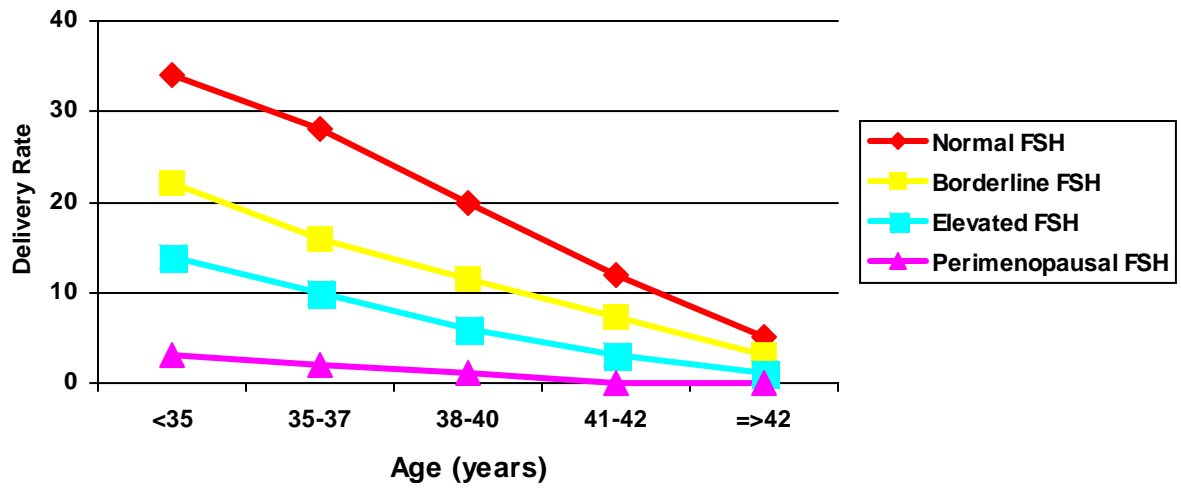


Figure 4.