Diminished ovarian reserve as measured by means of baseline follicle-stimulating hormone and antral follicle count is not associated with pregnancy loss in younger in vitro fertilization patients

Lauren A. Bishop, M.D.,[a] Kevin S. Richter, Ph.D.,[a] George Patounakis, M.D., Ph.D.,[b] Leslie Andriani, M.D.,[c] Kimberly Moon, M.D.,[a] and Kate Devine, MD[a]

[a] Shady Grove Fertility, Rockville, Maryland; [b] Reproductive Medicine Associates of Florida, Lake Mary, Florida; and [c] Georgetown University School of Medicine, Washington, DC

Objective: To assess the relationship between diminished ovarian reserve and pregnancy outcomes in a large cohort of women achieving pregnancy through in vitro fertilization (IVF). We evaluated antral follicle count (AFC) and baseline FSH as a measure of ovarian reserve. Secondarily, we assessed whether diminished ovarian reserve was associated with aneuploidy among spontaneous abortions.
Design: Retrospective cohort study.
Setting: Multicenter private practice.
Patient(s): All patients aged 21–44 years undergoing fresh autologous IVF cycles during 2009–2013 that resulted in positive serum hCG with recorded baseline FSH levels.
Intervention(s): None.
Main Outcome Measure(s): Live births per early pregnancy, biochemical pregnancies, clinical pregnancy losses, and aneuploidy rates in products of conception among pregnancy losses.
Result(s): A total of 9,489 cycles among 8,214 patients were analyzed. There was no association between live birth and ovarian reserve among pregnant IVF patients under the age of 35 years. Among patients 35 years of age and older, elevated baseline FSH was associated with a higher risk of pregnancy loss, which increased with increasing age. AFC was not significantly associated with pregnancy loss at any age. No associations were found between ovarian reserve measures and aneuploidy in products of conception in age-adjusted analyses, although the power to effectively evaluate this was limited.
Conclusion(s): Diminished ovarian reserve is not associated with an increase in miscarriage among younger women achieving pregnancy through IVF. Elevated FSH is associated with a higher risk of IVF pregnancy loss among older patients. We found no evidence to confirm that diminished ovarian reserve is associated with increased aneuploidy among spontaneous abortions. (Fertil Steril® 2017;108:980–7. ©2017 by American Society for Reproductive Medicine.)
Key Words: Diminished ovarian reserve, follicle-stimulating hormone (FSH), antral follicle count (AFC), live birth, pregnancy loss

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Reprint requests: Lauren A. Bishop, M.D., Shady Grove Fertility, 9601 Blackwell Rd., Rockville, MD, 20850 (E-mail: lauren.bishop@nih.gov).

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There is a marked decline in fertility with advancing age in female patients (1, 2). Ovarian response to stimulation during cycles of in vitro fertilization (IVF) declines concurrently (3). In some women this decline occurs prematurely. Therefore, there is a need for clinical tests to identify women with decreased oocyte quantity and quality at an early age. Serum FSH concentration as assessed on day 3 of the menstrual cycle is frequently used as a marker for ovarian reserve in women presenting for fertility evaluation. Earlier studies found that patients with diminished ovarian reserve have low conception rates and high rates of fetal loss (4–8). It has been suggested that age does not protect against the adverse effects of reduced ovarian reserve, because these patients have not only poor response to stimulation, but also elevated rates of miscarriage, indicative of poor oocyte quality (3). Therefore, treatment recommendations may be directed toward oocyte donation in patients with diminished ovarian reserve (9). More recent studies have contradicted these studies, finding similar pregnancy rates in patients with normal and elevated basal FSH levels (10–12). FSH levels may be of less value in predicting IVF outcomes than previously thought, particularly in younger patients (13–18).

Whereas decline in oocyte quantity corresponds with elevated FSH and advancing age, a correlation between basal FSH and oocyte quality is less clear. Fetal aneuploidy is primarily attributed to errors in maternal meiosis I (19). There are two theories to account for this phenomenon: 1) influence of chronologic age on the ovary; and 2) the limited pool hypothesis, which suggests that aneuploid frequency is inversely related to the size of the oocyte pool (20). It has been reported that elevated basal FSH levels have a positive predictive value for fetal aneuploidy risk (21, 22). However, these studies have been challenged by a number of comparable reports that do not demonstrate such a relationship (9, 23–27).

The aim of the present study was to determine if diminished ovarian reserve is associated with a reduction in the potential for early IVF pregnancies to survive to live birth in a large patient population, enabling a more definitive answer than available through previous studies of smaller samples. Our study also expands on previous research by evaluating an alternate measure of ovarian reserve, antral follicle count (AFC), in addition to the more traditional measure of baseline FSH. In addition, we attempted to determine if ovarian reserve correlated with aneuploidy among spontaneous abortions. This information could enable us to better counsel pregnant IVF patients with diminished ovarian reserve markers, and potentially avoid unnecessary treatment with the use of donor oocytes.

MATERIALS AND METHODS

This study was a retrospective cohort analysis of patients undergoing IVF from 2009 to 2013 at a single large private-practice fertility center. All fresh autologous IVF cycles performed during the study period that resulted in a post-treatment serum hCG level >5 mIU/mL among patients aged 21–44 years who had one or more previously recorded baseline serum FSH concentration within 1 year of cycle start were included in the analysis. For patients with multiple baseline FSH measurements before the treatment cycle, the highest of these was used in the analysis. This study was approved by an independent Institutional Review Board.

The primary treatment outcome for analysis was live birth. Secondary outcomes included biochemical pregnancy loss, defined as a cycle with a positive serum hCG but without development of a gestational sac identifiable by ultrasound examination, and clinical pregnancy loss, defined as a cycle with a confirmed gestational sac, with or without cardiac activity, that failed to result in live birth. In addition, when available, the products of conception from clinical pregnancy losses underwent chromosomal analysis through cytogenetic analysis or microsatellite analysis and were classified as either euploid or aneuploid. Cases of 46,XX where maternal cell contamination could not be ruled out were excluded from the analysis.

These outcomes were compared among patients with clinically normal baseline serum FSH concentration (<10 mIU/mL), moderately elevated FSH (10–13.9 mIU/mL), and highly elevated FSH (≥ 14 mIU/mL) within each of the standard age groups used by the Society for Assisted Reproductive Technology (SART; <35; 35–37; 38–40; 41–42; and 43–44 years). Comparable age-stratified comparisons were made among patients with AFCs in the lower quartile, interquartile range, and upper quartile. Statistical comparisons of outcomes among groups were conducted by means of chi-square or Fisher exact test as appropriate.

In addition, for more powerful tests of potential associations with ovarian reserve measures across the entire patient population, live birth outcomes were evaluated by means of generalized estimating equation (GEE) analysis, accounting for repeated cycles by individual patients and adjusting for patient age, body mass index (BMI), infertility diagnosis, and racial group.

All statistical analyses were performed with the use of JMP version 11.2.0 (SAS Institute) and IBM SPSS Statistics for Windows, version 22.0. A P value of $< .05$ was considered to be statistically significant.

RESULTS

A total of 9,489 autologous IVF cycles among patients aged 21–44 years performed from 2009 to 2013 resulted in a positive post-transfer hCG level, which we defined as early pregnancy, and therefore met the inclusion criteria. These IVF cycles were among 8,214 unique patients and included 931 cycles with moderately elevated baseline FSH and 329 cycles with highly elevated baseline FSH as defined in the methods section. Baseline AFCs, in addition to baseline serum FSH, were available for 90% of these cycles (n = 8,529). The mean age of this patient population was 34.6 years, with an average BMI of 25.6 kg/m^2. The majority of patients identified as white (59.8%). Male factor was the most common infertility diagnosis (32.7%), followed by unexplained (25.5%) and ovulation disorders (16.7%). Overall, these early pregnancies progressed to 8,117 clinical pregnancies (85.5% per positive hCG) and 6,575 live births (81.0% per clinical pregnancy).

Comparison of Live Birth and Pregnancy Loss Cycles

Compared with cycles with live birth, cycles with pregnancy loss were associated with significantly higher patient age, BMI, and baseline serum FSH concentration and significantly lower baseline AFC (Table 1). Diagnoses of diminished ovarian reserve and uterine factor were more common and male factor and ovulatory dysfunction were less common among patients experiencing pregnancy loss. Black patients were disproportionately overrepresented among the cycles with pregnancy loss.

Pregnancy Loss According to Ovarian Reserve Measures

Primary and secondary pregnancy and birth outcomes, subdivided by age and ovarian reserve (FSH and AFC) groups, are illustrated in Figure 1. All subgroup sample sizes, numerical outcomes, and AFC quartile ranges are summarized in Supplemental Tables 1 and 2 (available online at www.fertstert.org). Biochemical pregnancy losses were more frequent ($P=.048$) among 35–37-year-olds with moderately elevated FSH compared with those with normal FSH (Fig. 1A). Among 38–40-year-olds, biochemical pregnancy losses were less frequent for women with normal FSH compared with those with either highly elevated FSH ($P=.01$) or moderately elevated FSH ($P=.03$; Fig. 1A). Biochemical pregnancy loss rates did not differ significantly among AFC groups within any age group (Fig. 1B). Clinical pregnancy loss rates also did not differ significantly within any age group, either among FSH groups or among AFC groups (Figs. 1C and 1D).

TABLE 1

Patient characteristics compared between pregnancies with versus without live birth.

Characteristic	Live birth	No live birth	*P* value
No. of pregnancies	6,575	2,914	
Age (y)	34.1 ± 4.2	35.6 ± 4.5	<.0001
BMI (kg/m^2)	25.4 ± 5.2	26.0 ± 5.4	<.0001
Baseline (day 3) FSH (mIU/mL)	7.5 ± 3.0	7.7 ± 3.0	.0007
Normal (<10 mIU/mL)	87.8%	84.3%	<.0001
Moderate (10–13.9 mIU/mL)	9.0%	11.6%	
High (≥14 mIU/mL)	3.2%	4.1%	
Baseline antral follicle count	16.5 ± 9.8	15.3 ± 9.4	<.0001
Diagnoses			
Diminished ovarian reserve	8.8%	14.0%	<.0001
Endometriosis	6.3%	6.9%	NS
Male factor	33.6%	30.8%	.007
Ovulation disorders/PCOS	17.5%	15.2%	.006
Tubal factor	12.8%	12.6%	NS
Uterine factor	2.8%	4.7%	<.0001
Unexplained	26.0%	24.0%	NS
Race/ethnicity			
White	61.0%	57.2%	.001
Asian	14.2%	15.4%	NS
Black	11.2%	14.8%	<.0001
Latino	4.0%	3.6%	NS
Other/not available	9.6%	9.0%	NS

Note: Values are presented as mean ± SD or percentage of total cyclese. BMI = body mass index; NS = not significant; PCOS = polycystic ovary syndrome.

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Live Birth According to Ovarian Reserve Measures

The primary end point of live birth combines the cumulative effects of early (biochemical) pregnancy losses and clinical pregnancy losses. Among patients under 35 years of age (which included 281 pregnancies among women with moderately elevated FSH and 94 among women with highly elevated FSH) there was no indication that diminished ovarian reserve was associated with a reduction in live birth (Figs. 1E and 1F). Of the 375 early pregnancies among women under 35 years of age with elevated FSH, 286 progressed to live birth (76%, 95% confidence interval 71%–80%), compared with a birth rate of 75% for women with normal FSH. Similarly, patients under 35 years of age with AFC in the lowest quartile had live births just as frequently as those with AFC in the highest quartile (75.5% vs. 75.0%). Live births per early pregnancy declined from 75%–76% among patients under 35 years to ~30% among patients 43–44 years of age.

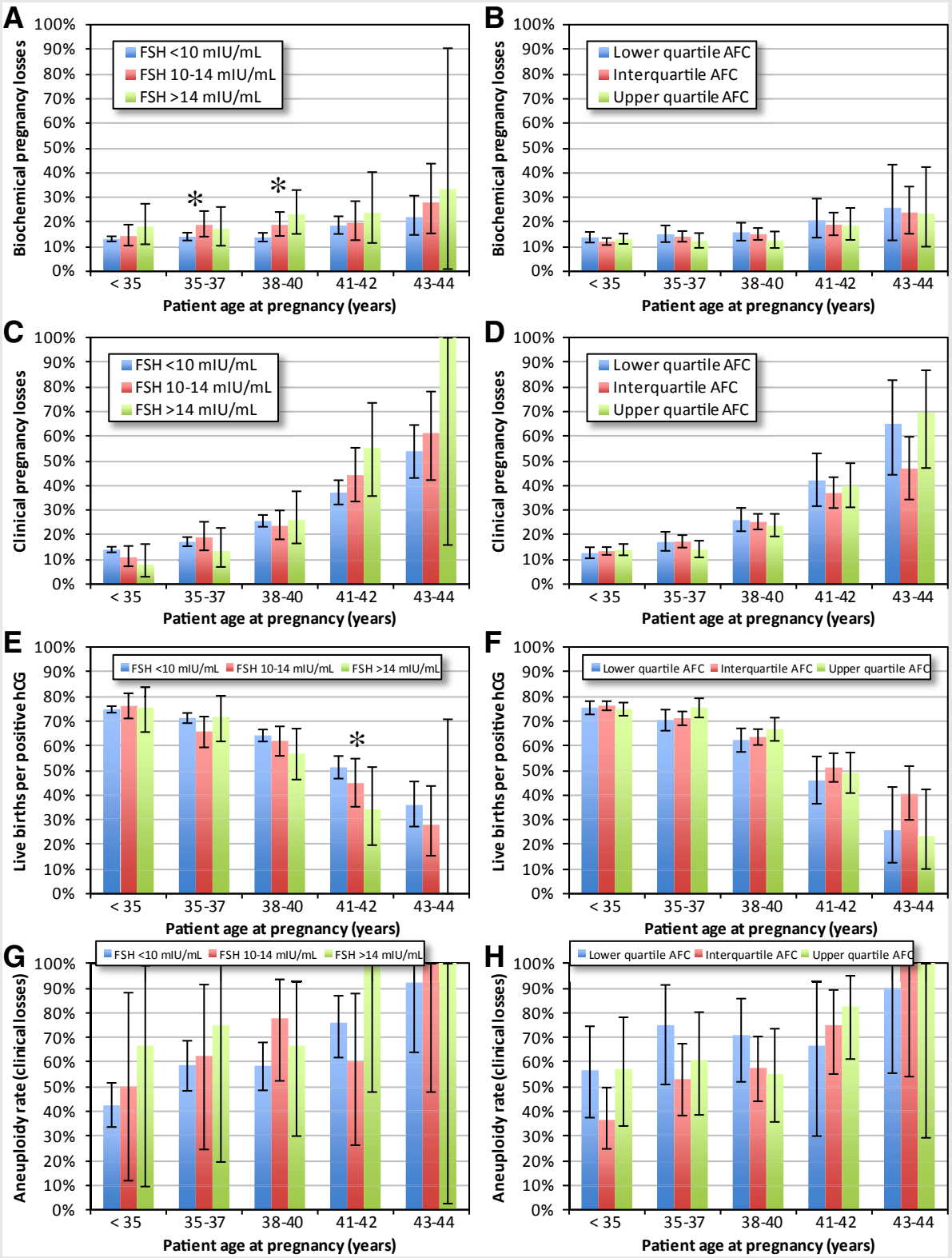
Live birth rates per cycle with positive hCG also did not differ significantly ($P>.08$) among either the FSH groups or the AFC groups within any of the older age groups, with the exception of patients aged 41–42 years (Fig. 1E). In the 41–42-year age group, the live birth rate was lower in the highly elevated FSH group (≥14 mIU/mL) compared with the normal FSH group (<10 mIU/mL; 34% vs. 51%; $P=.043$). The difference in live birth between normal FSH (<10 mIU/mL) versus elevated FSH (≥10 mIU/mL) was nearly significant at the $P<.05$ threshold (51% vs. 42%; $P=.053$). Because of the borderline significance of FSH-related trends within this one age group only, without adjustment for the multiple comparisons conducted within all five age groups, this result alone was not considered to be sufficient evidence of an association between FSH and pregnancy loss.

However, when examined collectively rather than within discrete age groups, it is interesting to note that although the live birth rate was nearly identical between the normal and elevated FSH groups among patients under 35 years of age, in all four of the older age groups the birth rate was numerically lower for patients with elevated FSH (Fig. 2A). Relative birth rates increasingly favored those with normal versus elevated baseline FSH with each successively older age group (Fig. 2B). The relative difference in observed birth rates for patients with normal versus elevated FSH was only 2% (in favor of those with elevated FSH) among patients under 35 years of age. In the 35–37- and the 38–40-year age groups, live birth rates per early pregnancy were 5%–6% lower for women with elevated FSH relative to those with normal FSH. The relative reduction in birth rate associated with elevated FSH rose to 18% for women aged 41–42 years, and to 26% for women aged 43–44 years.

Multivariate GEE Analysis of Birth According to Ovarian Reserve Measures

Multivariate GEE analysis provides a more powerful method of evaluating potential associations between ovarian

FIGURE 1



Clinical outcomes according to Society for Assisted Reproductive Technology age group and ovarian reserve (FSH or antral follicle count [AFC]) groups: biochemical pregnancy losses subdivided by (**A**) FSH group and (**B**) AFC group; clinical pregnancy losses subdivided by (**C**) FSH group and (**D**) AFC group; live births subdivided by (**E**) FSH group and (**F**) AFC group; and aneuploidy rates among pregnancy loss products of conception subdivided by (**G**) FSH group and (**H**) AFC group. Error bars indicate 95% confidence intervals. *$P<.05$.

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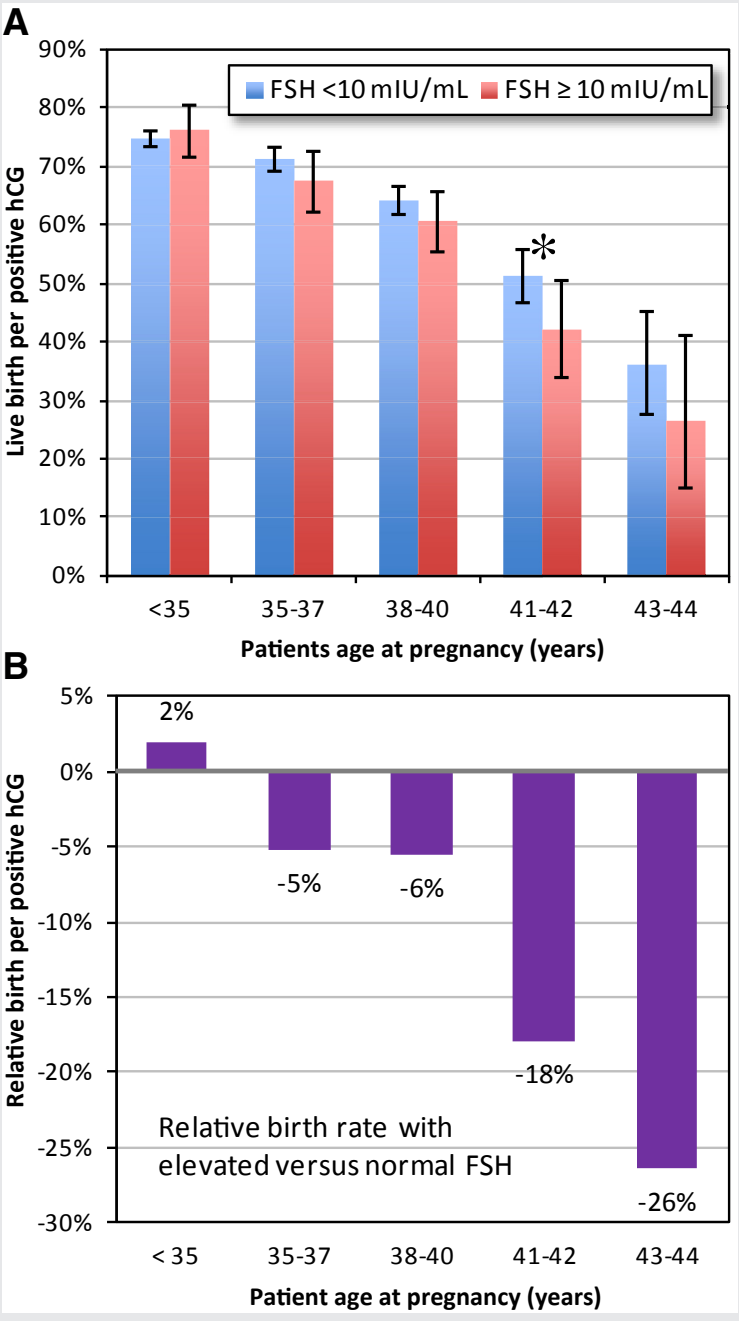
FIGURE 2



Live birth outcomes according to Society for Assisted Reproductive Technology age group and FSH category. (**A**) Observed live births per early pregnancy with normal (<10 mIU/mL) versus elevated (≥10 mIU/mL) baseline serum FSH; error bars indicate 95% confidence intervals. *P=.053 for normal versus elevated FSH among patients aged 41–42 years. (**B**) Relative difference in birth rates in patients with elevated compared with normal baseline serum FSH.

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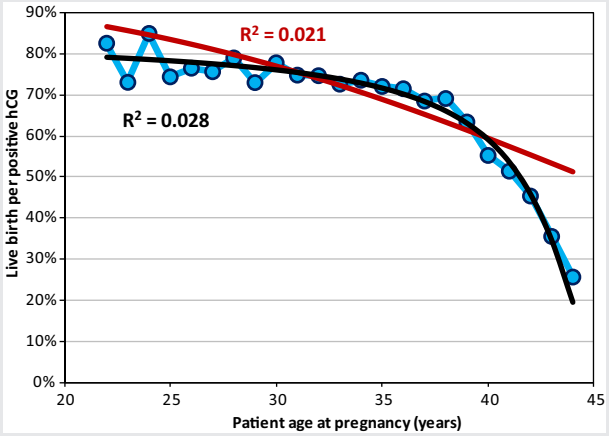
reserve measures and birth outcomes across the entire patient population rather than in discrete age groups. However, conventional logistic analysis of untransformed age data does not accurately model the relationship between age and live birth per early pregnancy; it overestimates birth rates at the extremes of age (<30 and >40 years) and underestimates birth rates for 33–39-year-old patients (Fig. 3, *red curve*). To correct for this inaccuracy and properly adjust for age in the multivariate models, we used an empirically derived transformation, 1/(47 − age), which maximized

FIGURE 3



Observed live birth rates per early pregnancy by age at pregnancy (*blue*). Fitted logistic regression models based on untransformed age data (*red*) and age data transformed according to the formula 1/(47 − age) (*black*), and associated R^2 values, are superimposed for comparison.

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the fit between the model and the observed data (Fig. 3, *black curve*).

Multivariate GEE analysis of live birth outcomes, including (transformed) age, BMI, diagnosis, and race as potential confounders, confirmed that live birth was significantly negatively associated with both age ($P<.0001$) and BMI ($P<.0001$). Live birth per positive hCG cycle declined with increasing age and increasing BMI, as would be expected. This analysis also indicated significantly lower birth rates associated with uterine-factor infertility ($P=.001$) and among black patients ($P=.005$). No other diagnoses or racial groups were significantly associated with birth outcomes after adjusting for these variables. In addition, after adjusting for age, BMI, diagnosis, and racial group, there was a significant negative age–by–baseline FSH interaction ($P=.002$), signifying that as age increased, elevated FSH had an increasing negative effect on birth rates. This significant interaction of age and FSH in the multivariate GEE model confirms the significance of the trend toward lower relative birth rates associated with elevated FSH as patient age increases, as illustrated in Figure 2B. A subgroup analysis limited to patients in the 35–44-year age range also indicated significantly lower birth rates associated with elevated versus normal baseline FSH ($P=.008$), with no significant age-by-FSH interaction, after adjusting for age, BMI, diagnosis, and racial group. Comparable multivariate GEE analysis of AFC indicated no equivalent relationship between AFC and live birth per early pregnancy. Neither the interaction between age and AFC nor AFC itself was significantly related to birth outcomes ($P>.3$ for both) in multivariate GEE models adjusting for age, BMI, diagnosis, and racial group.

Pregnancy Loss Aneuploidy According to Ovarian Reserve Measures

Among all 1,542 clinical pregnancy losses in the study group, 916 patients underwent a dilation-and-curettage procedure secondary to the clinical pregnancy loss, with 504 electing to have a karyotype analysis performed on the products of conception. Forty-four of these samples could not be accurately evaluated owing to maternal cell contamination, leaving 460 karyotypes available for analysis. Two hundred nineteen specimens (47.6%) were found to have aneuploidy, the most common finding being trisomy 16 (23.7%), followed by trisomy 22 (18.3%) and trisomy 21 (16%). Chi-square analysis did not reveal any associations between either FSH or AFC and ploidy status within any age group (Figs. 1G and 1H). As expected, the oldest patients, 41–44 years, were found to have the highest aneuploidy rates. GEE analysis of these karyotypes indicated that although age was significantly positively associated with aneuploidy ($P<.0001$) and BMI was negatively correlated with aneuploidy ($P=.029$), neither FSH nor AFC were related to aneuploidy among spontaneously aborted products of conception ($P>.3$). However, our power to identify ovarian reserve–related trends in pregnancy loss aneuploidy rates was extremely limited, as illustrated by the wide confidence intervals in Figures 1G and 1H.

DISCUSSION

The prognostic value of ovarian reserve measures on oocyte quality remains a topic of controversy. Although earlier studies indicated that elevated baseline serum FSH levels correlated with poor pregnancy outcomes, more recent studies have contradicted this thought. The availability of records from more than 9,000 autologous IVF pregnancies from a single center, including more than 900 among patients with moderately elevated baseline serum FSH (10–13.8 mIU/mL) and more than 300 among patients with highly elevated FSH ($\geq$ 14 mIU/mL), enabled a stronger test of association between ovarian reserve measures and pregnancy outcome than possible in previous smaller studies.

Our results definitively demonstrate that among women less than 35 years of age, diminished ovarian reserve, as measured by either baseline FSH or AFC, is not associated with any clinically significant increase in the risk of IVF pregnancy loss. Within this age range, patients with elevated FSH ($\geq$ 10 mIU/mL; n = 375) were no less likely to have a live birth than those with normal FSH (76.3% vs. 74.8%). Likewise, the birth rate for patients in the lowest AFC quartile was nearly identical to the birth rate among women with higher baseline AFC (75.5% vs. 75.8%). The narrow confidence intervals associated with the high sample sizes for these estimates indicate that if any actual effect exists, its magnitude is very small and thus of little if any clinical relevance.

Conversely, there was an apparent reduction in live birth rates associated with elevated FSH among women aged 35–44 years. A multivariate GEE analysis of birth outcomes among this patient subgroup, adjusting for age and other potential confounders, revealed a significant reduction in birth associated with elevated FSH for women in this age range. The significant negative age-by-FSH interaction in the

whole-population GEE analysis, along with the observed trend in relative birth rates with elevated versus normal FSH by age group, indicates that elevated FSH is an increasingly negative indicator as age increases. Among patients aged 35–40 years, the relative reduction in birth associated with elevated FSH was only 5%–6% and therefore of minor clinical significance. However, the relative reduction in birth associated with elevated versus normal baseline FSH rose to 18% among patients 41–42 years of age and to 26% among patients 43–44 years of age.

We also looked at rates of aneuploidy in products of conception of patients undergoing dilation and curettage as a proxy for oocyte quality and to determine if there was an independent association with ovarian reserve measures. Rates of aneuploidy among spontaneous abortions were noted to increase with age. The most common aneuploidy identified was trisomy 16, followed by trisomies 22 and 21. We were unable to confirm any independent association between ovarian reserve measures and aneuploidy among pregnancy losses, but our sample was not sufficiently powered to detect plausible differences in this outcome. A further limitation of our analysis of aneuploidy is that we were able to obtain data for only 30% of all pregnancy losses and therefore may be subject to reporting bias. This weakness may be largely unavoidable, given that lost products of conception are often not retrievable for analysis, especially with very early (e.g., biochemical) losses.

To our knowledge, this is the largest study to date analyzing the chances of IVF pregnancy progressing to live birth according to ovarian reserve as measured by baseline FSH, and the only one to also analyze failed pregnancy karyotypes. Unlike previous investigations of this issue, we also evaluated AFC as an alternate measure of ovarian reserve. However, we lacked sufficient data to adequately evaluate antimüllerian hormone (AMH), a third marker of ovarian reserve that is being increasingly used in clinical practice as evidence accumulates of its greater clinical utility than FSH, because we have incorporated routine AMH testing among our patients only recently. Another limitation of this study is its retrospective nature, but the question posed can not be readily addressed through prospective or interventional means.

According to our results, if younger patients with diminished ovarian reserve, as indicated by either elevated basal FSH or low AFC, conceive, their pregnancy is as likely to progress to a live birth as those in the same age group with normal ovarian reserve measures. Our results reinforce previous studies suggesting that although ovarian reserve measures predict the quantity of oocytes that will be obtained with the use of controlled ovarian stimulation, diminished ovarian reserve does not correlate strongly with oocyte quality and subsequent miscarriage (10, 28). Younger patients should be counseled differently than older patients with diminished ovarian reserve. The protective effect of young age should be taken into consideration when evaluating patients during stimulation cycles who are found to have a low number of follicles, particularly when contemplating cycle cancellation for poor ovarian response. Ultimately, age is the most important predictor of pregnancy outcomes, and in general, young patients with FSH elevation should be reassured of their good prognosis for live birth, particularly once implantation has occurred.

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