One thousand seventy-eight autologous IVF cycles in women 45 years and older: the largest single-center cohort to date

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Abstract

Purpose The purpose of this study was to determine IVF outcomes in women 45 years and older using autologous oocytes.

Methods This is a retrospective cohort study reviewing all IVF cycles in women ≥ 45 years old from January 1995 to June 2015 that were conducted at one academic medical center. One thousand seventy-eight fresh, autologous IVF cycles met inclusion criteria. PGD/S, natural IVF, and donor egg cycles were excluded. Outcomes were analyzed for the different age groups (age 45, $n = 773$; age 46, $n = 221$; age 47, $n = 57$; age 48, $n = 22$; age 49, $n = 5$). Primary outcome measures included IVF cycle characteristics, total pregnancy loss, clinical pregnancy, and live birth rates, and were stratified according to patient age.

Results Mean age of patients in the study cohort was 45.4 ± 0.72 . 11.7% of patients did not start due to an elevated FSH or cyst and 28.5% of patients were canceled prior to oocyte retrieval. The overall pregnancy rate per transfer was 18.7% (117/626), of which 82.1% ended in a pregnancy loss. The overall clinical pregnancy and live birth rates per transfer were 9.6 and 3.4%, respectively, which did not differ between age groups. Per cycle start women aged 45 had significantly higher positive pregnancy rates compared to women aged 46 and 47 (14.1 vs. 8.6 vs. 5.9%, $p = 0.04$). For women 45 years old, the live birth rate was 2.9% per cycle start and was 4.4% per embryo transfer. Of the 21 live births, 20 were in women aged 45 and one live birth was in a 46-year-old woman. There were no live births in any patient with ≤ 4 oocytes retrieved.

Conclusion Autologous IVF in women aged 45 with acceptable ovarian reserve is not futile; however, it does carry very low prognosis. Patients aged 46 and older should be counseled appropriately that a live birth seems highly unlikely.

Keywords ART · Advanced reproductive age · Advanced maternal age · Autologous IVF · Age 45 and older

Introduction

The trend to delay childbirth has steadily increased over the last several decades. The mean age of first-time mothers increased from 21.4 years in 1970 to 26.3 years in 2014, and this trend holds true across all races and geographical areas within the USA [1]. While birthrates decreased annually over the last three decades for women < 30 years old, the opposite trend was seen for women aged 30–44. More notably, since 2007, women over 40 comprise the largest increase in birth rates of 15%, compared to increases of 9 and 1% for women aged 35–39 and 30–34, respectively [2]. Women in their late 40s are also conceiving more frequently as the number of births to women older than 45 increased by 6% from 2014 to 2015 [1]. From these statistics, it is clear that the challenges associated with advanced maternal age will only become more pertinent in assisted reproduction.

Classic population-based studies showed that fecundity decreases with maternal age, beginning around age 32 and more dramatically after age 37 [3]. The age-related decline in fertility is not only related to decreasing number of available oocytes but also due to increases in oocyte aneuploidy in the remaining oocyte pool [4]. Trophoblast biopsies of $> 15,000$ blastocysts showed that rates of aneuploidy steadily increase from age 31 and plateau around 85% at age 43 [5]. As expected, clinical miscarriage rates increase from $< 15\%$ in

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women aged 35 years old to > 50% in women aged 44 years or older, and this association exists even after ultrasound detection of a fetal heart [6, 7]. Due to these reproductive phenomena, female age is viewed as the most important prognostic factor in determining IVF success [8, 9].

Despite the sharp decline in IVF success rates with women over 40, this older population made up 17% of all fresh, non-donor IVF cycles in 2013. In 2013, women ≥ 45 years old comprised 1.5% ($n = 1379$ cycles) of all autologous IVF cycles, with a live birth rate of 2% [10]. As more women over 40 are pursuing assisted reproductive technology (ART), SART has only recently begun further stratifying women aged 43 and older. Stratifications beyond age 45 have not been made due to insufficient data.

To date, most studies analyzed success rates in women over 40 and therefore have extremely small numbers in the advanced age group of 45 and older. The only study to further stratify outcomes by age in women > 44 years old was performed at this institution more than a decade ago with a total of 288 patients [6]. IVF pregnancies in women over 45 are limited to isolated case reports and therefore are unable to estimate accurate pregnancy rates to guide practice management [11, 12]. To that end, we queried our clinical database to further evaluate pregnancy outcomes in women ≥ 45 years old pursuing IVF with autologous oocytes.

Materials and methods

Cycle inclusion/exclusion criteria

This study was approved by the Weill Cornell Medical College Institutional Review Board. All IVF cycles performed at Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine from January 1995 to June 2015 were reviewed. A total of 45,532 fresh IVF cycles occurred at our center during the study period and were screened for retrospective analysis. Inclusion criteria were fresh IVF cycles performed in women 45 years and older using autologous oocytes. Natural IVF cycles and patients who underwent prenatal genetic screening (PGS) or diagnosis (PGD) prior to embryo transfer were excluded from analysis. Patient demographics, IVF cycle characteristics, total pregnancy loss, clinical pregnancy, and live birth rates were analyzed for the different age groups (age 45, $n = 773$; age 46, $n = 221$; age 47, $n = 57$; age 48, $n = 22$; age 49, $n = 5$).

Clinical/laboratory protocol

Protocols for controlled ovarian stimulation (COS), oocyte retrieval, IVF, and embryo transfer procedures were previously described [13, 14]. Patients were either downregulated with a GnRH agonist (Leuprolide acetate: Abbott Pharmaceuticals

North Chicago, IL) followed by gonadotropin stimulation using a combination of FSH and HMG (Follistim: Merck, Whitehouse Station, NJ; Gonal-F: EMD-Serono, Rockland, MA; Menopur: Ferring, Parsippany, NJ) once pituitary suppression was confirmed or was stimulated with gonadotropins until criteria were met for suppression with a GnRH antagonist (Ganirelix Acetate: 0.25 mg Organon, Roseland, NJ; Cetrotide 0.25 mg: EMD-Serono, Rockland, MA). GnRH antagonist downregulation was administered in a flexible protocol when either the lead follicle attained 13 mm mean diameter or estrogen exceeded 300 pg/mL. Luteal suppression for antagonist-based protocols, when utilized, was achieved with estradiol patches starting 8 to 10 days post-LH surge or by using oral contraceptive pills (OCPs). All protocols were individualized based on patients' age, weight, ovarian reserve, and prior response to COS.

Ten thousand international units human chorionic gonadotropin (Profasi: EMD-Serono, Rockland, MA; Novarel: Ferring Pharmaceuticals, Parsippany, NJ; or Pregnyl: Schering-Plough, Kenilworth, NJ) was generally administered when at least two follicles reached 17 mm. Earlier or later administration of hCG was performed based on the individuals' prior IVF performance. Oocyte retrieval was performed 35 to 37 h after hCG trigger. One day following oocyte retrieval, luteal progesterone supplementation was initiated using 25–50 mg of intramuscular (IM) progesterone. Embryo transfer was performed on day 3 or day 5 with a Wallace catheter (Marlow/Cooper Surgical, Shelton, CT). The decision for day of embryo transfer was individualized based on the patient's clinical history and morphologic markers of embryo development. Serum hCG test was drawn on cycle day 28 and repeated in 48 h. First ultrasound in the setting of a positive pregnancy test was done at 5 weeks gestational age.

Outcome variables assessed

Demographic characteristics of all patients 45 years and older were reviewed. These variables included age, gravidity, parity, number of prior IVF attempts, and ovarian reserve testing (AMH pg/mL and cycle day 3 FSH mIU/mL). Of note, the AMH assay was not routinely used at our center until 2010, and therefore, day 3 FSH was included as this covers the entire study period. IVF cycle characteristics such as start and total dose of gonadotropins (IU), days of stimulation, and peak estradiol (pg/mL) levels at trigger were also assessed. Intermediate IVF outcomes analyzed included number of oocytes harvested, mature oocytes, 2PNs, embryos transferred, and percent cycles with no embryo transfer.

Primary outcomes included positive pregnancy, clinical pregnancy, and live birth rates per retrieval. Clinical pregnancy was defined as a viable fetus as evidenced by fetal cardiac activity by ultrasound at 7 weeks. Live birth was defined as at least one live-born child delivered at > 24 weeks gestation. Pregnancy loss rate was defined by all cycles that resulted in

a biochemical pregnancy plus clinical miscarriage divided by the total number of cycles that resulted in a positive pregnancy. All IVF outcomes were further stratified by age ≥ 45 .

Statistical analysis

Data analysis was performed with STATA Statistical Software Version 11 (StataCorp LP; College Station, TX). Differences in demographic characteristics, IVF outcomes according to age, and predictors of positive pregnancy in the study cohort were calculated with the Fisher exact *t* test, chi-square, and one-way ANOVA with multiple comparison. Statistical analyses accounted for correlated outcome measurements caused by repeated measures. In all cases, $p < 0.05$ was considered to be statistically significant.

Results

Of the 45,532 fresh IVF cycles that occurred over the 20-year study period, 2.4% (1078 cycles) met inclusion criteria. There were 773, 221, 57, 22, and 5 cycles in patient's aged 45, 46, 47, 48, and 49, respectively. The mean age of patients in the study cohort was 45.4 ± 0.72 . 11.7% ($n = 126$) of patients did not start the IVF cycle due to presence of an ovarian cyst or elevated FSH and 28.5% ($n = 271$) of patients were canceled prior to egg retrieval due to a poor response to gonadotropin stimulation. 92.1% ($n = 626/680$) of patients who had oocytes retrieved underwent an embryo transfer and 96.8% of the study cohort underwent a day 3 embryo transfer.

Demographic characteristics between age groups are shown in Table 1. Specifically, there were no differences in baseline characteristics such as parity, number of prior IVF attempts, BMI, and ovarian reserve testing (day 3 FSH or AMH levels).

Significant differences were noted in the start and total dose of gonadotropins and peak E2 levels for women aged 49 compared to other age groups. These demographic differences are likely falsely skewed due to small sample size in the 49-year-old age group even after correcting for repeated measures. There was no difference in intermediate IVF cycle outcomes such as no. of fertilized, no. of mature oocytes, and % cycles with no embryo transfer (Table 2). The mean number of oocytes harvested was 7.2 ± 4.8 and mean number of embryos transferred was 3.4 ± 1.9 , which did not vary between age groups.

In the study cohort, the overall pregnancy rate per transfer was 18.7% (117/626), of which 82.1% ended in a pregnancy loss. The overall clinical pregnancy and live birth rates were 9.6 and 3.4%, respectively. Pregnancy outcomes (per transfer) stratified by age are depicted in Table 3 and showed no statistical differences between age groups. There was a trend for positive pregnancy in women aged 45; however, this did not reach significance ($p = 0.07$). Of the 21 live births, 20 were in women aged 45 (LBR 4.4%), while only one woman aged 46 delivered a live born (LBR 0.8%). There were no live births in women 47 and older.

Given that 28.5% of patients were canceled prior to oocyte retrieval due to lack of a response to stimulation, we also included an intention-to-treat analysis, as shown in Table 4. Per cycle start, women aged 45 exhibited a significantly higher positive pregnancy rate of 14.1% compared to women 46 and older ($p = 0.04$). Per cycle start, women aged 45 had clinical pregnancy and live birth rates of 7.4 and 2.9%, respectively, which did not differ from other age groups. There were no statistical differences in pregnancy loss, clinical pregnancy, or live birth rates on an intention-to-treat analysis.

Predictors of positive pregnancy are shown in Table 5. There was no difference in number of prior IVF attempts or days of

Table 1 Demographic characteristics of women ≥ 45 undergoing autologous IVF

Demographic characteristics						
Age	45	46	47	48	49	<i>p</i> value
<i>n</i> (total cycles)	773	221	57	22	5	
No. of patients	505	139	41	14	3	
Gravidity (median)	1	1	1	1	1.5	0.52
Parity (median)	0	0	0	1	0	0.17
No. of prior IVF attempts	3.0 ± 2.8	3.3 ± 3.1	3.0 ± 3.1	3.9 ± 2.8	4.3 ± 4.9	0.33
BMI	24.3 ± 4.6	23.6 ± 3.7	24.5 ± 5.1	24.2 ± 4.9	21.8 ± 3.0	0.2
Day 3 FSH (mIU/mL)	11.4 ± 7.0	11.3 ± 7.2	11.9 ± 5.7	13.2 ± 6.9	12.0 ± 3.2	0.77
AMH (ng/mL)	0.7 ± 0.8	0.6 ± 0.6	0.3 ± 0.2	0.7 ± 1.3	1.4 ± 0.8	0.06
Start dose (IU)**	506.0 ± 107.6	526.1 ± 103.2	502.8 ± 135.6	491.7 ± 121.3	412.5 ± 143.6	0.03
Total gonadotropins (IU)**	4509.3 ± 1933.9	4900.5 ± 1972.2	4144.5 ± 1954.9	4312.5 ± 1654.9	3545.0 ± 1858.0	0.02
Peak E2 (pg/mL)**	1246.4 ± 745.8	1333.0 ± 848.3	1024 ± 411.5	1071.9 ± 459.2	3546.5 ± 938.3	< 0.0001
Days of stimulation	10.3 ± 2.2	10.2 ± 2.4	10.3 ± 2.7	10.3 ± 2.7	12.0 ± 1.4	0.5

** $p < 0.05$ significant

Table 2 Intermediate IVF outcomes of women aged ≥ 45 undergoing autologous IVF

Intermediate IVF outcomes						
Age	45	46	47	48	49	<i>p</i> value
<i>n</i> (total cycles)	773	221	57	22	5	
No. of patients	505	139	41	14	3	
No. of oocytes harvested	7.1 $\pm$ 4.8	7.4 $\pm$ 4.8	6.3 $\pm$ 5.0	6.1 $\pm$ 5.2	16 $\pm$ 2.8	0.08
No. of mature oocytes	5.7 $\pm$ 4.1	5.9 $\pm$ 3.9	4.7 $\pm$ 3.6	5.0 $\pm$ 4.0	10.5 $\pm$ 0.7	0.28
No. of 2PN	4.0 $\pm$ 3.3	4.2 $\pm$ 3.2	3.1 $\pm$ 3.0	2.9 $\pm$ 2.4	6.5 $\pm$ 0.7	0.29
No. of embryos transferred	3.4 $\pm$ 1.8	3.5 $\pm$ 2.1	2.9 $\pm$ 1.7	2.9 $\pm$ 2.1	5.0 $\pm$ 0.0	0.29
% cycle starts with no ET	32.8%	32.8%	45.1%	63.2%	60.0%	0.53

stimulation between those who conceived vs. those who had an unsuccessful cycle. Baseline factors that were significantly associated with likelihood of positive pregnancy were age (45.2 ± 0.6 vs. 45.4 ± 0.7 , $p = .03$), day 3 FSH (9.9 ± 5.5 vs. 11.6 ± 7.0 , $p = 0.02$), and AMH (1.1 ± 1.1 vs. 0.6 ± 0.7 , $p = .05$). As expected, a more robust response to stimulation in terms of oocytes harvested (9.4 ± 5.4 vs. 6.7 ± 4.6), no. of mature oocytes (7.8 ± 4.8 vs. 5.3 ± 3.8), no. of 2PN (5.7 ± 3.7 vs. 3.6 ± 3.0), and higher number of embryos transferred (4.3 ± 1.8 vs. 3.2 ± 1.9) was also associated with a positive pregnancy ($p < 0.0001$). No patient with an AMH less than 0.4 pg/mL or less than four mature oocytes harvested achieved a delivery. The minimum number of embryos transferred in a live birth cycle was two and all cycles underwent a day 3 embryo transfer.

Discussion

The current study was undertaken to evaluate pregnancy outcomes in women aged 45 and older pursuing IVF with autologous oocytes. One thousand seventy-eight cycles met inclusion for analysis, after excluding PGS/D and natural IVF cycles. IVF success rates in this advanced age group have been extrapolated from previous literature looking specifically at outcomes in women over 40 [15]. Studies have concluded that IVF should be limited to women ≤ 44 years old as live birth rates ranged from 0 to 1.4% for those aged 45 and older

[16–20]. Although they provide valuable insight into the challenges of treating older women, small study cohorts ranging from 23 to 69 cycles for women ≥ 45 may limit the accuracy of their predicted outcomes. Similarly, the two largest series to date conducted by Serour and Tsafrir et al. reported live birth rates per transfer of 1% ($n = 219$ cycles) and 0.6% ($n = 192$ cycles) [21, 22]. These two papers concluded that autologous IVF in women ≥ 43 years old is not justified. Contrary to prior studies, our data shows higher overall clinical pregnancy and live birth rates per transfer of 9.6 and 3.4%, respectively.

Given inadequate population size, previous data was also unable to further stratify by age > 45 . Our data shows that this advanced age group may not be completely homogenous in terms of ART outcomes. Although there was no difference in pregnancy outcomes per transfer when stratifying by age, positive pregnancy rates did trend to significance for women aged 45 ($p = 0.07$). More importantly, the intention-to-treat analysis exhibited significantly higher positive pregnancy for women aged 45 compared to women ≥ 46 . The live birth rate per transfer was 4.4% in women aged 45, while only one woman aged 46 had a delivery (LBR 0.8%). There were no live births in women aged 47–49, although they did achieve a positive pregnancy. Our study demonstrates that despite a very low prognosis, IVF for women aged 45 is not futile. Women aged 46 and 47–49 exhibited positive pregnancy rates of $> 10\%$; however, live birth rates were $< 1\%$ and therefore should be counseled on their extremely low prognosis. Despite a low

Table 3 IVF pregnancy outcomes per transfer of women aged ≥ 45 undergoing autologous IVF

IVF pregnancy outcomes per transfer						
Age	45	46	47	48	49	<i>p</i> value
<i>n</i> (total cycles)	456	133	28	7	2	
No. of patients	350	100	21	7	1	
Positive pregnancy rate	21.1%	12.8%	10.7%	0%	50%	0.07
Clinical pregnancy rate	11.0%	6.8%	3.6%	0%	0%	0.35
Live birth rate	4.4%	0.8%	0%	0%	0%	0.76
Pregnancy loss rate (BC + SAB/total pregnancy)	79.2%	94.1%	100%	N/A	100%	0.38

N/A not available

Table 4 IVF pregnancy outcomes per cycle start of women aged ≥ 45 undergoing autologous IVF

IVF pregnancy outcomes per cycle start						
Age	45	46	47	48	49	<i>p</i> value
<i>n</i> (total cycles)	679	198	51	19	5	
No. of patients	469	135	38	13	3	
Positive pregnancy rate**	14.1%	8.6%	5.9%	0%	20%	0.04
Clinical pregnancy rate	7.4%	4.5%	2.0%	0%	0%	0.23
Live birth rate	2.9%	0.5%	0%	0%	0%	0.19
Pregnancy loss rate (BC + SAB/total pregnancy)	79.2%	94.1%	100%	N/A	100%	0.38

N/A not available

** $p < 0.05$ significant

prognosis in this advanced age group, decisions to attempt an autologous IVF must be individualized as some couples need to feel as though they have explored all treatment options before committing to oocyte donation.

This study also highlights the exceptionally high pregnancy loss rate after conception in women ≥ 45 years old. Of all positive pregnancies, 82% ($n = 96$) ended with a pregnancy loss and roughly 50% of the losses were biochemical pregnancies. Although we excluded PGS/D cycles, prior studies have analyzed using prenatal genetic screening in women with advanced maternal age. Despite lower miscarriages in the PGS group, studies have arrived at disparate conclusions in terms of clinical pregnancy and live birth rates [23–28]. A more recent RCT evaluating PGS in women aged 38–41 showed lower miscarriage rates in the PGS group; however, no difference was seen in cumulative pregnancy rates [29]. To date, only Ubaldi et al. have reported on PGS and subsequent clinical outcomes in older women aged 44–46 [30]. Twenty-six and 62% of cycles in women aged 45 and 46, respectively,

had embryos that did not reach blastocyst, which highlights that day 3 embryo transfer may be more appropriate when in vitro attrition is of concern. Despite lower miscarriage rates, the live birth rate per retrieval was 2.6 and 0% in 45- and 46-year-olds, respectively, which are slightly lower than our results [30]. Given that the exact role of PGS in advanced maternal age remains unclear, data on pregnancy outcomes without prenatal genetic testing is still needed.

The present study is limited by its retrospective nature. Another limitation is the extended study duration of 20 years as lab techniques and practice patterns have undoubtedly evolved over this time period. The current cohort represents 2.6% of all autologous fresh IVF cycles performed at our center over the 20-year span, and therefore, shorter study duration would have noticeably compromised the sample size and validity of our results. Analyzing national data from SART/CDC, although valuable, may introduce bias by incorporating a wide variety of practice patterns across many different IVF centers. The present study represents the largest single-center cohort to date and therefore maximizes power while minimizing bias arising from poor reproducibility. Although overall pregnancy outcomes are still low in this advanced population, our live birth rates may be up to two times that reported in SART's most recent national statistics.

Table 5 Predictors of positive pregnancy in women ≥ 45 undergoing autologous IVF

Predictors of positive pregnancy			
	Positive BHCG	Not pregnant	<i>p</i> value
<i>n</i> (total cycles)	117	960	
No. of patients	107	684	
Age (mean)**	45.2 $\pm$ 0.6	45.4 $\pm$ 0.7	0.03
No. of prior IVF attempts	3.0 $\pm$ 2.7	3.2 $\pm$ 3.1	0.55
Day 3 FSH**	9.9 $\pm$ 5.5	11.6 $\pm$ 7.0	0.03
AMH**	1.1 $\pm$ 1.1	0.6 $\pm$ 0.7	0.05
Days of stimulation	10.1 $\pm$ 1.8	10.3 $\pm$ 2.3	0.31
No. of oocytes harvested**	9.4 $\pm$ 5.4	6.7 $\pm$ 4.6	< 0.0001
No. of mature oocytes**	7.8 $\pm$ 4.8	5.3 $\pm$ 3.8	< 0.0001
No. of 2PN**	5.7 $\pm$ 3.7	3.6 $\pm$ 3.0	< 0.0001
No. of embryos transferred**	4.3 $\pm$ 1.8	3.2 $\pm$ 1.9	< 0.0001

** $p < 0.05$ significant

Conclusion

This report serves as an important counseling tool for women 45 years and older desiring to undergo ART with autologous oocytes. Given the poor prognosis in this advanced age group, analyzing predictors of a positive pregnancy may offer guidance as to which patients have the best chance to conceive with COS. Patients should be aware of not only the high cancellation rates prior to or during stimulation but also the high rates of pregnancy loss after conception. Our data shows that although autologous, fresh IVF carries a very low prognosis, it is not futile in women aged 45 with acceptable ovarian reserve and at least four mature oocytes retrieved. Women

46 and older should be counseled appropriately that a live birth seems highly unlikely.

Compliance with ethical standards This study was approved by the Weill Cornell Medical College Institutional Review Board.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval For this type of study, formal consent is not required.

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