

Establishing an Evidence Based Cutoff: Basal Follicle Stimulating Hormone (FSH) Levels of 8 or Greater to Detect Diminished Ovarian Reserve in Young Women



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INTRODUCTION

-Assessment of ovarian reserve with cycle day 2 or 3 FSH and estradiol is one of the critical steps in evaluation of couples seeking treatment for infertility (1).
-Traditionally, an FSH greater than 10 mIU/mL is the level at which diminished ovarian reserve is diagnosed (1).

-Prior studies have shown those with “premature ovarian aging” to have FSH levels less than 10 mIU/mL but who are in either greater than the 95% confidence interval (5,6), or in the highest quartile in their age groups (7).
-Young women in the premature ovarian aging groups had decreased number of oocytes retrieved after ovarian stimulation for in vitro fertilization (IVF) compared to their counterparts despite technically normal FSH levels.

-As FSH level is a widely used marker to guide treatment, it would be valuable to obtain further data regarding pregnancy outcomes in the younger age group of women undergoing IVF to see if a new cut-off level should instead be used.

OBJECTIVES

The aim of this study was to assess whether high-normal basal FSH levels between 8-10 lead to significantly different outcomes for women ages 35 or younger undergoing in vitro fertilization, compared to women with FSH levels less than 8. The primary outcome was clinical pregnancy rates, defined by the presence of fetal heartbeat(s) on ultrasound.

METHODS

-Chart review of all women age 35 or younger who underwent their first IVF attempt between 1/1/2010 and 12/19/2016, all of whom had a day 2/3 FSH and estradiol drawn within one year of their IVF cycle.

-Powered to detect a 20% lower probability of clinical pregnancy in patients with FSH between 8 and 10 compared to FSH under 8 at a one-sided 5% significance level based on prior data (8).

-For the primary analysis, the focus was on comparing patients with FSH under 8 and those with FSH 8 – 10. The probability of clinical pregnancy was compared between the two groups using Pearson’s chi-squared test at a 5% significance level. The difference in the proportion of patients with clinical pregnancy was estimated, and reported with a 95% confidence interval.

RESULTS

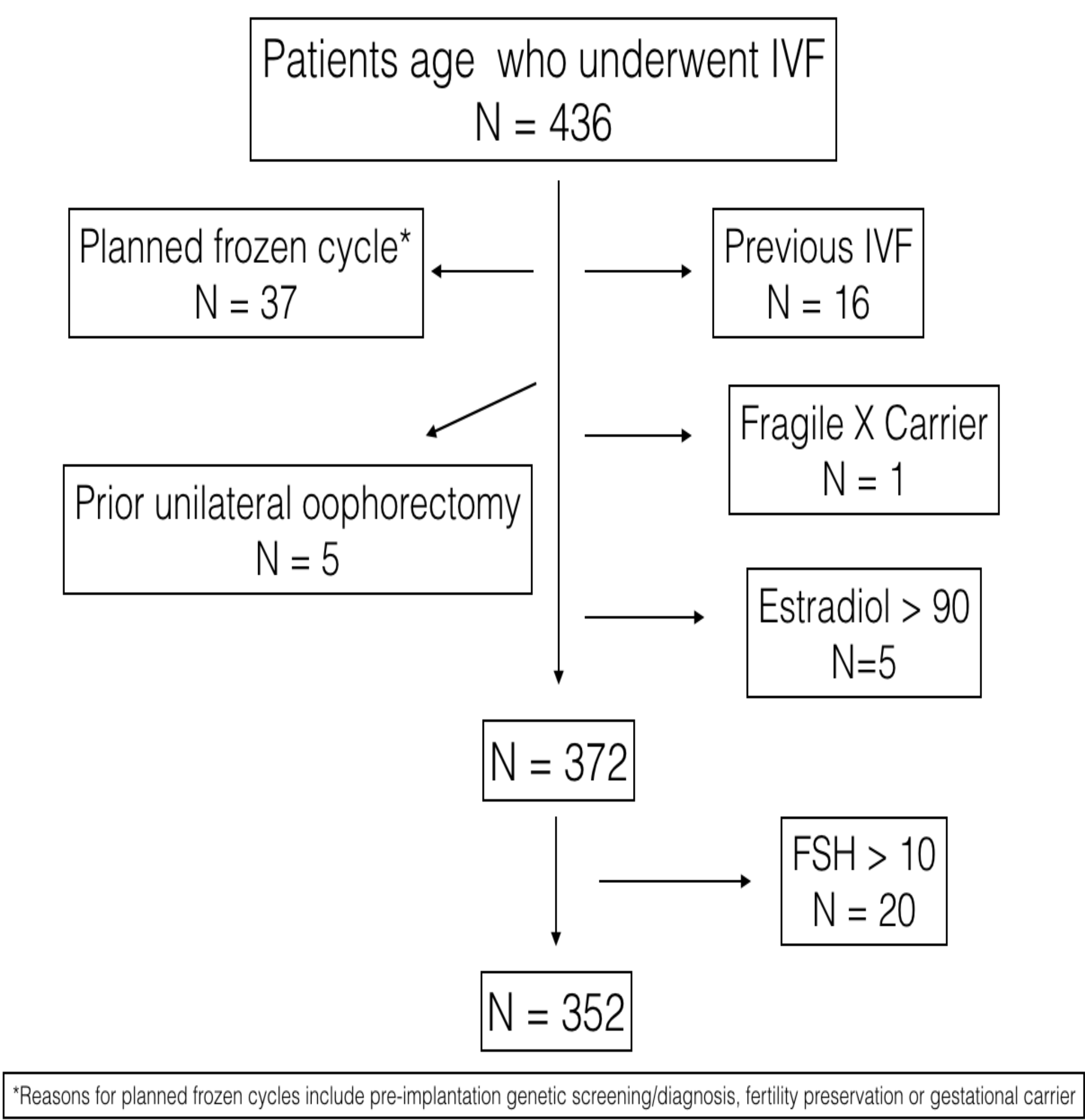


Figure 1. Subject numbers after screening for exclusion criteria

	<8 N=298	>=8 to <=10 N=54	P Value
Days of stimulation	10.0 +/- 1.7	10.2 +/- 1.5	0.37
Ampules of gonadotropins	33.0 +/- 16.4	36.9 +/- 13.1	0.10
Total oocytes retrieved	13.7 +/- 7.2	12.6 +/- 6.9	0.31
Mature Oocytes	10.5 +/- 5.9	9.8 +/- 5.9	0.41
Total number of embryos	7.9 +/- 5.0	7.3 +/- 5.1	0.44

Table 3. Ovarian stimulation outcomes

	<8 N=298	>=8 to <=10 N=54	P Value
Positive bHCG	174 (59.8%)	29 (54.7%)	0.49
Clinical pregnancy	127 (43.8%)	15 (28.3%)	0.035

Table 4. Pregnancy outcomes

	<8 N=298	>=8 to <=10 N=54	P Value
Age	30.9 +/- 2.4	31.1 +/- 2.3	0.58
BMI	27.2 +/- 6.0	25.5 +/- 5.4	0.06
Ethnicity			0.66
Asian	17 (5.7 %)	1 (1.9 %)	
Hispanic	16 (5.4 %)	3 (5.6 %)	
Indian	5 (1.7 %)	0 (0.0 %)	
Non-Hispanic black	8 (2.7 %)	1 (1.9 %)	
Non-Hispanic White	257 (84.6 %)	49 (90.7 %)	

Table 1. Demographic data

	<8 N=298	>=8 to <=10 N=54	P Value
Day 3 Estradiol (pg/mL)	37.6 +/- 16.0	40.3 +/- 14.5	0.248
Antral follicle count	17.6 +/- 10.1	13.8 +/- 7.3	0.008
AMH level (ng/mL)	4.7 +/- 4.7	3.0 +/- 3.1	0.010

Table 2. Markers of ovarian reserve

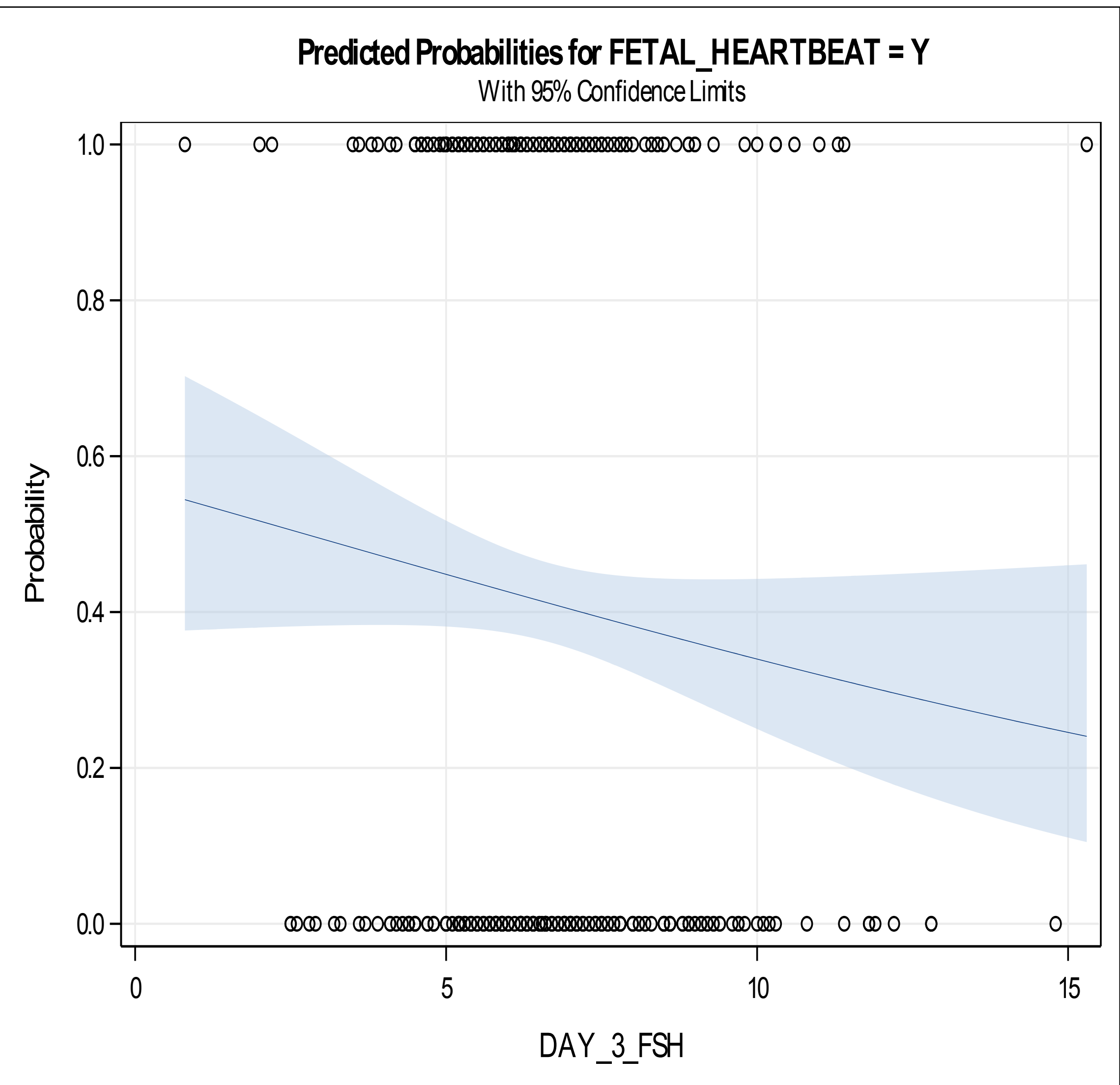


Figure 2. Clinical pregnancy rate by FSH level

Findings still significant when logistic regression analysis performed, controlling for age, day 3 estradiol level, day of transfer (3 versus 5), number of embryos transferred, ovulation trigger (Lupron plus hCG versus hCG) and type of transfer (fresh versus frozen.)

A receiver operator characteristic curve was also created using FSH levels as a predictor for clinical pregnancy rates (not shown.) The area under the curve was 0.55. The highest combination of sensitivity and specificity were seen at an FSH of 6.70 at 64% and 47%, respectively.

DISCUSSION

Our findings suggest that an FSH level of 8 or greater may be predictive of poorer outcomes with IVF in young women, specifically, with lower clinical pregnancy rates seen in the FSH 8-10 group versus FSH <8. This finding was still significant when controlling for confounding variables via logistic regression analysis. This suggests that in young women, using a cutoff of 8 rather than 10 may identify those who may benefit from more aggressive fertility treatment.

Strengths:

- Powered for primary outcome
- High number of single embryo transfers
- Homogenous stimulation protocols

Weaknesses:

- FSH has some inherent variability and is limited as a screening test
- Retrospective study
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REFERENCES

1. The Practice Committee of the American Society for Reproductive Medicine. Testing and interpreting measures of ovarian reserve: a committee opinion. Fertil Steril 2015;103(3):e9-e17.
2. Levi AJ, Raynault MF, Bergh PA, Drews MR, Miller BT, Scott RT Jr. Reproductive outcome in patients with diminished ovarian reserve. Fertil Steril 2001;76:666-9.
3. Navot D, Rosenwaks Z, Margalioth EJ. Prognostic assessment of female fecundity. Lancet 1987;2:645-7
4. 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;51:651-4
5. Barad DH, Weghofer A, Gleicher N. Age-specific levels for basal follicle-stimulating hormone assessment of ovarian function. Obstet Gynecol. 2007;109:1404-10.
6. Fang T, Su Z, Wang L, Yuan P, Li R, Ouyang N, Zheng L, Wang W. Predictive value of age-specific FSH levels for IVF-ET outcome in women with normal ovarian function. Repro Bio and Endo. 2015;13:63.
7. Weghofer A, Mergreiter M, Fauster Y, Schaetz T, Brandstetter A, Boehm D, et al. Age-specific FSH levels as a tool for appropriate patient counselling in assisted reproduction. Hum Reprod. 2005;20:2448-52.
8. Kumbak B, Oral E, Kahraman S, Karlikaya G, Karagozoglu H. Young patients with diminished ovarian reserve undergoing assisted reproductive treatments: a preliminary report. Repro BioMed Online. 2005;11(3):294-299.

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