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# Natural cycle *in vitro* fertilization implantation rates compared to stimulated *in vitro* fertilization and role of serum antimullerian hormone levels

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## ABSTRACT

**Objective:** The objective of this study is to compare implantation and singleton live birth rates between natural cycle *in vitro* fertilization (NCIVF) and stimulated IVF. Stratify the results by age and antimullerian hormone (AMH). **Design:** Retrospective cohort trial of patients who underwent unstimulated IVF between 2007 and 2011. Stimulated patient data from the 2010 Centers for Disease Control (CDC) report. **Setting:** Private practice. **Patients:** Infertility patients < 43-year-old. **Intervention:** None. Main **Outcome Measures:** (1) Implantation rates stratified by age and AMH (2) singleton pregnancy rates. **Results:** A total of 1288 cycles of NCIVF were compared to 94,976 cycles from CDC. In patients <35 years the implantation rates for NCIVF and stimulated IVF were 35.1% versus 36.9%. In patients 35-37, 38-40 and 41-42 years old, the NCIVF and stimulated IVF implantation rates were 33.9% versus 27.0%, 30.4% versus 17.7%, and 21.4% versus 9.6%. NCIVF implantation rates were independent of AMH at all ages and all levels of AMH. The singleton live birth rates per embryo transfer for both NCIVF and the CDC reported stimulated IVF were similar for all age groups. **Conclusions:** Implantation rates were superior in patients 35-40 undergoing NCIVF compared with stimulated IVF. In NCIVF implantation rate was independent of AMH. The live singleton birth rates per embryo transfer for NCIVF and stimulated IVF are similar.

**Key Words:** Antimullerian hormone, implantation, *in vitro* fertilization, natural cycle *in vitro* fertilization, unstimulated *in vitro* fertilization

## INTRODUCTION

Natural cycle *in vitro* fertilization (NCIVF) is performed worldwide with acceptable clinical pregnancy rates, but stimulated IVF is the predominant form of IVF utilized in the United States.[1-5] Data from the United States Centers for Disease Control (CDC) clearly show a progressive decline in the embryo implantation rates in patients over 35-year-old as compared with younger patients using stimulated IVF.[6] This age-related effect is also present in patients who undergo NCIVF. There is a suggestion that NCIVF implantation rates do not suffer the same age-related decline as seen in stimulated IVF,[1] but this study was carried out with pooled national (SART)



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data and thus hindered by the confounders inherent with pooled data for a technique rarely used by most clinics. This study is the first to look at a large number of NCIVF cycles from a single clinic and see how implantation rates compared to the national stimulated averages. NCIVF is defined as oocyte retrieval, fertilization and embryo transfer after human chorionic gonadotropin (HCG) trigger without luteinizing hormone (LH) suppression or ovarian stimulation.

It is thought that the age related decline in embryo implantation is related, in part, to ova quality and possibly direct adverse effects of exogenous gonadotropin stimulation on both the oocyte and endometrium.[7,8] Impairment of endometrial receptivity and implantation has been reported following ovarian stimulation for IVF.[9-11]

Decreased ovarian reserve further reduces the likelihood of success with stimulated IVF in patients of advanced reproductive age.[12-14] Evidence is mixed as to the potential benefits of NCIVF in patients with poor ovarian reserve. In a study of 500 consecutive cycles of NCIVF in patients who had demonstrated poor ovarian reserve defined as failure of gonadotropin stimulation for IVF, Schimberni *et al.* found NCIVF was an effective treatment.[15] In another study using the Bologna criteria to define poor ovarian reserve, patients treated with NCIVF did not show any substantial benefits, although control patients with normal ovarian reserve did.[16] In the only randomized controlled trial comparing NCIVF to stimulated IVF in poor responders, significantly higher implantation rates were found using NCIVF.[17] Using serum antimullerian hormone (AMH) as a measure of ovarian reserve, Lamazou reported no differences in implantation rates in patients with normal or abnormal AMH treated using modified NCIVF.[18] The success rates of NCIVF as a function of AMH has not been reported.

In this study, we compared our implantation rates for NCIVF to the 2010 CDC IVF reported implantation rates with respect to age. The implantation rate for NCIVF was then stratified by the serum AMH levels for patients who underwent NCIVF (CDC AMH data was not available). Singleton live birth rates were also studied.

## MATERIALS AND METHODS

### Ethics

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. This study was deemed exempt by an independent review board.

### Study design

We utilized the 2010 CDC IVF data submitted by clinics in the United States to obtain implantation data on patients undergoing stimulated IVF. While the 2010 CDC database does include both stimulated and unstimulated IVF, only 1% was unstimulated. This small percentage was not sufficient to impact the overall CDC data in a meaningful way; thus the 2010 CDC data is used to reflect national stimulated IVF results for the purposes of this study. This data were compared to implantation results in our NCIVF program for the years 2007-2011. The implantation results as reported by CDC include all patients regardless of their ovarian reserve status. The implantation rates were then compared for both types of IVF for ages <35-year-old and between 35 and 37, 38 and 40, and 40 and 42 years old as formatted by the CDC. Implantation rates were also compared based upon AMH levels in NCIVF patients. It is acknowledged that the CDC IVF patients would include both patients with normal and abnormal AMH levels. We chose the CDC IVF registry to compare stimulated IVF to our NCIVF results as we believed this to be a less biased comparison than using our own stimulated patients as most of our patients first select NCIVF before undergoing stimulated IVF. Therefore, our stimulated patients represent a subset expected to respond more poorly to additional treatment, which could falsely inflate the significance of our findings. All treatments were performed at a single private practice reproductive center in the United States between January 1, 2007 and December 31, 2011.

The CDC report for 2010 included 41,744 patient cycles <35-year-old and 53,232 cycles in patients 35-42 years old. A total of 615 patients whose median age was 35-year-old (range 23-42) underwent 1288 cycles of NCIVF in our clinic. For our NCIVF program, all patients had regular menstrual cycles, defined as every 23-36 days. All patients had a standard infertility evaluation with ovarian reserve testing, a pelvic sonogram, hysterosalpingogram, and semen analysis. All patients offered stimulated IVF were also offered NCIVF. Patients were enrolled into our NCIVF program regardless of the status of their current or past ovarian reserve testing or previous failures with stimulated IVF at our or other IVF centers, or the need for testicular sperm extraction with intracytoplasmic sperm injection (ICSI). Patients requiring preimplantation genetic diagnosis were excluded. For NCIVF, no ovarian stimulation medications or gonadotropin-releasing hormone analogs were used. Our methodology has been previously reported.[19] The patient's cycle was monitored beginning on day 2 or 3 of their menstrual cycle and again beginning on day 7 using transvaginal ultrasound (Siemens)

and serum estradiol (E2), progesterone (P4) and LH testing (Immulite 2000) until follicle maturity (>15 mm mean diameter) at which time 10,000 units of HCG, pregnyl, organon, Roseland, NJ was administered.

Oocyte retrieval occurred 35 h after HCG using transvaginal ultrasound-guided aspiration using a 17-gauge single channel IVF needle (Cook Echotip Norfolk aspiration needle) followed by up to 12 flushes of the follicle using modified human tubal fluid (Irvine Scientific: Irvine, CA) media. Most patients received 10 mg of oral diazepam 30 min prior to the oocyte retrieval and 0-3 mg of intravenous midazolam immediately prior to aspiration. All patients received oral doxycycline 100 mg twice daily for 10 days beginning at the time of HCG and oral cephalexin 1000 mg the morning of oocyte retrieval. ICSI was performed in all patients unless the couple had proven fertility or otherwise declined. Assisted hatching was performed in all patients >37 years of age and in those with a history of failed IVF. All patients underwent a day 3 embryo transfer until October 2009 when our program adopted a blastocyst transfer protocol for all patients (either day 5 or 6). All embryos were transferred using an afterload technique with a Wallace embryo or Cook echotip microvolume catheter (Wallace Sureview Embryo Transfer catheter) with abdominal ultrasound guidance. Serum HCG was obtained 14 days after the embryo transfer and all pregnancies were confirmed using transvaginal ultrasound once the serum HCG level was at least 2000 IU/ml. All patients received luteal support using oral estradiol valerate 2 mg/day and progesterone vaginal suppositories 100 mg bid beginning on the day of oocyte retrieval. Ongoing pregnancies were defined as a pregnancy showing an intrauterine gestational sac with normal fetal cardiac activity using transvaginal ultrasound at 6 weeks gestation. Implantation rate was defined as number of gestational sacs seen on 6 week ultrasound divided by the number of embryos transferred. In the event of a monozygotic twinning event as evidenced by two sacs after a single embryo transfer, the implantation rate was corrected to one. The singleton live birth rate was defined as the number of live born singletons divided by the number of embryo transfers performed in the patient cohort. All deliveries were confirmed directly with patients.

We compared implantation rates based upon AMH levels in NCIVF patients, acknowledging that this data were unavailable from the CDC for comparison.

### Statistical analysis

The implantation rates were compared for both types of IVF for ages <35-year-old and between 35 and 37, 38 and 40, and 40 and 42 years old as formatted by the CDC. All statistical tests were performed with Chi-square analysis followed by Fisher's exact test as required (Prism G Graphpad Software, La Jolla, CA). As we analyzed all available cycles at our center and through the CDC, we were unable to increase our sample size, and thus we did not perform a power analysis.

## RESULTS

The median age for all NCIVF patients was 35, range 23-42. There were 259 patients and 488 cycles in patients <35-year-old, and 356 patients and 800 cycles in patients 35-42 years old. The median duration of infertility was 2.0 (range 1-17) years and the median body mass index 23 (range 16.8-45.1). Demographics are provided in Table 1.

The 2007-2011 NCIVF and 2010 CDC IVF implantation rates for all patients and for patients <35, and 35-37, 38-40 and 41-42 years old with respect to AMH levels are shown in Table 2. For all patients <35-year-old the implantation rates for NCIVF and CDC IVF patients were similar, 35.1% versus 36.9% ($P > 0.05$). In patients 35-37, 38-40 and 41-42 years old the implantation rates for NCIVF and CDC IVF were 33.9% versus 27.0% ($P < 0.05$), 30.4 versus 17.7% ($P < 0.05$) and 21.4%

**Table 1: Demographics and cycle characteristics of patients (*n*=615) undergoing NCIVF from 2007 to 2011. Descriptive statistics are given as median (range)**

| 2007-11 NCIVF patient demographics and cycle characteristic overview | |
|---|---|
| **Patient demographics (*n*=615)** | **Median (range)** |
| Age (years) | 35 (23-42) |
| BMI | 23 (16.8-45) |
| Duration of infertility (years) | 2.0 (1-17) |
| Hormone profiles | |
| AMH (ng/ml) | 1.3 (0.1-16) |
| Day 3 FSH (IU/L) | 6.7 (1.6-30) |
| Day 3 estradiol (pg/ml) | 47.0 (3.5-347) |
| Day of HCG | |
| Estradiol (pg/ml) | 183 (50-433) |
| LH (IU/L) | 5.5 (1.4-24) |
| Progesterone (ng/ml) | 0.3 (0.2-2.1) |
| Indications for NCIVF (*n*=615) (%) | |
| Male factor | 197 (32) |
| Decreased ovarian reserve | 189 (31) |
| Tubal | 99 (16) |
| Unexplained | 56 (9) |
| Endometriosis | 24 (4) |
| Other/multifactorial | 50 (8) |

NCIVF: Natural cycle *in vitro* fertilization; BMI: Body mass index; AMH: Antimullerian hormone; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; HCG: Human chorionic gonadotropin

**Table 2: A comparison of implantation rates: Natural IVF cycles categorized by patient AMH and age (DF 2007-2011), to the stimulated IVF cycles of all US clinics (CDC 2010)**

| NCIVF (DF 2007-11) versus stimulated IVF (CDC 2010) | | | | | |
|---|---|---|---|---|---|
| Age grouping (years) | All | <35 | 35-37 | 38-40 | 41-42 |
| Implantation rate, % (CDC 2010) | | 36.9 | 27.0 | 17.7 | 9.6 |
| Singleton live birth/ET, % (CDC 2010) | | 31.4 | 27.3 | 21.5 | 13.7 |
| NCIVF singleton live birth/ET, % (DF 2007-11) | | 32.7 | 29.4 | 23.5 | 10.0 |
| All NCIVF, DF (2007-2011) | | | | | |
| Patients | 615 | 259 | 142 | 160 | 54 |
| Cycles | 1288 | 488 | 308 | 354 | 138 |
| Rate of retrieval, % | 76.6 | 78.9 | 76.6 | 76.0 | 70.3 |
| Retrievals with oocyte collection per cycle, % | 65.6 | 67.4 | 66.2 | 64.7 | 60.1 |
| Fertilization rate, % | 79.4 | 83.6 | 70.6 | 80.7 | 80.2 |
| DF implantation rate, % | 32.4 | 35.1 | 33.9 | 30.4 | 21.4 |
| Clinical pregnancy | 154 | 66 | 38 | 41 | 9 |
| SAB rate % (total=22) | 13.8 | 1.4 | 15.4 | 24.4 | 55.6 |
| Live birth/cycle, % | 10.6 | 13.9 | 10.7 | 8.8 | 2.9 |
| Live birth/ET, % | 28.3 | 34.2 | 30.3 | 23.5 | 10.0 |
| NCIVF w/AMH≤0.5, DF (2007-2011) | | | | | |
| Patients | 152 | 20 | 40 | 63 | 29 |
| Cycles | 347 | 33 | 88 | 145 | 81 |
| Rate of retrieval, % | 71.8 | 69.7 | 77.3 | 71.7 | 66.7 |
| Retrievals with oocyte collection per cycle, % | 59.1 | 48.5 | 62.5 | 60.7 | 56.8 |
| Fertilization rate, % | 77.3 | 94.1 | 68.4 | 75.3 | 85.7 |
| DF implantation rate, % | 33.3 | 27.2 | 38.7 | 37.5 | 22.2 |
| Clinical pregnancy | 37 | 2 | 11 | 18 | 6 |
| SAB rate % (total=10) | 25.6 | 0.0 | 25.0 | 27.8 | 33.3 |
| Live birth/cycle, % | 8.4 | 9.1 | 10.2 | 9.0 | 4.9 |
| Live birth/ET, % | 26.1 | 30.0 | 30.0 | 28.3 | 16.0 |
| NCIVF w/AMH<1.0, DF (2007-2011) | | | | | |
| Patients | 236 | 58 | 57 | 83 | 38 |
| Cycles | 526 | 102 | 132 | 194 | 98 |
| Rate of retrieval, % | 73.4 | 79.4 | 75.0 | 72.2 | 67.3 |
| Retrievals with oocyte collection per cycle, % | 60.5 | 65.7 | 62.1 | 58.2 | 57.1 |
| Fertilization rate, % | 79.6 | 90.0 | 69.8 | 78.2 | 84.7 |
| DF implantation rate, % | 30.2 | 27.7 | 34.8 | 31.8 | 24.2 |
| Clinical pregnancy | 56 | 12 | 15 | 21 | 8 |
| SAB rate % (total=14) | 24.1 | 7.7 | 18.8 | 28.6 | 50.0 |
| Live birth/cycle, % | 8.4 | 11.8 | 9.8 | 7.7 | 4.1 |
| Live birth/ET, % | 24.0 | 27.3 | 29.5 | 23.4 | 12.9 |
| NCIVF w/AMH≥1.0, DF (2007-2011) | | | | | |
| Patients | 379 | 201 | 85 | 77 | 16 |
| Cycles | 762 | 386 | 176 | 160 | 40 |
| Rate of retrieval, % | 78.9 | 78.8 | 77.8 | 80.6 | 77.5 |
| Retrievals with oocyte collection per cycle, % | 69.2 | 67.9 | 51.7 | 59.4 | 67.5 |
| Fertilization rate, % | 79.3 | 81.9 | 72.2 | 83.2 | 70.4 |
| DF implantation rate, % | 33.6 | 37.1 | 32.9 | 29.6 | 10 |
| Clinical pregnancy | 98 | 54 | 23 | 20 | 1 |
| SAB rate % (total=8) | 7.9 | 0.0 | 13.0 | 20.0 | 100.0 |
| Live birth/cycle, % | 12.1 | 14.5 | 11.4 | 10.0 | 0.0 |
| Live birth/ET, % | 31.0 | 36.1 | 30.8 | 23.5 | 0.0 |

NCIVF: Natural cycle *in vitro* fertilization; CDC: Centers for disease control; SAB: Spontaneous abortion; AMH: Antimullerian hormone; DF: Dominion fertility

versus 9.6% (NS), respectively [Figure 1]. Although there was a trend toward higher implantation rates for NCIVF compared with CDC IVF in patients over 40-year-old, the sample size was too small to make a meaningful statistical comparison.

Comparison of implantation rates for NCIVF patients stratified by AMH levels is shown in Figure 2. For all patients within each age group, there were no statistical differences in implantation rates relative to AMH, even when comparing those patients with the lowest (<0.5) to the highest (>1.0) AMH values.

Among the 615 patients who underwent 1288 cycles of NCIVF, there were a total of 154 clinical pregnancies and 132 live births (10.6% and 27.5% live births/cycle and/embryo transfer, respectively) with 20 total spontaneous abortions, Table 2. The spontaneous abortion rate was 13.8%. Most pregnancies (80.6%) occurred within the first two embryo transfers. A total of 12 patients had two ova retrieved with one patient having two embryos transferred. There were five twin pregnancies (5/154, 3.2%), four monozygotic, and no higher order multiple pregnancies.

For CDC IVF and NCIVF, there was no significant difference in singleton live birth rates/embryo transfer, for patients <35, 31.4% versus 30.7% ($P$ = 0.8), 35-37, 27.3% versus 27.0% ($P$ = 0.7), 38-40, 21.5% versus 23.0% ($P$ = 0.7) and for 41-42 years old, 13.7% versus 9.5% ($P$ = 0.7), respectively. The twin rate for stimulated IVF was 32.9%/embryo transfer for patients <35-year-old, and 15-27.3% per embryo transfer for the three age groups representing patients 35-42 years old. The mean triplet rate for stimulated IVF was 3% for patients under age 42.

## DISCUSSION

It is well-established that embryo implantation rates for both stimulated and NCIVF decline with age.[3-6] This age effect is related, in part, to the increase in embryo aneuploidy with maternal age. In this study, we found embryo implantation for the naturally produced

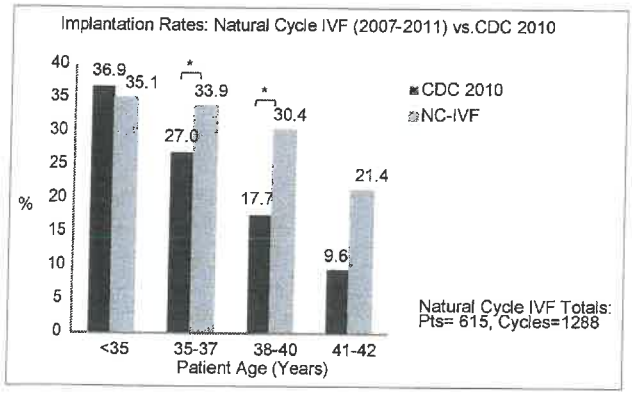


**Figure 1:** Comparison of natural *in vitro* fertilization cycle implantation rates versus all cycles reported to the Centers for Disease Control for 2010 (*$P < 0.05$)

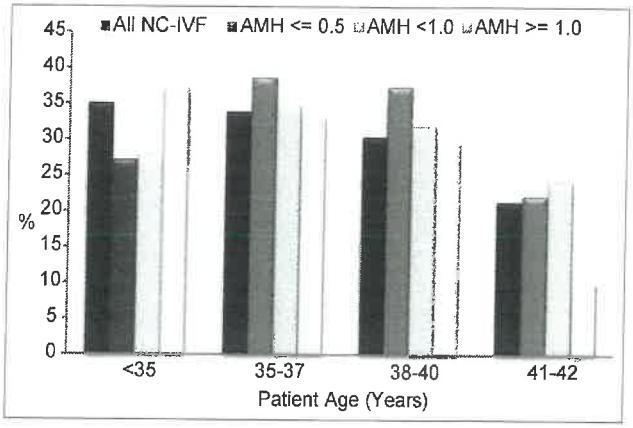


**Figure 2:** Implantation rates: Natural *in vitro* fertilization cycles by patient antimullerian hormone values of ≤0.5, <1.0, and ≥1.0. All comparisons within each age group were nonsignificant

embryo to be similar to the stimulated IVF embryo for patients <35-year-old, but superior in patients 35-40 years old. Thus, the decline in implantation for the naturally produced embryo was attenuated relative to that seen with a stimulated IVF embryo. The reason for this preservation of implantation with unstimulated IVF is unknown, but may be related to mechanisms involving oocyte selection in a physiologic cycle or to adverse endometrial changes that have been previously demonstrated in stimulated cycles.[7-11]

Antimullerian hormone has been shown to predict a decline in the efficacy of stimulated IVF, independent of age.[12-14,20,21] In our study, this negative correlation of AMH to outcome was not seen with NCIVF even at the lowest levels of AMH. Similar findings have been reported in patients undergoing modified NCIVF.[18] This further suggests that AMH is a quantitative biomarker for ovarian response to stimulation and not a marker for oocyte quality. Using the Bologna criteria to define poor ovarian reserve, Polyzos *et al.* in their study have reported NCIVF was beneficial in patients with normal ovarian reserve, but not in patients with poor ovarian reserve.[16] However, in a series of 500 consecutive cycles of NCIVF Schimberni *et al.* have reported NCIVF to be an effective treatment in poor responders (defined as having 0-1 follicle following gonadotropin stimulation for IVF[15]). Other studies have shown that poor responders to ovarian stimulation may benefit from an attempt at NCIVF.[22,23]

We elected to compare our NCIVF implantation rates with the CDC implantation rates, rather than our own stimulated IVF implantation rates. This was done because the majority of our patients elect to try NCIVF before stimulated IVF. Therefore, many of our patients who undergo stimulated IVF have already failed one or more cycles of NCIVF and comparing our stimulated IVF implantation results to our NCIVF program presented a bias, albeit one that would have made our results more rather than less significant. A comparison of first time NCIVF to first time stimulated IVF patients would be more meaningful, but we do not have sufficient numbers in those categories. It should be noted that in our program, any patient with regular menstrual cycles who was offered stimulated IVF, regardless of the status of her ovarian reserve or a history of previous IVF failures was also offered NCIVF, but many patients who were not candidates for stimulated IVF were offered NCIVF. Thus, some patients in the NCIVF group were in a particularly low prognosis group; as demonstrated by the median AMH of the NCIVF group being only 1.3 ng/ml [Table 1].

The singleton live birth rates per embryo transfer for stimulated IVF as reported by the CDC for 2010 was similar to those treated with NCIVF, yet the twin rate for NCIVF was only 3.2% as compared to 15-32.9% for stimulated IVF patients. With NCIVF, only one embryo was typically transferred, whereas the CDC reported that the average number of embryos transferred for stimulated IVF ranged from 2.0 to 3.2 embryos in the age groups studied. Similar singleton live birth rates/embryo transfer occurred using NCIVF as compared with stimulated IVF, but with a much lower multiple pregnancy rate. Although the clinical outcome of a singleton live birth/embryo transfer may be similar, NCIVF has many limitations. Cycle cancellations for NCIVF are high due to LH surge, failed oocyte retrieval, fertilization or embryo arrest. This leads to a pregnancy rate/cycle start of 10-14%. Due to the cycle cancellation rate we recommend that NCIVF be considered as a course of treatment, with reassessment if no pregnancy after 2-3 embryo transfers. In our study, the NCIVF rate of retrievals/cycle start was 76.6% with 57.8% of retrievals with eggs having an embryo transfer. With stimulated IVF many eggs and embryos are usually produced, hence the

percentage of cycle starts resulting in embryo transfer, pregnancy and a live birth are superior. Despite the cycle cancellation rate with NCIVF, many of our patients still prefer a series of simpler NCIVF treatments as a route to an embryo transfer in place of a single stimulated IVF cycle. Similar patient expectations have been reported in other clinics that perform NCIVF.[24,25]

Limitations of our study include its retrospective nature and its largely heterogeneous population. Considering the limitations in our patient population, we were still able to demonstrate equal or superior embryo implantation rates in our patients undergoing NCIVF even when including poor prognosis patients who were not candidates for stimulated IVF or who had previously failed stimulated IVF. Including these patients may have also contributed to our high cycle cancellation rates. We do not have CDC data stratified by AMH levels, so we could not make a comparison matched by both age and AMH. We were able to demonstrate that in NCIVF the AMH level did not affect outcome; it has been previously established that AMH levels affect outcome in stimulated cycles, although we did not have the data to independently demonstrate that in the current study.

In this paper, we have provided evidence that once embryo transfer is reached, NCIVF and stimulated IVF have a statistically identical singleton delivery rate/transfer. AMH levels appear to not have an impact on outcomes of NCIVF. Finally, and most intriguingly, there is evidence that implantation rates for embryos derived from NCIVF are superior to those derived from stimulated IVF in patients 35-40 years of age.

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