The Test Tube Baby: Out of Reach or Out of Luck?

A Retrospective Look at the Impact of Basal FSH and Age on In Vitro Fertilization Success in a Clinic Operating Without Laboratory Value Thresholds or Age Limits?

A Thesis submitted to the University of Arizona College of Medicine Phoenix in partial fulfillment of the requirements for the Degree of Doctor of Medicine

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Dedication

This thesis is dedicated to all women who postpone pregnancy,
temporarily or not,
purposefully or not,
while pursuing travel, education, careers and other endeavors

Acknowledgements

This study would like to acknowledge and thank Dr. Robert McGaughey and Dr. Wilson-Rawls for their help and guidance on this project.

Abstract

Objective: To assess the impact of age and FSH on IVF outcomes in an assisted reproductive technology clinic that does not have treatment thresholds based on age or laboratory FSH values.
Design: Retrospective cohort study
Setting: The Arizona Center For Fertility Studies in Phoenix, AZ
Patient(s): Women who sought fertility treatment (with the exclusion of patients using donor or frozen oocytes) ages 18-50, representing a total of 1388 IVF cycles
Intervention(s): IVF using nondonor embryos
Main Outcome Measure(s): Live-birth rate per cycle started
Result(s): A total of 1388 IVF cycles with autologous oocytes were analyzed to determine the impact of basal FSH and age on therapy outcomes. The pregnancy rates for individuals 18-34 years old were not significantly different and ranged from 41.1% to 34%. Pregnancy rates for individuals aged 35-39 years old exhibited a reduced pregnancy rate that ranged from 24.7% to 19.8%. For the eldest patients, a significant reduction in pregnancy rates was demonstrated with patients over the age of 40 having a pregnancy rate of 14.3%, and for those 41 years old and 42 and older having pregnancy rates of 7% and 6% respectively. The live birth rate also mirrored this trend with the youngest age group having a live birth rate of 38.9% and the eldest group of individuals aged 42-50 years having a live birth rate of 3.4%. While increasing FSH levels were associated with reduced numbers of oocytes retrieved and transferred during the IVF procedures, there was no statistically significant reduction in pregnancy rate or live birth rate in those with elevated basal FSH levels.
Conclusion: The data analysis revealed that increasing age in this population does correlate with decreasing successful outcomes in IVF. At ages 36 and 40 years, there are significant reductions in pregnancy rate. At ages 38 and 40, there are significant reductions in live birth rate. Interestingly, there were no significant differences in pregnancy rate or live birth rate based on basal FSH level.

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Introduction

It is estimated that 10-15% of American couples are infertile (9). Many infertile couples will seek medical assistance in becoming pregnant and some of these couples will attempt to become pregnant with the use of assisted reproductive technologies (ART). Recent reports of success rates for ART, from Baker et al (2010), indicate a pregnancy rate of 43.4% and a live birth rate of 38.2% in the United States of America (3). Assisted reproductive technologies are not covered by many insurance plans and can be financially, physically and emotionally stressful for infertile couples (10).

Since its introduction in 1978, in vitro fertilization (IVF) has offered reproductively challenged couples a chance at having children. It has also has been under scrutiny since its inception for ethical and economic evaluation. One report of cost-effectiveness in 1990s of IVF revealed a cost per successful delivery after using IVF techniques ranged from $67,000 if the delivery occurred after one cycle, to a cost of $114,000 if the delivery occurred after six cycles (10). In the past years, ART has increased its successful outcome rates, but continues to be assessed for ethical and economic stress on patients and society. Therefore, predictive factors for success with IVF have been examined in order to optimize success and minimize cases of unrewarded attempts.

Over the past several years, many factors have been examined to assess predictive patterns for success with IVF. Initially, these factors were examined to assess the validity of subjective age thresholds for women seeking IVF. As global ART rates of utilization and success increased, factors were assessed in order to determine ways to increase successful outcomes, expand the option of therapy to those who might benefit and reduce expensive repeat therapies for clients who would likely not become pregnant. Two of the most consistent factors evaluated and found to affect ART success are age and basal level of follicle stimulating hormone (FSH)(19).

These two common factors espoused as predictors of IVF success have been linked to the concept of diminished ovarian reserve which denotes low fertility due to a low number of oocytes or a decreased ability to recruit available oocytes (19). For a pregnancy to occur many anatomically and physiologically necessary steps must occur successfully. One of the earliest stages required for fertilization and thus pregnancy, is the development of a prominent follicle in an ovary to be released during the menstrual cycle. Thus it is understandable that a low number of total oocytes could affect this stage in reproduction. Starting with a lower number of oocytes available to be stimulated could decrease the fertility of an individual. With normal aging, the number of available oocytes in a woman's ovaries decreases (11).

Similarly, a decreased ability to stimulate oocytes, even an appropriate number of oocytes, could result in decreased pregnancy rates.

The level of FSH at the beginning of a woman's cycle, days two through four, has been described as a measure of this physiologic function as it is normally low in women with normal fertility due to a negative feedback loop of circulating hormones. An elevated FSH has been interpreted in many studies to indicate a diminished ovarian reserve, which in turn has been extrapolated to women seeking IVF as a poor prognostic factor. In fact, one of the technological breakthroughs that led to improvement of IVF outcome rates was the technique of controlled ovarian stimulation that increases the number of oocytes recruited and developed in a single cycle (11). This technological innovation helped to correct the diminished ovarian reserve of some patients with advanced age or elevated FSH, and thus, increased the rate of successful outcomes in IVF (16).

Rates for spontaneous conception and ART success decrease with advanced maternal age (2). In fact, some studies have asserted that age is the single most important and predictive factor in determining successful pregnancy rates in ART and in natural, or unassisted, conception (14). It is important to understand the impact of age on ART success rates as the age of first birth is postponed in many women in America. In fact, in the early 2000s, nearly 20% of all women utilizing ART in America were over 40 years old (14).[14]

Many studies have claimed that successful ART outcome rates were significantly decreased with advanced maternal age (12,14). One study asserted that as maternal age increases over 36 years, pregnancy rate and live birth rate in IVF begin to decline (6). Similarly, an analysis of the Society for Assisted Reproductive Technology database revealed that the likelihood of IVF treatment resulting in a live birth delivery for patients over the age of 40 was 52.8% lower than women aged 38-40 years of age, 65% lower than women 35-37 years of age, and 70% lower than women under the age of 35 year old (15). While decreasing fertility with increased age has been suspected and demonstrated in several studies, a proposed cutoff for ART patients has been controversial and disputed. Initially, a subjective cut off of 40 years old was loosely applied to the ART world, as a significant decrease in successful ART pregnancies were seen in women over the age of 40 (8). Then, the upper limit of IVF was arbitrarily moved to 41 or 42 years old (8). Next, a study showed that while the pregnancy rates for women up to 43 years of age were lower than those of patients at age 40, the live birth rate was still deemed acceptable (8).

Several studies have shown an elevated FSH level can yield lower pregnancy rates with ART (4). One study examining FSH impact in patients aged 40-44 years old found a prognostic day 3 FSH cutoff of 11.1 mIU/mL over which no pregnancy was carried past 20 weeks. However, there was no impact of increasing age on the pregnancy rate in this older population (17). This implied that a threshold for FSH level could be used to identify patients who should potentially be advised against undergoing IVF with autologous oocytes due to low probability of success and encouraged to seek other options such as using donor eggs or adoption. However it may be more complicated, as FSH and age are often related. Some studies indicate that women with elevated basal FSH levels, especially younger women, are able to achieve adequate pregnancy rates. One study found that a history of an elevated day 3 FSH level was associated with a reduced live birth rate compared to women with normal day 3 FSH levels also undergoing ART therapy, however the live birth rate was still approximately 20% (1). This questions the necessity or fairness of a threshold for any specific basal FSH level should be used to deter a woman from a chance of becoming pregnant. Additionally, another study found that younger women with elevated FSH had a higher live birth rate than their older counterparts with elevated FSH (19). Thus, these factors are not only conceptually linked but possibly impact one another. Despite the reduction in live birth rate in IVF with elevated FSH, Abdalla (1) claimed that an elevated FSH level is not a contraindication to IVF as reasonable live birth rates and pregnancy rates were able to be achieved.

The last 10 years have been marked with increased success in ART for all age groups. Many clinics, and thus data for clinical studies, have thresholds, for either basal FSH level or age. This could be done to possibly maintain a clinic's success rate and decrease wasteful spending by patients who have a low likelihood of success. However, this provoked the question about what would be seen in a clinic's data that had no threshold for age or basal FSH level? The Arizona Center For Fertility Studies in Scottsdale, AZ offers a chance at fertility to any patient, regardless of lab parameters and age. As some studies have found a strong correlation with basal FSH levels and others have found none, and the average age of women seeking ART continues to increase this clinic offers an interesting and unique ability to assess the impact of these two prominent factors on the success of ART within its own population.

Methods

Patient Description

Data of the patients who underwent IVF treatment at the clinic is routinely collected and sent to the Society for Assisted Reproductive Technology national database. For patients at the clinic who underwent IVF treatment between the years 1999- 2007 the data was selected and analyzed in this study. The data for 1388 cycles were identified. Patients who underwent more than one cycle were analyzed on a per cycle basis, as the aim of the study was to identify basal FSH and age affect per cycle on success outcomes of IVF. There was no cutoff for age or FSH level. The patients ranged in age from 18 to 50 years. A basal FSH was identified for each patient, as well as cause of infertility if known. An IRB was approved for this project by the Scottsdale Health Care system. Information that could be used to identify patients was removed by the principle investigator before this project took place. Each cycle was identified by a number code.

The age groups were combined in order to have a similar sample size in each group, varying between 68 and 148 cycles per age group. Keeping as many per year age groups as possible was desired in this study instead of combining many ages to identify even slight differences in trends of success by age. The basal FSH were divided into five groups based on concentration <5, 6-10, 11-15, 16-20, and >20 mIU/mL. This is consistent with the distribution of measured FSH levels in the Abdalla and Thum(1) study evaluating the impact of elevated FSH in IVF success.

Of the 1388 cycles analyzed, only 5 were unstimulated cycles (0.3% of cases). All other cycles underwent ovarian stimulation, or hyperstimulation of the ovary using hormones to produce multiple follicles during one cycle. The multiple follicles produced by this process were retrieved with transvaginal ultrasound techniques. The retrieved oocytes were fertilized by sperm and then transferred to the female reproductive tract as either a gamete, zygote or embryo. Then these patients were followed-up with an ultrasound to evaluate for intrauterine pregnancy.

Exclusion Criteria

Women who used donor oocytes or frozen oocytes were not included in the sample. Additionally, women who were undergoing stimulation in order to donate oocytes were not included in the sample.

Outcomes measured

Outcomes were defined as number of oocytes retrieved following ovarian stimulation, number of transferred embryos, gametes or zygotes to their perspective locations (uterus or fallopian tubes), a confirmed intrauterine gestation via ultrasound, and a live birth. Twins or triplets

would be considered one live birth. A canceled cycle was defined as an ovarian stimulation cycle that had been started with the expectation to proceed with ART, but did not proceed with oocyte retrieval. A total of 146 of 1388 cycles were canceled (10.5%).

Statistical analysis

The data was compiled and analyzed in Microsoft Excel. All p-values result from single-variable variance analysis using ANOVA as a tool on EXCEL. ANOVA was utilized to determine whether or not the means of the group's analyzed are similar or difference. The probability level for statistical significance was taken to be $p<0.05$.

Results

Among the 1,388 cycles included in this analysis, the mean age of the patients was 35.13 ± 4.9 years (mean ± SD). The mean maximal basal FSH detected on cycle day 1-4 in this analysis, was 11.6 ± 6.98 mIU/mL. The etiology of infertility, if known was identified in 88.6% of cycles with the most common causes listed as male factor (23.3% of cycles), tubal factor (21.6%) and endometriosis (16.5%). (See Table 1).

A total of 146 cycles (10.5% of all cycles) were canceled. While the majority of the canceled cycles were due to concurrent illness (n=47, 32.2% of canceled cycles), there were two reasons of canceled cycles that could be directly attributed to the process of stimulation. These included inappropriate response (n=4, 2.7% of canceled cycles), either low response or high response, and inadequate endometrial response (n=47, 32.2% of canceled cycles). (see Table 2). The mean FSH for cycles canceled for inappropriate response was elevated compared to cycles canceled for inadequate endometrial response, 26.25±12 mIU/mL compared to 12.2±7 mIU/mL. The age for inappropriate response was also elevated compared to the inadequate endometrial response, 42±2.4 years vs 36.0±4.1 years. (Table 3).

The maximal basal FSH by age group showed no significant change as age increased (see Figure 1). The maximal FSH for the youngest patients, ages 18-27 years, was 12.16±8.14 which was not significantly different from FSH level measured in the oldest age group patients, 42-50 years old with a value of 13.28±7.71. Interestingly, there were two age groups that had a significantly lower maximal FSH than the rest of the age groups that were located in the middle of the age groups. For 36 year old women, the maximal FSH was 9.46±4.62 ($p < 0.05$ when compared to all other ages). For 38 year old women the maximal FSH was 10.47±4.53 mIU/mL ($p < 0.05$ when compared to all other age groups). (Table 4).

Outcomes by Age

The data indicated a decrease in number of oocytes retrieved as age increased. As demonstrated in Table 5, the number of oocytes retrieved did not differ significantly for the first four age groups, ranging from 18-32 years old, values of 14.29±7.79 oocytes retrieved, 13.21±7.52, 13.1±7.5 and 11.9±8.1 oocytes retrieved respectively ($p = 0.2$). As the age increased to 33, 34, 35 and 36, the number of retrieved oocytes decreased to 11.06±6.6, 10.52±6.59, 10.13±6.2, and 10.29±6.6 ($p < 0.005$ when compared to youngest four age groups). Women over the age of 38, demonstrated a continued significant decrease in number of oocytes retrieved. The mean number of retrieved oocytes was 9.21±6.6 in patients 38 years old and 4.65±3.55 oocytes retrieved in patients over the age of 42 years old. Of note, the 37 year old patients had

a mean number of oocytes retrieved that was not significantly lower from the first four age groups (p=0.17 when compared to ages 18-32 years).

Assessing the number of oocytes or embryos that were transferred during the ART protocol illustrated no significant difference in the number of transferred oocytes or embryos as age ranged from 18-41 years. The mean number of transferred embryos or oocytes in the 18-27 year old age group was 3.43±1.81 which was not significantly different from the number transferred in the 41 year old age group, 3.5±2.25 embryos or oocytes (p= 0.06). The oldest age group of 42-50 year old patients had a significantly decrease in the mean number of oocytes or embryos transferred when compared to the other age groups with a mean number of 2.88±1.92 oocytes or embryos transferred (p=0.001 when compared to all other age groups).

The pregnancy rate (PR) was determined by ultrasound confirming an intrauterine gestation. This parameter showed a decrease as age increased. There was no significant difference in the pregnancy rate for the first five age groups, with a PR of 41.1% for patients 18-27 years old compared to a PR of 34% for the 34 year old age group (p=0.46). There was a decrease in the pregnancy rate for the 35 year old patients to a PR of 20%, but this decrease was not significant (p =0.06). Additionally, women who were 37 years of age had a pregnancy rate of 24.7%, less than younger women but not significant (p =0.06). The 36 year old patient age group was the first age group to show a statistically significant decrease in PR with a value of 19.1% (p <0.05). The age groups of 38 and 39 years old also had lower pregnancy rates of 22.3% and 19.8% respectively (p <0.05 when compared to the age groups 18-27, 28-29, 30-31, 32, 33, 34.). As age increased to 40 years and older the decrease in PR continues to become more pronounced with a PR of 14.3% (p<0.01) for the 40 year old age group, 7% at age 41, and 6% over the age of 42 (p< 0.001 when compared to the first six age groups).

The live birth rate(LBR) decreased with increased age, much the same way that pregnancy rate decreased. Again, there was no difference in the live birth rates between the groups 18-27, 28-29, 30-31, 32, 33, and 34 (p= 0.3). At age 35, the live birth rate measured was reduced to 18.2% and at age 36 the LBR was reduced to 17.6%. The patients aged 37 had a 20.6% LBR though these decreases were not statistically significant (p <0.1 when compared to the LBRs of ages 18-35). For patients aged 38 years, the measured LBR was significantly lower compared to the younger LBRs with a value of 18%, and at 39 years old the LBR was 16.9% (p <0.05 when compared to LBRs of ages 18-35). At ages 40 and 41 the live birth rate decreased even more significantly to 13.2% and 7% respectively p <0.01). The eldest age group had the significantly lowest live birth rate of 3.4% (p <0.001).

Outcomes by FSH level

Follicle stimulating hormone can be used to assess for an indirect measurement of ovarian reserve. Due to hormone suppression, an FSH level should be low in reproductively aged women. An elevated FSH level in reproductively aged women could suggest that the ovaries are unable to be appropriately stimulated to release an adequate hormone suppression on FSH. The levels examined in this study were described as low if measured <5 and 6-10 mIU/ml. The moderate FSH level was 11-15 mIU/mL, and the FSH measurements above 15 were defined as elevated.

When evaluating the effect of maximal basal FSH, there was no significant difference in mean age between the FSH concentrations <5, 11-15, 16-20, and >20 mIU/ml. Interestingly, the group with a measured FSH of 6-10mIU/mL had a significantly lower average age than for the other groups with a value of 34.7±4.87years ($p<0.05$).

When evaluating the mean number of oocytes retrieved there was similarity demonstrated in the two lowest FSH levels measured, which yielded 11.35±7.78 and 11.60±7.28 oocytes retrieved respectively ($p=0.7$). As seen in Figure 2, as the level of FSH increased above 10 mIU/mL the number of oocytes retrieved decreased. There was a significant decrease in the number of oocytes retrieved for the elevated FSH group of 16-20 mIU/mL, which had a mean number of oocytes retrieved of 9.14±7.15 ($p<0.01$ when compared to the lowest FSH groups). The moderately elevated FSH group of 11-15 mIU/mL and the very elevated FSH of >20 mIU/mL had significantly less oocytes retrieved compared to the lowest FSH levels. The FSH group of 11-15 mIU/mL had a mean number of oocytes retrieved of 8.88±6.2 ($p<0.001$). The FSH group >20 mIU/mL had a mean number of oocytes retrieve of 8.30±6.98 (P-value <0.001).

As expected based on the above observations there was no difference in the number of oocytes or embryos transferred between the lowest FSH groups. The individuals with an FSH <5 mIU/mL, had a mean number of oocytes and embryos transferred of 4.15±2.28 and the FSH group 6-10 mIU/mL had a mean number of oocytes or embryos transferred of 4.10±2.03 ($p=0.7$). The group of individuals with FSH group of 11-15 mIU/mL had a reduced mean number of oocytes and embryos at 3.70±2.02 ($p<0.05$ when compared to FSH groups <5 and 6-10mIU/mL). The elevated measured FSH group 16-20 mIU/mL had a similar number of oocytes or embryos transferred at 3.56±1.85 though this was not significantly statistically different ($p=0.05$ when compared to FSH levels of <5 and 6-10 mIU/mL). The group of patients with the most elevated basal FSH level of >20 mIU/mL showed a significant reduction in the number of oocytes or embryos transferred at 2.89±1.77 ($p<0.001$ when compared to group's with FSH levels <10 mIU/mL) (Figure 3).

Interestingly, the pregnancy rate was not significantly different when compared against basal FSH values (p =0.06 for all groups). The lowest FSH group and the highest FSH group had lower pregnancy rates than the middle FSH groups but not significantly (Table 6). A similar trend was noted with live birth rates, the extremes of FSH level had lower live birth rates than the middle FSH levels, though this was not statistically significant (Table 6). The oldest patient to have a live birth was 42, The highest basal FSH measured to result in a live birth was measured in a 32 year old patient with an FSH level 44 mIU/mL. Patients over the age of 40, FSH levels that resulted in live births were much lower. The highest FSH measured that resulted in a live birth by a 40 year old patient was 12 mIU/mL and by a 41 year old patient 15 mIU/mL. The highest FSH measured to result in live birth in a 42 year old patient was 15, and this occurred in two patients at this age. No patient experienced a live birth over the age of 42 years old, regardless of FSH level.

Figures:

Table 1. Demographic Data

Age (years)	35.13 ± 4.9
Maximal basal FSH (mIU/ml)	11.6 ± 6.98
Cause of Infertility	
Male Factor	322 (23.2)
Endometriosis	229 (16.5)
Ovulation Disorder or PCOS	9 (0.6)
Diminished Ovarian Reserve	60 (4.3)
Tubal Factor	300 (21.6)
Uterine Factor	12 (0.8)
Other	565 (40.7)
Unknown	173 (12.4)

Values are expressed as mean ± SD. Values in parentheses are percentages.

Table 2. Cycle and Laboratory Data

Total number of cycles	1388
Number of cycles canceled	146 (10.5)
Cancellation Reason	# (% of cancelled cycles)
1. Inappropriate Response	4/146 (2.7)
2. Inadequate Endometrial Response	47 (32.2)
3. Concurrent Illness	84 (57.5)
4. Withdrawal for personal reason	12 (8.2)
No. of oocytes retrieved	10.4 ± 7.1
No. of oocytes or embryos transferred	3.86 ± 2.04

Values are expressed as mean ± SD. Values in parentheses are percentages.

Table 3. Mean FSH and Age for Cycle Cancellation Etiology

Cancellation Reason	1	2	3	4
Mean FSH	26.25± 12	12.2±7	13.6±8	11.6±5
Mean Age	42±2.4	36.9±4.1	38.3±4	33.0±2.17

Values are expressed as mean ± SD. Values in parentheses are percentages.
Cancellation Reasons listed in Table 2.

Table 4. Maximal basal FSH by Age Group

Age, years	Maximal basal FSH (mIU/mL)
18-27	12.16 ± 8.14[a]
28-29	9.51 ± 4.6[a]
30-31	10.33 ± 5.8[a]
32	11.26 ± 7.91[a]
33	12.56 ± 7.1[a]
34	12.13 ± 8.2[a]
35	11.47 ± 7.0[a]
36	9.46 ± 4.62[b]
37	11.13 ± 5.87[a]
38	10.47 ± 4.53[b]
39	12.59 ± 7.57[a]
40	12.10 ± 7.87[a]
41	14.72 ± 7.69[a]
42-50	13.28 ± 7.71[a]

Values are expressed as mean ± SD. Values in parentheses are percentages.
[a] denotes P-value = 0.12 between compared groups.
[b] denotes P-value <0.05 compared to age groups 18-27, 28-29, 30-31, 32, 33, 34, 35, 37, 39, 40, 41 and >42.

Figure 1: Mean Measured Maximal FSH by Age Group

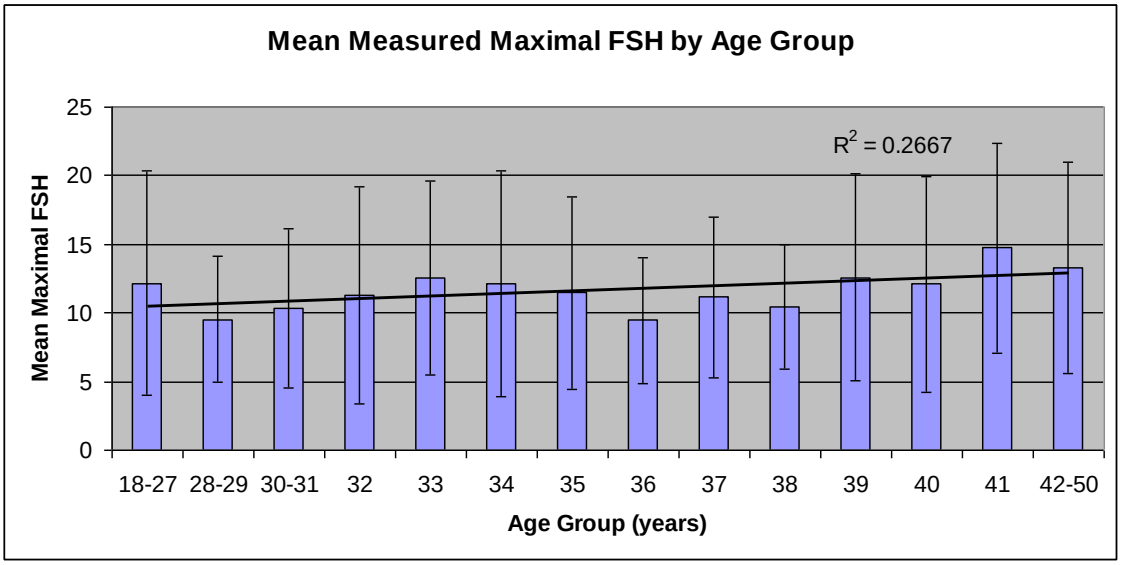

Table 5. Cycle Outcome based on Age

	No. cycles N = 1388	%	No. oocytes retrieved	No. oocytes or embryos transferred	Pregnancy Rate (%)	Live Birth Rate
Age, years						
18-27	90	6.48	14.29 ± 7.79[Ϫ]	3.43 ± 1.81[1]	37/90 (41.1)[a]	35/90 (38.9)[f]
28-29	85	6.12	13.21 ± 7.52[Ϫ]	4.02 ± 1.69[1]	28/85 (32.9)[a]	23/85 (27.1)[f]
30-31	148	10.66	13.1 ± 7.5[Ϫ]	4.04 ± 1.86[1]	43/148 (29.05)[a]	41/148 (27.7)[f]
32	97	6.98	11.9 ± 8.1[Ϫ]	3.55 ± 1.96[1]	28/97 (28.8)[a]	24/97 (24.7)[f]
33	106	7.63	11.06 ± 6.6[Ψ]	3.96 ± 1.77[1]	33/106 (31.1)[a]	31/106 (29.2)[f]
34	97	6.98	10.52 ± 6.59[Ψ]	4.11 ± 2.03[1]	33/97 (34)[a]	28/97 (28.8)[f]
35	115	8.28	10.13 ± 6.2[φ]	3.79 ± 2.07[1]	23/115 (20)[b]	21/115 (18.2)[g]
36	68	4.89	10.29 ± 6.6[Ψ]	4.15 ± 2.04[1]	13/68 (19.1)[c]	12/68 (17.6)[g]
37	97	6.98	11.74 ± 8.68[Ω]	4.18 ± 2.17[1]	24/97 (24.7)[b]	20/97 (20.6)[g]
38	94	6.77	9.21 ± 6.6[Ÿ]	3.74 ± 2.14[1]	21/94 (22.3)[c]	17/94 (18)[h]
39	106	7.63	7.07± 4.09[Ÿ]	3.98 ± 2.11[1]	21/106 (19.8)[c]	18/106 (16.9)[h]
40	98	7.06	8.98 ± 5.58[Ÿ]	4.57 ± 2.49[1]	14/98 (14.3)[d]	13/98 (13.2)[i]
41	71	5.11	6.78± 5.32[Ÿ]	3.5 ± 2.25[1]	5/71 (7)[e]	5/71 (7.0)[j]
42-50	116	8.35	4.65± 3.55[Ÿ]	2.88± 1.92[2]	7/116 (6)[e]	4/116 (3.4)[j]

Values are expressed as mean ± SD. Values in parentheses are percentages.

[1] denotes a P-value = 0.06

[2] denotes a P-value <0.001 when compared to all other age groups.

[Ϫ] denotes a P-value = 0.2

[Ψ] denotes a P-value <0.05 when compared to age groups 18-27, 28-29, 30-31, and 32.

[φ] denotes a P-value <0.01 when compared to age groups 18-27, 28-29, 30-31, and 32.

[Ω] denotes a P-value =0.17 when compared to age groups 18-27, 28-29, 30-31, and 32.

[Ÿ] denotes a P-value <0.001 when compared to age groups 18-27, 28-29, 30-31, and 32.

[a] denotes a P-value = 0.46

[b] denotes a P-value = 0.06 when compared to age groups 18-27, 28-29, 30-31, 32, 33 and 34.

[c] denotes a P-value <0.05 when compared to age groups 18-27, 28-29, 30-31, 32, 33 and 35.

[d] denotes a P-value <0.01 when compared to age groups 18-27, 28-29, 30-31, 32, 33 and 35.

[e] denotes a P-value <0.001 when compared to age groups 18-27, 28-29, 30-31, 32, 33 and 35.

[f] denotes a P-value = 0.3

[g] denotes a P-value <0.1 when compared to age groups 18-27, 28-29, 30-31, 32, 33 and 34.

[h] denotes a P-value <0.05 when compared to age groups 18-27, 28-29, 30-31, 32, 33 and 35.

[I] denotes a P-value <0.01 when compared to age groups 18-27, 28-29, 30-31, 32, 33 and 35.

[j] denotes a P-value <0.001 when compared to age groups 18-27, 28-29, 30-31, 32, 33 and 35.

Figure 2: Mean Number of Oocytes Retrieved per Measured FSH Level

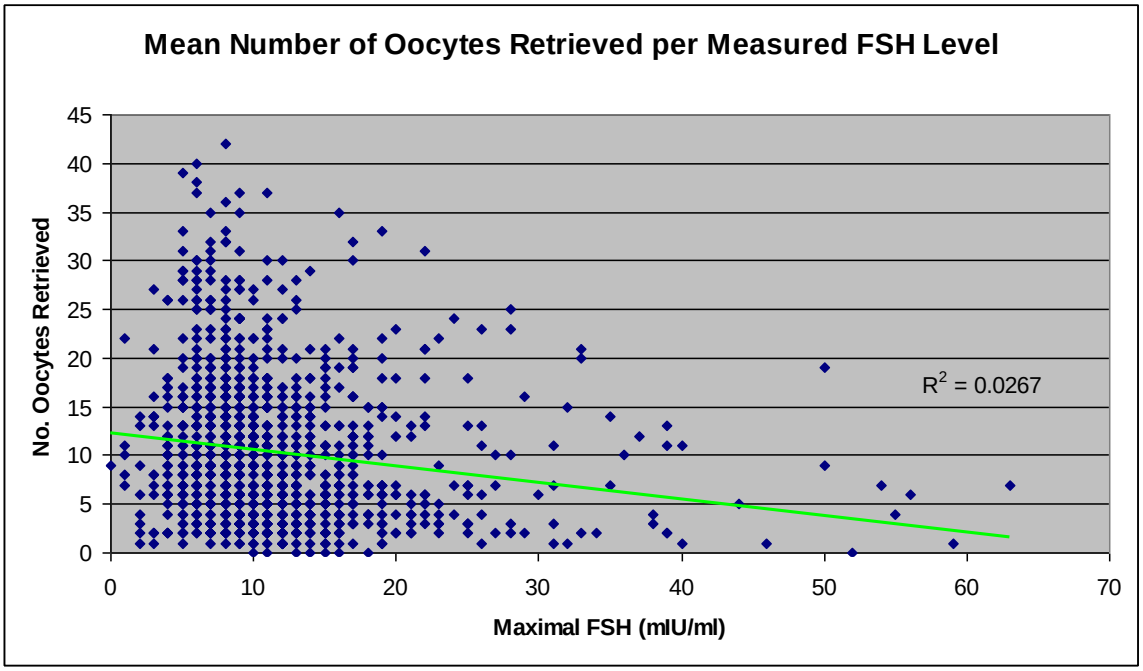

Figure 3: Number of Transferred Oocytes per Measured FSH Level

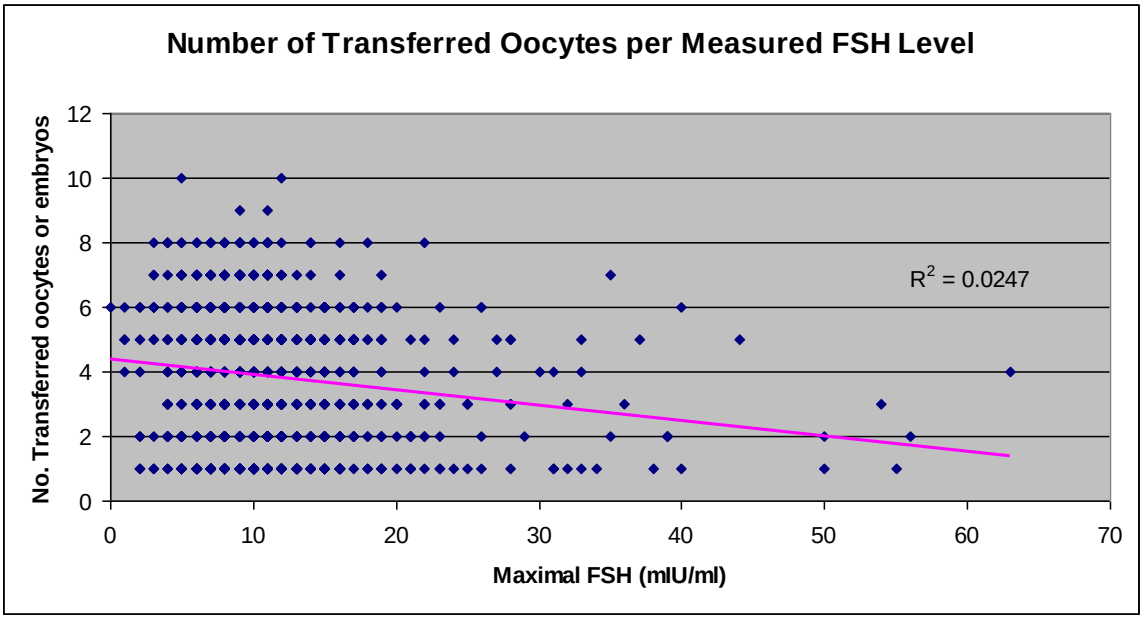

Table 6. Cycle Outcome Data based on Basal FSH

Basal FSH	# of cycles	Age	# Oocytes Retrieved	# oocytes or embryos transferred	# CIG+ cycles (Pregnancy Rate per Cycle)	# cycles with a live birth (Birth Rate per Cycle)
<5	125	35.2±4.34	11.35±7.78[1]	4.15±2.28[1]	21 (16.8)[a]	15 (12.0) [b]
6-10	644	34.7±4.87[*]	11.60±7.28[1]	4.1±2.03[1]	172 (26.7)	148 (22.9)
11-15	379	35.6±4.91	8.88±6.2[**]	3.70±2.02 [*]	91 (24.0)	82 (21.6)
16-20	128	35.3±5.00	9.14±7.15 [Ψ]	3.56±1.85[2]	28 (21.9)	27 (21.1)
>20	112	35.54±5.4	8.30±6.98[**]	2.89±1.77[**]	20 (17.8)	20 (17.8)

Values are expressed as mean ± SD. Values in parentheses are percentages.
[1] denotes a P-value =0.7.
[*] denotes P-value <0.05 when compared to FSH groups <5, and 6-10.
[2] denotes a P-value = 0.05 when compared to FSH groups <5, and 6-10.
[**] denotes P-value <0.001 when compared to FSH groups <5, and 6-10.
[Ψ] denotes P-values <0.01 when compared to FSH <5 and 6-10.
[a] denotes P-value = 0.06 for all age groups
[b] denotes P-value = 0.07 for all age groups

Discussion

This study was undertaken to determine the impact, if any, that age and FSH level had on IVF success in the Arizona Center For Fertility Studies that did not discriminate against possible ART patients based on thresholds of age or lab parameters.

Age

Age impacted the predictors of IVF of number of oocytes and the number of transferred oocytes or gametes, as age increased these predictors decreased. Age also negatively impacted the successful outcomes of pregnancy rate and live birth rate, as age increased these outcomes decreased.

This data analysis revealed that increasing age in this population does correlate with decreasing successful outcomes in IVF defined as confirmed intrauterine gestation and live births. Once a woman reaches 38 years of age, her pregnancy rate and live birth rate becoming significantly lower than that of younger patients ($p < 0.05$). The ages of 40 and 42 also indicate more significant decreases in pregnancy rate and live birth rate compared to women under the age of 35. This finding is similar to many studies that have identified age as a factor impacting IVF outcomes. This is similar to what the 2007 Canadian ART Registry reported, as age increased the number of oocytes decreased. The reported clinical pregnancy rates for patients undergoing IVF with autologous oocytes under the age of 35 years, 35-39 years, and ≥40 years were 37.5%, 29.5% and 15.8% respectively (7). The oldest patient in this study to undergo IVF with a resulting live birth was 42 years old. Thus, patients over 42 years old seeking ART at this center will be able to use this fact to guide their decisions about IVF therapy.

The results showing a significant decrease in successful IVF outcomes associated with patients over the age of 41 years old could be supportive of age thresholds in other ART clinics. The information from this sample could be used to initiate conversations with patients 41 years old and older who are struggling with infertility about alternative options to IVF with autologous oocytes, such as utilization of donor oocytes or adoption.

FSH:

The mean maximal FSH level negatively impacted the predictors of IVF but did not appear to impact the outcomes of IVF therapy. This analysis revealed that while basal FSH can result in lower numbers of oocytes retrieved and transferred, there was no affect on pregnancy rate and live birth rate. This was an interesting finding as it was surmised that an elevated FSH would represent decreased ovarian reserve which has been identified in the literature as being a poor indicator for IVF success. Decreased ovarian reserve has been described as a quantitative and qualitative predictor for pregnancy, including ART pregnancy rates. The

observations from this study indicate that the quantity of oocytes able to be retrieved and transferred are diminished when associated with elevated levels of FSH. Importantly, it does not appear that the quality of these oocytes have a decreased capacity to be fertilized or carried to term.

The highest basal FSH to result in a live birth was 44 mIU/mL. This finding is consistent with the literature that reports that young age can overcome elevated FSH levels. For example in 2005, Klipstein et al. found that elevated FSH levels above 15 mIU/mL in 40 year old patients had a pregnancy rate of 4.55%, which was declared nearly acceptable in the studies assumption that a pregnancy rate or live birthrate above 5% was acceptable (8). This result was higher than Watt found for a threshold of elevated FSH in women of the age of 40 years old. In that study, Watt asserted a prognostic cutoff of an FSH of 11.1 mIU/mL in women over the age of 40 (17).

For patients over the age of 40, the highest measured FSH level that resulted in a live birth was 15 mIU/mL. This is consistent with the highest basal FSH associated with a live birth in Klipstein's study of over 2,700 IVF cycles in patients over the age of 40. The highest basal FSH to result in a live birth was 15.4 in a 40 year old female (8). Thus older patients with normal or moderate levels of FSH are able to have successful outcomes with IVF, and younger patients with elevated levels of FSH are able to overcome this poor prognostic factor and give birth.

While there was no statistically significant decrease in pregnancy rate and live birth rate as FSH levels increased, there was a decrease in many of the measurable stages of IVF such as number of oocytes retrieved and transferred. Studies have shown that the number of oocytes retrieved and transferred have been associated with increased live birth rate (LBR)(11). In 2004, a study aiming to determine the quantitative and qualitative claims of the FSH impact on IVF success found that higher levels of FSH (described as 10-15, >15, and >20) were associated with lower number of eggs collected, eggs transferred, and lower pregnancy and live birth rates (1).

Future Directions

While this study showed that increasing age does impact IVF success defined as confirmed intrauterine pregnancies and live births, which is consistent with many other studies, the association with basal FSH levels did not show a similar response with the IVF outcomes. The impact of ethnic variation with ART success with this Southwestern clinic would be interesting. One study in 2008 revealed that ethnic disparities in ART success rates exist between black women and white women, as depicted in increased spontaneous abortions in black women and a live birth rate of 18.7% in black women compared to 26.3% in white women (13). Additionally, a large multivariate analysis of national ART data revealed that white women had a significantly higher pregnancy rate then Asian women, black women and Hispanic women (2). The ethnicities of the women in this study, if known, were removed before the study took place. As the Southwestern United States has a large Hispanic population, it would be interesting to see the ethnic makeup of the women who underwent ART at this clinic.

Conclusion

The analysis revealed that increasing age in this population does correlate with decreasing successful outcomes in IVF. Interestingly, there were no significant differences in pregnancy rate or live birth rate based on basal FSH level. In this clinic's population, age but not FSH level is an important factor affecting IVF outcomes. This finding helps validate the clinic's decision to not implement FSH level parameters for patients seeking therapy options. It also calls into question whether clinics that do operate with a FSH level threshold could offer IVF therapy with an adequate chance of success to women currently discouraged from their dreams of becoming pregnant based on a laboratory value.

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