National trends and outcomes of autologous in vitro fertilization cycles among women ages 40 years and older

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Abstract

Purpose The purpose of the study was to describe trends in and investigate variables associated with clinical pregnancy and live birth in autologous in vitro fertilization (IVF) cycles among women ≥ 40 years.

Methods We used autologous IVF cycle data from the National ART Surveillance System (NASS) for women ≥ 40 years at cycle start. We assessed trends in fresh and frozen cycles ($n = 371,536$) from 1996 to 2013. We reported perinatal outcomes and determined variables associated with clinical pregnancy and live birth in fresh cycles between 2007 and 2013.

Results From 1996 to 2013, the total number of cycles in women ≥ 40 years increased from 8672 to 28,883 ($p < 0.0001$), with frozen cycles almost tripling in the last 8 years. Cycles in women ≥ 40 years accounted for 16.0% of all cycles in 1996 and 21.0% in 2013 ($p < 0.0001$). For fresh cycles from 2007 to 2013 ($n = 157,890$), the cancelation rate was 17.1%. Among cycles resulting in transfer ($n = 112,414$), the live birth rate was 16.1%. The following were associated with higher live birth rates: multiparity, fewer prior ART cycles, use of standard agonist or antagonist stimulation, lower gonadotropin dose, ovarian hyperstimulation syndrome, more oocytes retrieved, use of pre-implantation genetic screening/diagnosis, transferring more

and/or blastocyst stage embryos, and cryopreserving more supernumerary embryos. Of the singleton infants born ($n = 14,992$), 86.9% were full term and 88.3% normal birth weight.

Conclusions The NASS allows for a comprehensive description of IVF cycles in women ≥ 40 years in the USA. Although live birth rate is less than 20%, identifying factors associated with IVF success can facilitate treatment option counseling.

Keywords In vitro fertilization (IVF) · Infertility · Older women · 40 years and over

Introduction

With increasing availability of effective contraception and access to educational and workplace opportunities, more women are delaying childbearing [1]. This is reflected by birth rates in women ages 40 to 44 years almost doubling in the USA between 1990 and 2013 [2]. Live birth rates, however, are dependent on the age of the oocyte; both spontaneous [3] and in vitro fertilization (IVF) conceptions with autologous oocytes decline with age. Live birth rates after IVF in women ≥ 40 years range from 4.7 to 9.7% per cycle started [4–6]. One study found that 1% of oocytes retrieved in this age group resulted in a live birth (“oocyte to baby rate”), compared to 6.8% in a donor oocyte population [7]. Cancelation rates are also high among women > 40 years with 15–30% of cycles canceled prior to oocyte retrieval even in a pre-selected IVF population [8, 9]. Below average success rates in this group translate to high IVF treatment costs. One prior analysis estimated that a live birth in women ages 40 years and older is 2.5 times more expensive than in women ages 35–39 years [10]. Others have questioned the ethics of providing fertility care in older women [11], especially in light of the potential for increased pregnancy morbidity [12, 13].

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As more couples delay childbearing, however, there is an increased need for fertility treatment in this population. In this analysis, our aim was to describe trends in the absolute number of autologous fresh and frozen IVF cycles conducted among women ≥ 40 years, the proportion of these cycles among IVF cycles in women of all ages, and the live birth rate among women ≥ 40 years. We also aimed to describe perinatal outcomes of infants conceived with fresh autologous IVF cycles started by women ≥ 40 years, to explore factors associated with clinical pregnancy and live birth, and to report the number of IVF cycles (fresh and frozen) initiated per live birth by each year of maternal age at oocyte retrieval.

Materials and methods

We used data from the Centers for Disease Control and Prevention's National Assisted Reproductive Technology Surveillance System (NASS), a federally mandated reporting system that captures over 97% of assisted reproductive technology (ART) cycles [14] performed in the USA. The data, which are certified by the medical director of each fertility clinic, are cycle-specific and include patient demographics, parity, diagnoses, cycle stimulation information, and treatment outcomes. Annually, a sample of clinics that submit data to NASS (approximately 5–10%) are validated by comparing reported data to medical charts [14].

We first described trends in the number of fresh and frozen autologous oocyte IVF cycles started, the live birth rate, and the number of resulting live births among women ≥ 40 years from 1996 to 2013. We also described the trend in the proportion of autologous oocyte cycles in women ≥ 40 years among cycles in women of all age groups. Linear regression analysis was used to test for linear and quadratic trends.

For all other analyses, we restricted the data to years 2007 to 2013 to reflect more recent practice patterns in the rapidly changing field of ART. In addition, starting in 2007, data were available to link frozen cycles to their originating oocyte retrieval for assessment of maternal age at oocyte retrieval. We calculated the number of autologous fresh and frozen IVF cycles started per live birth by each year of maternal age at oocyte retrieval. We included frozen cycles that could be linked to their prior fresh oocyte retrieval in order to capture all available transfer data from the initiating oocyte retrieval. We excluded frozen cycles that had no prior ART cycles or that were linked to a fresh cycle reporting zero embryos cryopreserved. After linkage and exclusions, 56.1% ($n = 18,732$) of the frozen cycles were included.

Next, we reported patient and cycle characteristics of fresh autologous IVF cycles in women ≥ 40 years. We limited this analysis to only fresh cycles because many of the variables of interest were not applicable to or available for frozen cycles (e.g., gonadotropin dose, stimulation type, use of

pre-implantation genetic screening/diagnosis (PGD/PGS)). PGD/PGS data are only captured in the NASS database for fresh cycles and not for cycles in which all embryos are screened for aneuploidy and frozen for storage in anticipation of a later future thaw and transfer. Among the infertility diagnoses, which are not mutually exclusive, diminished ovarian reserve (DOR) was not included because the NASS definition includes advanced maternal age (>40 years), regardless of ovarian reserve parameters.

We then investigated variables associated with clinical pregnancy, defined as a gestational sac(s) seen on ultrasound and live birth among fresh autologous cycles and transfers for women ≥ 40 years. Log binomial regression using generalized estimating equations with an independent correlation matrix to account for clustering by clinic was performed to produce unadjusted and adjusted risk ratios and confidence intervals. Multivariable models were created using backwards model building, with only those variables statistically significant at $\alpha = 0.05$ retained in the final model. Race and BMI were not considered for inclusion in the multivariable models due to a large percentage of data missing (40.0 and 26.2%, respectively); missing data for all other variables was less than 2.8%.

Lastly, we described perinatal outcomes including gestational age and birth weight at delivery of singleton and twin infants conceived with fresh autologous IVF cycles among women ≥ 40 years. Gestational age was missing for 0.25% of infants and gestational weight for 2.4% of infants.

Analyses were conducted using SAS v9.3 (SAS Institute, Inc., Cary, NC). The study was approved by the Institutional Review Board of the Centers for Disease Control and Prevention.

Results

In 1996, autologous IVF cycles in women ≥ 40 years ($n = 8672$) accounted for 16.0% of cycles in women of all ages ($n = 54,074$). This proportion increased to 21.0% ($n = 28,883/138,530$) in 2013.

The total number of autologous (fresh and frozen) IVF cycles for women ≥ 40 years increased from 8672 to 28,883 from 1996 to 2013 ($p < 0.0001$), with a peak in 2012 of 29,727 cycles (Fig. 1a). From 1996 to 2013, the number of fresh cycles increased overall from 7493 to 21,251 ($p < 0.0001$), but peaked in 2011 at 23,918 cycles and declined afterwards (Fig. 1a). The number of frozen cycles increased through the entire study period from 1179 in 1996 to 7632 in 2013 ($p < 0.0001$), more than tripling in the last 8 years. From 2006 to 2013, the proportion of frozen cycles among all cycles (fresh and frozen) increased from 11.3 to 26.4%. The number of live births increased significantly from 748 in 1996 to 4217 in 2013 ($p < 0.0001$). The live birth rate per fresh cycle started increased from 8.5% in 1996 (635 live births/7493 cycles) to

Fig. 1 Trends in IVF autologous oocyte cycles and outcomes among women ≥ 40 years at cycle start, 1996–2013. **a** Fresh and frozen IVF cycles, 1996–2013. **b** Live birth rate, 1996–2013

10.6% in 2013 (2262 live births/21,251 cycles), peaking in 2010 at 12.0% (Fig. 1b).

Figure 2, which describes the number of fresh and frozen autologous IVF cycles initiated per live birth by year of maternal age at oocyte retrieval, shows an exponential increase from 5.4 cycles per live birth in women who were 40 years at the time of oocyte retrieval to 92.9 cycles per live birth in women who were ≥ 46 years of age. In women older than

44 years, the live birth rate was 1–2%. The ratio of the number of live births to the number of IVF cycles started for each year of age was as follows: 117:5811 for 45 years, 23:2582 for 46 years, 12:1199 for 47 years, 8:601 for 48 years, and 10:536 for 49 years and older.

Among all fresh autologous IVF cycles started by women ≥ 40 years between 2007 and 2013 ($n = 157,890$), 17.1% ($n = 26,990$) were canceled (Table 1). Among cycles that

Fig. 2 Number of IVF cycles started per live birth by maternal age at oocyte retrieval, 2007–2013

Table 1 Patient and cycle characteristics of autologous fresh IVF cycles in women ≥ 40 years, 2007–2013

	Fresh cycles	
	<i>n</i>	%
Total number of cycles	157,890	
Maternal age (years)		
40	44,749	28.3
41	39,101	24.8
42	30,590	19.4
43	21,411	13.6
44	11,980	7.6
45	5,469	3.5
>45	4,590	2.9
Race/ethnicity ^a		
Non-Hispanic white	62,856	39.8
Non-Hispanic black	9,146	5.8
Asian/Pacific islander	13,470	8.5
Hispanic	9,031	5.7
Other	218	0.0
Missing data	63,169	40.0
BMI (kg/m ²) ^a		
<18.5	2,799	1.8
18.5–24.9	63,317	40.1
25.0–29.9	28,839	18.3
>30	21,651	13.7
Missing data	41,284	26.1
No. of prior pregnancies		
0	52,177	33.1
1	42,356	26.9
>2	62,922	40.0
No. of prior spontaneous abortions		
0	92,775	59.2
1	37,703	24.0
>2	26,382	16.8
No. of prior births		
0	101,958	64.9
1	39,236	25.0
>2	15,894	10.1
No. of prior ART cycles		
0	70,581	44.7
1	35,162	22.3
>2	52,054	33.0
Infertility diagnosis		
Male factor	42,232	26.8
Endometriosis	10,076	6.4
Ovulatory dysfunction	8,558	5.4
Tubal factor	21,431	13.6
Uterine factor	10,482	6.6
Unexplained	15,637	9.9
Other	28,112	17.8

Table 1 (continued)

	Fresh cycles	
	<i>n</i>	%
Stimulation type		
None (natural cycle)	4,228	2.7
Oral meds only	1,618	1.0
Oral meds + gonadotropins	5,520	3.5
Gonadotropins only (antagonist)	74,750	48.0
Gonadotropins only (no suppression)	5,312	3.4
Gonadotropins only (flare)	30,859	19.8
Gonadotropins only (standard agonist)	32,545	20.9
Other	990	0.6
Gonadotropin dose (international dose)		
0–2,000	21,971	14.3
2,001–4,000	52,962	34.5
4,001–6,000	56,127	36.5
$>6,000$	22,570	14.7
Cycle cancellation		
Yes	26,990	17.1
No	130,900	82.9
Ovarian hyperstimulation syndrome		
No	157,448	99.7
Yes	442	0.3
Total number of retrievals	130,900	
No. of oocytes retrieved		
0–4	37,445	28.6
5–9	46,360	35.4
>10	47,095	36.0
Used intracytoplasmic sperm injection		
No	34,688	27.0
Yes	93,803	73.0
Used pre-implantation genetic diagnosis/screening (PGS/PGD)		
No	119,758	94.1
Yes	7,554	5.9
Use of PGD for aneuploidy screening	4,515	84.8
Use of PGD for other reasons	812	15.2
No. of supernumerary embryos cryopreserved		
0	109,717	85.9
1–2	9,516	7.5
3–4	4,721	3.7
>5	3,784	3.0
Total number of transfers	112,414	
Used assisted hatching		
No	37,720	33.6
Yes	74,694	66.5
No. of embryos transferred		
1	18,498	16.5
2	28,053	24.9
3	30,501	27.2
>4	35,291	31.4

Table 1 (continued)

	Fresh cycles	
	<i>n</i>	%
Embryo stage at transfer		
Days 2/3	82,823	73.8
Days 5/6	26,161	23.3
Other	3316	3.0
Treatment outcome		
Not pregnant	72,848	65.1
Ectopic pregnancy	655	0.6
Biochemical pregnancy	9868	8.8
First trimester loss	9183	8.2
Therapeutic abortion	599	0.5
Second/third trimester loss	777	0.7
Live birth	18,023	16.1

^a Greater than 20% of the observations are missing values for this variable

proceeded to embryo transfer ($n = 112,414$), 65.1% ($n = 72,848$) did not result in pregnancy, 8.8% ($n = 9868$) resulted in a biochemical pregnancy, 8.2% ($n = 9183$) resulted in a first trimester pregnancy loss, and 16.1% ($n = 18,023$) resulted in a live birth. The biochemical pregnancies and first trimester losses accounted for 48.7% of all pregnancies.

Among women ≥ 40 years of age undergoing embryo transfer following a fresh IVF cycle during 2007 to 2013, the following characteristics were significantly associated with clinical pregnancy and live birth (Table 2): younger maternal age, higher parity, fewer prior ART cycles, use of a standard agonist or antagonist stimulation, lower gonadotropin dose (≤ 2000 IU), having had ovarian hyperstimulation syndrome, transferring more embryos, transferring blastocyst stage embryos, and cryopreserving more supernumerary embryos. Tubal factor and uterine factor were associated with lower rates of clinical pregnancy and live birth, and ovulatory dysfunction with lower rate of live birth. More oocytes retrieved and use of PGS/PGD were associated with live birth only. Use of ICSI was associated with lower rate of clinical pregnancy and live birth. Reporting year was not significantly associated with clinical pregnancy or live birth rate, indicating no significant change from 2007 to 2013 (24.9 to 25.6% and 15.8 to 15.7%, respectively).

We also assessed variables associated with clinical pregnancy and live birth among all IVF cycles started by women ≥ 40 years to account for canceled cycles (data not shown). The majority of the variables significantly associated with the outcomes were similar with a few exceptions; the number of prior ART cycles was not associated with clinical pregnancy or live birth, while ovulatory dysfunction and unexplained infertility were both positively associated with clinical pregnancy and live birth.

Among women ≥ 40 years between 2007 and 2013, there were 20,714 infants born, of which 14,992 (72.3%) were singletons. Of the singleton infants, 13,034 (86.9%) were born at term (≥ 37 weeks), 1582 (10.6%) between 32 and 37 weeks, and 339 (2.3%) at less than 32 weeks. The majority of singleton infants born (88.2%; $n = 13,233$) were of normal birth weight (>2500 g), with 1170 (7.8%) weighing between 1501 and 2500 g, and 257 (1.7%) weighing less than 1500 g. Of the twin live-born infants ($n = 5722$), 2442 (42.7%) were at term, 2632 (46.0%) between 32 and 37 weeks, and 634 (11.1%) at less than 32 weeks.

Discussion

From 1996 to 2013, there was an increase in both the total number of IVF cycles in women ≥ 40 years and the proportion of cycles in this population among all cycles in women of all ages. During 2007 to 2013, the live birth rate did not improve significantly; however, for cycles resulting in a singleton live birth, perinatal outcomes were similar to the rest of the IVF population. The number of cycles per live birth exponentially increased with each successive year of maternal age. Although maternal age is the most significant determinant of live birth following IVF, we were able to identify other variables associated with successful outcomes.

In the last 8 years studied (2006–2013), the increase in the number of total cycles was driven by the number of frozen cycles almost tripling. They were 11.3% of all cycles in 2006 and 26.4% in 2013. The increase in the ratio of frozen to fresh cycles in this population likely reflects the growing practice of embryo freezing for a later transfer of thawed embryos [15]. This is commonly done to optimize either the endometrium or for aneuploidy screening, which often entails biopsying blastocyst embryos for PGS and then transferring the embryo(s) in a later frozen cycle in an effort to increase implantation rates and decrease miscarriage rates. NASS does not currently collect information on whether frozen embryos thawed for transfer underwent PGS, but the percentage of cycles that involved freezing all embryos in 2013 was 22.7%, with higher rates in older women (56.3% in women >44 years) [16].

Although there was a slight improvement in live birth rate from 1996 to 2013 in women ≥ 40 years, it has only varied slightly in the last 10 years. This finding is consistent with a recent Society for Assisted Reproductive Technology (SART) publication analyzing long-term trends in ART cycles that found no change in live birth rates since 2003 in women >42 years of age [17]. In addition, almost half of the positive pregnancy tests in our study ended in a first trimester loss or biochemical pregnancy. Among live-born singleton infants, however, adverse perinatal outcomes were the minority with 12.9% of infants born premature and 9.5% with low birth weight. These are similar to previously published rates among all ART singletons (13.3%

Table 2 Variables associated with clinical pregnancy and live birth in women ≥ 40 years in autologous fresh IVF transfers, 2007–2013

	Clinical pregnancy				Live birth			
	<i>n</i>	% ^a	RR (95% CI)	aRR (95% CI)	<i>n</i>	% ^a	RR (95% CI)	aRR (95% CI)
Reporting year								
2007	3762	24.92	Reference	NS	2388	15.81	Reference	NS
2008	4226	26.53	1.06 (1.02–1.11)	NS	2594	16.28	1.03 (0.98–1.08)	NS
2009	4345	26.35	1.06 (1.01–1.11)	NS	2709	16.42	1.04 (0.98–1.10)	NS
2010	4286	26.18	1.05 (1.00–1.10)	NS	2692	16.43	1.04 (0.98–1.10)	NS
2011	4381	25.36	1.02 (0.97–1.07)	NS	2776	16.04	1.01 (0.96–1.07)	NS
2012	4238	25.32	1.02 (0.96–1.07)	NS	2602	15.52	0.98 (0.92–1.05)	NS
2013	3688	25.61	1.03 (0.97–1.09)	NS	2262	15.68	0.99 (0.92–1.07)	NS
Maternal age (years)								
40	11,524	33.74	Reference	Reference	7935	23.21	Reference	Reference
41	8434	29.31	0.87 (0.85–0.89)	0.89 (0.87–0.91)	5361	18.61	0.80 (0.78–0.83)	0.82 (0.80–0.85)
42	5150	23.68	0.70 (0.68–0.73)	0.74 (0.72–0.77)	2915	13.39	0.58 (0.55–0.60)	0.62 (0.59–0.64)
43	2532	17.49	0.52 (0.50–0.54)	0.57 (0.55–0.59)	1303	8.99	0.39 (0.37–0.41)	0.43 (0.41–0.46)
44	904	11.87	0.35 (0.33–0.38)	0.40 (0.38–0.43)	367	4.82	0.21 (0.19–0.23)	0.24 (0.22–0.27)
45	270	8.34	0.25 (0.22–0.28)	0.31 (0.27–0.35)	102	3.14	0.14 (0.11–0.17)	0.18 (0.14–0.22)
>45	112	4.90	0.15 (0.12–0.17)	0.20 (0.17–0.24)	40	1.75	0.08 (0.05–0.11)	0.11 (0.07–0.16)
Race/ethnicity ^b								
Non-Hispanic white	12,041	27.01	Reference	N/A	7595	17.03	Reference	N/A
Non-Hispanic black	1346	22.27	0.82 (0.76–0.89)	N/A	781	12.90	0.76 (0.69–0.83)	N/A
Asian/Pacific islander	2121	22.59	0.84 (0.79–0.88)	N/A	1276	13.56	0.80 (0.74–0.86)	N/A
Hispanic	1601	25.01	0.93 (0.86–0.99)	N/A	987	15.38	0.90 (0.82–0.99)	N/A
Other	31	21.38	0.79 (0.55–1.15)	N/A	18	12.16	0.71 (0.44–1.17)	N/A
BMI (kg/m ²) ^b								
<18.5	472	23.74	0.91 (0.83–0.99)	N/A	291	14.64	0.89 (0.78–1.01)	N/A
18.5–24.9	11,883	26.12	Reference	N/A	7484	16.43	Reference	N/A
25.0–29.9	5390	25.95	0.99 (0.96–1.03)	N/A	3319	15.96	0.97 (0.93–1.01)	N/A
>30	4092	26.19	1.00 (0.97–1.04)	N/A	2478	15.84	0.96 (0.92–1.01)	N/A
No. of prior pregnancies								
0	8536	23.56	Reference	Reference	5297	14.60	Reference	Reference
1	8144	26.52	1.13 (1.10–1.15)	1.07 (1.04–1.10)	5116	16.65	1.14 (1.10–1.18)	1.08 (1.04–1.13)
>2	12,180	27.02	1.15 (1.12–1.18)	1.08 (1.04–1.11)	7561	16.75	1.15 (1.11–1.19)	1.10 (1.05–1.16)
No. of prior spontaneous abortions								
0	16,445	25.17	Reference	NS	10,322	15.78	Reference	Reference
1	7424	26.84	1.07 (1.04–1.10)	NS	4566	16.50	1.05 (1.01–1.08)	0.98 (0.94–1.02)
>2	4843	26.06	1.04 (0.99–1.07)	NS	2979	16.02	1.01 (0.98–1.05)	0.94 (0.90–0.98)
No. of prior births								
0	17,625	24.47	Reference	Reference	10,849	15.05	Reference	Reference
1	8160	28.48	1.16 (1.13–1.19)	1.12 (1.09–1.15)	5228	18.22	1.21 (1.17–1.25)	1.15 (1.11–1.20)
>2	2975	26.90	1.10 (1.06–1.14)	1.09 (1.04–1.13)	1840	16.60	1.10 (1.05–1.15)	1.07 (1.01–1.13)
No. of prior ART cycles								
0	13,210	26.62	Reference	Reference	8337	16.78	Reference	Reference
1	6509	25.66	0.96 (0.94–0.99)	0.99 (0.96–1.02)	4077	16.05	0.96 (0.92–0.99)	1.00 (0.96–1.03)
>2	9195	24.70	0.93 (0.89–0.97)	0.95 (0.93–0.98)	5602	15.03	0.90 (0.85–0.94)	0.94 (0.90–0.97)
Infertility diagnosis								
Male factor	8452	26.89	1.06 (1.03–1.10)	1.03 (1.00–1.05)	5316	16.90	1.08 (1.03–1.12)	NS
No male factor	20,474	25.32	Reference	Reference	12,707	15.70	Reference	NS
Endometriosis	1845	25.41	0.99 (0.94–1.04)	NS	1128	15.52	0.97 (0.91–1.03)	NS

Table 2 (continued)

	<i>n</i>	Clinical pregnancy			<i>n</i>	Live birth		
		% ^a	RR (95% CI)	aRR (95% CI)		% ^a	RR (95% CI)	aRR (95% CI)
No endometriosis	27,081	25.78	Reference	NS	16,895	16.07	Reference	NS
Ovulatory dysfunction	1940	30.00	1.18 (1.11–1.24)	NS	1210	18.70	1.18 (1.10–1.26)	0.94 (0.89–0.99)
No ovulatory dysfunction	26,986	25.50	Reference	NS	16,813	15.87	Reference	Reference
Tubal factor	3982	25.15	0.97 (0.94–1.01)	0.91 (0.88–0.94)	2442	15.41	0.95 (0.91–1.00)	0.89 (0.86–0.93)
No tubal factor	24,944	25.86	Reference	Reference	15,581	16.14	Reference	Reference
Uterine factor	1796	23.98	0.93 (0.87–0.98)	0.92 (0.88–0.97)	1035	13.79	0.85 (0.80–0.91)	0.85 (0.80–0.91)
No uterine factor	27,130	25.89	Reference	Reference	16,988	16.19	Reference	Reference
Unexplained	3599	29.15	1.15 (1.09–1.22)	NS	2345	18.97	1.21 (1.13–1.29)	NS
No unexplained	25,327	25.34	Reference	NS	15,678	15.67	Reference	NS
Other	5038	26.51	1.04 (0.99–1.08)	NS	3191	16.77	1.06 (1.00–1.11)	NS
No other	23,888	25.60	Reference	NS	14,832	15.88	Reference	NS
Stimulation type								
None (natural cycle)	367	16.60	0.66 (0.55–0.79)	0.94 (0.83–1.07)	207	9.34	0.60 (0.45–0.79)	0.89 (0.76–1.04)
Oral meds only	75	10.82	0.43 (0.33–0.55)	0.86 (0.74–0.99)	40	5.69	0.36 (0.28–0.47)	0.86 (0.70–1.07)
Oral meds + gonadotropins	461	15.66	0.62 (0.50–0.76)	0.81 (0.68–0.95)	261	8.85	0.56 (0.45–0.71)	0.78 (0.65–0.93)
Gonadotropins only (antagonist)	13,710	25.28	Reference	Reference	8507	15.67	Reference	Reference
Gonadotropins only (no suppression)	731	23.65	0.94 (0.83–1.06)	0.94 (0.85–1.04)	436	14.08	0.90 (0.79–1.02)	0.91 (0.82–1.02)
Gonadotropins only (flare)	5384	24.17	0.96 (0.91–1.01)	1.00 (0.96–1.04)	3310	14.85	0.95 (0.89–1.01)	1.00 (0.95–1.05)
Gonadotropins only (agonist)	7781	30.87	1.22 (1.16–1.28)	1.08 (1.05–1.11)	5005	19.84	1.27 (1.20–1.34)	1.08 (1.04–1.12)
Other	202	31.17	1.23 (1.08–1.41)	1.23 (1.09–1.38)	125	19.29	1.23 (1.01–1.50)	1.27 (1.12–1.44)
Gonadotropin dose (international dose)								
0–2000	3390	26.60	Reference	Reference	2146	16.80	Reference	Reference
2001–4000	11,689	30.22	1.14 (0.98–1.32)	0.96 (0.92–1.00)	7460	19.27	1.15 (0.96–1.37)	0.95 (0.90–1.00)
4001–6000	10,226	24.34	0.92 (0.78–1.07)	0.86 (0.82–0.90)	6218	14.79	0.88 (0.73–1.06)	0.83 (0.78–0.88)
>6000	3153	19.13	0.72 (0.61–0.85)	0.77 (0.73–0.82)	1908	11.57	0.69 (0.57–0.84)	0.76 (0.70–0.82)
Ovarian hyperstimulation syndrome								
Yes	143	53.96	2.10 (1.57–2.81)	1.47 (1.20–1.81)	101	37.97	2.38 (1.66–3.40)	1.60 (1.25–2.03)
No	28,783	25.69	Reference	Reference	17,955	15.98	Reference	Reference
No. of oocytes retrieved								
0–4	3747	14.08	Reference	NS	2083	7.81	Reference	Reference
4–9	10,395	24.66	1.75 (1.68–1.82)	NS	6318	14.97	1.92 (1.81–2.03)	1.08 (1.02–1.14)
>10	14,784	33.96	2.41 (2.30–2.52)	NS	9622	22.09	2.83 (2.66–3.01)	1.13 (1.07–1.20)
Used intracytoplasmic sperm injection								
No	8460	27.97	Reference	Reference	5292	17.49	Reference	Reference
Yes	20,433	24.97	0.89 (0.85–0.93)	0.95 (0.92–0.99)	12,714	15.52	0.89 (0.84–0.94)	0.95 (0.91–0.99)
Used pre-implantation genetic diagnosis/ screening								
No	27,379	25.54	Reference	NS	16,862	15.72	Reference	Reference
Yes	1409	31.76	1.24 (1.16–1.33)	NS	1078	24.24	1.54 (1.42–1.68)	1.28 (1.17–1.39)
Used assisted hatching								
No	11,073	29.39	Reference	NS	7180	19.03	Reference	NS
Yes	17,853	23.93	0.81 (0.76–0.87)	NS	10,843	14.52	0.76 (0.71–0.82)	NS
No. of embryos transferred and embryo stage at transfer								
Cleavage (day 2/3)								
1	1056	7.94	Reference	Reference	559	4.20	Reference	Reference
2	2918	16.14	2.01 (1.87–2.16)	1.82 (1.69–1.96)	1736	9.59	2.26 (2.04–2.50)	1.95 (1.76–2.16)
3	5394	25.53	3.20 (3.01–3.40)	2.66 (2.49–2.85)	3279	15.51	3.68 (3.36–4.03)	2.79 (2.53–3.07)
>4	9272	30.69	3.83 (3.59–4.08)	3.37 (3.14–3.61)	5677	18.78	4.42 (4.06–4.80)	3.57 (3.27–3.91)

Table 2 (continued)

	<i>n</i>	Clinical pregnancy			<i>n</i>	Live birth		
		% ^a	RR (95% CI)	aRR (95% CI)		% ^a	RR (95% CI)	aRR (95% CI)
Blastocyst (day 5/6)								
1	988	22.75	Reference	Reference	669	15.40	Reference	Reference
2	3645	39.66	1.74 (1.57–1.93)	1.44 (1.31–1.58)	2449	26.62	1.72 (1.50–1.97)	1.44 (1.30–1.60)
3	3470	40.52	1.77 (1.59–1.97)	1.58 (1.42–1.75)	2302	26.86	1.72 (1.49–1.99)	1.62 (1.44–1.83)
>4	1457	36.07	1.58 (1.42–1.76)	1.66 (1.50–1.84)	900	22.27	1.43 (1.23–1.67)	1.68 (1.50–1.89)
Other								
1	84	10.34	Reference	Reference	60	7.38	Reference	Reference
2	142	19.16	1.92 (1.50–2.46)	1.80 (1.42–2.29)	97	13.07	1.83 (1.40–2.41)	1.72 (1.33–2.22)
3	196	25.82	2.52 (1.82–3.50)	2.15 (1.59–2.92)	116	15.24	2.10 (1.46–3.02)	1.77 (1.30–2.42)
>4	275	27.58	2.69 (1.95–3.71)	2.51 (1.87–3.37)	163	16.32	2.30 (1.62–3.26)	2.19 (1.66–2.89)
No. of supernumerary embryos cryopreserved								
0	22,459	23.15	Reference	Reference	13,712	14.12	Reference	Reference
1–2	3241	41.15	1.78 (1.72–1.84)	1.30 (1.26–1.33)	2164	27.44	1.94 (1.86–2.03)	1.32 (1.26–1.37)
3–4	1773	45.16	1.95 (1.86–2.04)	1.36 (1.31–1.41)	1165	29.63	2.10 (1.97–2.23)	1.35 (1.27–1.42)
≥5	1308	47.36	2.05 (1.94–2.16)	1.42 (1.35–1.48)	903	32.69	2.31 (2.16–2.48)	1.47 (1.38–1.56)

NS not significant in the multivariable model, N/A not available

^a Proportion (%) that resulted in outcome of interest (e.g., clinical pregnancy or live birth)

^b Greater than 20% of the observations are missing values for this variable; therefore, the variable was not included in the multivariable analysis

rate of prematurity and 9.0% rate of low birth weight) [18]. The results are more encouraging than some other retrospective studies that found infants of older mothers were at higher risk for prematurity and low birth weight [12, 19], though the other studies included non-ART pregnancies whereas ours focuses solely on IVF pregnancies.

For women in their 40s, the number of fresh and frozen IVF cycles started per live birth increased substantially for each additional year of age at oocyte retrieval. These findings are consistent with prior literature that demonstrated decreasing live birth rates with incremental increases in age for women in their 40s [4, 6, 8]. The large number of unsuccessful IVF cycles in this older age group represents a large physical, financial, and emotional toll for women and their partners.

There are other variables aside from maternal age that were associated with positive outcomes. Some are intuitive and consistent with prior literature in older women, including the retrieval of more oocytes [5, 9, 20], the transfer of more embryos [4, 6, 21] at a more advanced embryonic stage, and the cryopreservation of more supernumerary embryos [22]. Similar to what has been seen previously [23], our study found that a lower gonadotropin dose was associated with higher rates of clinical pregnancy and live birth in the multivariable analysis. This could be attributed to the fact that patients with a higher ovarian reserve (and thus better prognosis) receive less gonadotropins; however, another study found lower live birth rates with higher doses of gonadotropins in other populations (e.g., good prognosis patients), irrespective of the number of oocytes retrieved [23].

Our study is one of the first to show the benefit of parity in an older population undergoing IVF. One recently published study of fecundability in a non-ART population similarly found that nulliparous women had lower fecundity [24]. Although some prior studies have indicated that older women with tubal factor [25] or ovulatory dysfunction [26] may have a reproductive advantage, we did not find this to be the case among women having transfers. No infertility diagnoses were associated with increased rates of live birth.

Our data represents a selected population of women who were thought to have enough ovarian reserve to proceed with IVF; we have no data regarding the number of women who were not able to access or initiate fertility care with autologous oocytes due to projected poor success. We can conclude, however, that there is an increased demand for fertility treatment in older women, as reflected by the rise in the proportion of cycles in women ≥40 years from 1996 to 2013. This increase may be attributable to an increase in the number of women ≥40 years seeking treatment, an increase in the number of cycles per woman, or both.

The primary limitation of our study is that the data are cycle-specific and not patient-specific. For example, Fig. 2 (number of IVF cycles started per live birth by maternal age at oocyte retrieval) cannot be used to predict the number of IVF cycles necessary to achieve a live birth in an individual. Also, Fig. 2 includes the 56% of the frozen cycles meeting our study criteria, as the other 44% could not be linked to their originating retrieval, which potentially could result in an

under- or overestimation of the reported ratios. In addition, since data were not collected on whether PGS/PGD was performed for frozen cycles in the NASS, we were unable to include frozen cycles in the analyses of cycle characteristics and reproductive outcomes. We also had limited ovarian reserve data, although this is somewhat reflected in the number of oocytes retrieved.

Strengths of this study include the use of a large national database, which allowed for description of nationwide trends in IVF cycles among women ≥ 40 years and the ability to control for many variables that can influence IVF outcomes. A recent publication from the SART database analyzed the history of IVF and trends in IVF over the last two decades [17]. We were able to explore in detail a smaller subset of cycles among women ≥ 40 years, including the demographics of this population, cycle characteristics, factors associated with live birth, and perinatal outcomes. In addition, we were able to explore changes in practice patterns over time, such as the recent increase in the number and proportion of cycles using frozen embryos. Although ART success in this population is higher using donor oocytes, a genetically related child is often the initial goal of women embarking on fertility treatment. As the percentage of cycles in this group of women continues to increase, the identification of factors associated with higher live birth rates may facilitate option counseling and informed decisions prior to the initiation of treatment.

Compliance with ethical standards The study was approved by the Institutional Review Board of the Centers for Disease Control and Prevention.

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Conflict of interest Dr. Grainger receives speaking fees from Abbvie, Inc. and Shionogi, Inc. on topics unrelated to the study question.

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