

Reproductive outcome of women 43 years and beyond undergoing ART treatment with their own oocytes in two Connecticut university programs

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Abstract

Purpose The aim of this study was to analyze the outcomes of IVF/ICSI cycles in women aged 43 and beyond.

Methods Retrospective analysis of clinical pregnancy and live birth rates in 168 fresh, non donor, ART cycles performed in two Connecticut university IVF programs.

Results In women of 43 and 44 years the overall clinical pregnancy and live birth rates were 8.3 % and 5.3 % per initiated cycle, respectively. There were no clinical pregnancies in women ≥ 45 years old. First cycle characteristics were not different from repeated cycles in terms of duration of ovulation induction, number of collected oocytes and transferred embryos ($p > 0.05$).

Conclusions Pregnancies can still be achieved with IVF/ICSI up to the age of 44. Since most pregnancies occurred within the first 3 cycles, another attempt may be a reasonable option before resorting to oocyte donation for patients who failed two previous cycles. Women 45 years and beyond do not benefit from ART procedures using their own oocytes.

Keywords IVF · ICSI · Advanced age · Pregnancy success

Capsule Women ≥ 45 years old do not benefit from ART procedures using their own oocytes.

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Introduction

Since the first live birth following IVF in 1978, the use of assisted reproductive technologies (ART) has steadily increased, and in the United States about 12 % of women of childbearing age currently receive infertility treatment ([26]; 2009). Live birth rates after IVF have also increased and in fact from 1996 to 2010, the live birth rates for women younger than 35 increased 42 % (from 33.6 % to 47.7 %). Over the same time period, live birth rates increased 30 % for women 35–37 (from 29.9 % to 38.8 %) and 38 % for women 38–40 (from 21.6 % to 29.9 %). Interestingly, live birth rates have either failed to increase or remained similar for women 41–42 (from 11.5 % to 12.5 %) and for women older than 42 (from 5.4 % to 4.1 %), possibly indicating that more cases are opting for donor oocytes and that the more difficult cases remain ([26]; 2009).

A significant group of women older than 40 years (about 15 % according to the recent CDC registry) that have either voluntarily or involuntarily postponed their desire for pregnancy are now requesting reproductive treatments. In particular the number of women 43 years and older seeking IVF treatment is also on the rise, but there is little data available regarding treatment outcomes [6,11,12,19,24]. For many years, the upper limits for allowing IVF attempts were arbitrarily chosen (usually age 41 or 42 years) and strictly enforced by some centers [11]. Recent studies have reported a reasonable success rate up to 44 years of age [11,24] and it is only recently that the Society for Assisted Reproductive Technology (SART) has begun to provide data on cycle characteristics and pregnancy outcomes for patients aged 43–44 utilizing their own oocytes. However, the data for these specific age groups (43 and 44) and older are still limited and moreover, cumulative ART cycle characteristics are still unknown in patients older than 43 years old.

Thus the purpose of the present study was to investigate the characteristics of ART cycles and cumulative success

rates of repetitive cycles in women seeking infertility treatment at ages 43 years and beyond, together with a review of the literature. Information about clinical outcomes for those specific ages separately would be helpful for counseling and offering realistic treatment options.

Materials and methods

Coded SART data of patients ($n=109$ for a total of 168 cycles) 43 years of age and beyond enrolled in ART cycles between 2006 and 2009 at two Connecticut university hospitals, were retrospectively reviewed. All published data available related to advanced age ART cycles, were also reviewed. We searched MEDLINE (1970–2009), EMBASE (1974–2006), and Cochrane Library (2009:1), for relevant studies. A combination of Medical Subject Headings (MeSH) and text words were used to generate two subsets of citations, one including studies of advanced age, in vitro fertilization (IVF), (intra cytoplasmic sperm injection) (ICSI), cumulative pregnancy rates and the other studies of IVF and ICSI.

Main outcomes considered were clinical pregnancy and live birth rates per cycle. Secondary outcomes were the cycle cancellation rate, the mean number of oocytes retrieved, the embryos transferred per cycle, biochemical pregnancy and the spontaneous abortion rate. Embryo grading was performed using standard parameters of measuring cell numbers and fragmentation for cleavage stage day 2 and 3 embryos. For blastocysts the alphanumeric scoring system of Gardner and Schoolcraft [4] was used. In patients with repetitive cycles, we compared cycle characteristics of the first cycle with their subsequent cycles in order to evaluate inter cycle differences. Ovarian reserve tests obtained were cycle day 3 FSH, estradiol and Antral Follicle Count (AFC). Patients with high FSH levels (>15 IU/mL) and/or AFC less than three were used as an exclusion criteria.

For the outcome analysis, a clinical pregnancy was defined as visualization of fetal heartbeat on ultrasound. Biochemical pregnancies were defined as those with positive hCG but never reaching a level compatible with the ultrasound visualization of a gestational sac. Pregnancies lost before 20 weeks were considered as spontaneous miscarriages. Prior to ART cycle, all patients had the uterine cavity evaluated by hysterosalpingography, sonohysterography or hysteroscopy.

Controlled ovarian stimulation was performed with a microdose gonadotropin releasing hormone (GnRH) agonist flare protocol in 42 cycles, a GnRH antagonist protocol in 73 cycles and a long protocol GnRH agonist (Leuprolide acetate) protocol started on the luteal phase of the preceding menstrual cycle in 53 cycles. The starting dose of recombinant FSH and/or hMG varied and depended upon the

previous response to ovarian stimulation and basal ultrasound assessment. In general, the initiating total dose of gonadotropins ranged between 150 and 600 IU/day. Ovulation was triggered with recombinant hCG in all cases and luteal phase supported with intramuscular progesterone (50 mg/day).

All statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL). Values are expressed as mean \pm SD. The two-tailed Mann–Whitney U test was used to determine the significance of differences between nonparametric data. The Fisher's exact test was utilized to compare outcomes between age groups. The Spearman coefficient was used to determine correlations between cycle characteristics. Kaplan Meier test were used to calculate probability of pregnancy rate for the next cycle. Differences were considered statistically significant with a P value less than 0.05.

Results

A total of 109 women (age ≥ 43) who were considered candidates for ART underwent a total of 168 IVF/ICSI cycles with their own oocytes. A total of 1145 oocytes were deemed suitable (MII) for fertilization and of these 613 showed signs of fertilization (2PN, 54 %). When the IVF/ICSI cycles were calculated per patient, there were 67 women who underwent only one cycle; 28 women had two consecutive cycles; 11 women had three consecutive cycles and a fourth cycle was performed in only three women. The average patient's age was 43.9 ± 1.05 years. Indications for IVF/ICSI treatment were male factor ($n=40$, 36.6 %), tubal ($n=4$, 3.6 %), diminished ovarian reserve ($n=49$, 44.9 %), uterine ($n=2$, 1.9 %) endometriosis ($n=4$, 3.6 %), and unexplained infertility ($n=10$, 9.1 %). The highest number of cycles ($n=51$) were for male factor infertility with 7.8 % live birth rate followed by diminished ovarian reserve (DOR) ($n=28$) with a live birth rate of 7.2 %. The highest live birth rate (20 %) was seen in cycles ($n=10$) with unexplained infertility (see Table 1).

Table 1 Distribution of etiology of infertility and live birth according to cycles in women ≥ 43 years old

Diagnosis	One cycle	Two cycles	Three cycles	Four cycles	Total	Live birth
Male	30	15	6	0	51	4 (7.8 %)
DOR	21	5	2	0	28	2 (7.1 %)
Tubal	10	3	1	0	14	1 (7.1 %)
Endometriosis	1	1	1	1	4	–
Unexplained	5	2	1	2	10	2 (20 %)
Uterine	0	2	0	0	2	–
Total	67	28	11	3	109	9 (8.2 %)

The cycle cancellation rate was 27.8 %, with 123 cycles reaching oocyte retrieval, and 108 cycles (64.3 %) achieving embryo transfer. The mean number of oocytes per retrieval was 8.8 ± 5.8 and the mean number of embryos transferred was 2.16 ± 2.04 . In 99 cycles the embryo transfer was performed on day 3 while in 8 cycles transfer was performed on day 5 (blastocyst transfer) and in one case on day 4. In total 284 embryos were transferred. None of the excess embryo met criteria for cryopreservation. A total of 14 clinical pregnancies were established (5 % implantation rate) and 12 were biochemical.

The overall clinical pregnancy rate and the overall live birth rate for all cycles were 8.3 % and 5.3 % per initiated cycle, respectively in all ages combined (Table 2). Although there was no statistical difference in live birth rate between ages 43 and 44 years due to the small numbers, there was a trend for a higher live birth rate in women age 43. Cancellation rates were statistically lower in the 43 year old group than all the other age groups ($P < 0.001$).

There were no clinical pregnancies in women ≥ 45 years old (only one biochemical pregnancy). Women 44 years old had a higher risk of miscarriage compared to 43 year old (66.6 % versus 12.5 %, respectively; $p = 0.06$). Of the patients who achieved a successful pregnancy ($n = 9$), 22.2 % (2/9) did it after two cycles, 88.8 % (6/9) after three cycles, and only one additional pregnancy was obtained after completing the fourth treatment cycle. At the end of the fourth cycle, cumulative clinical pregnancy rates were 21.4 % per patient (Table 3).

Analysis of baseline hormonal parameters showed no significant difference in baseline FSH, peak E2 levels on the day of hCG administration, the number of retrieved oocytes, embryo grade, and number of embryos available for transfer between pregnant and non pregnant cycles

($P > 0.05$) (Table 4). In comparing the clinical pregnancy and live birth rates of our study with previous studies that evaluated women undergoing ART cycles at similar age, there were no statistical differences (Table 5).

Discussion

Demographic trends have seen a significant group of women in their forties seeking reproductive treatments. In fact, according to the latest SART data, approximately 10 % of the total ART usage in the USA were performed in women over the age of 40 [22]. Although it is well documented that natural fecundity declines with increasing maternal age [12] and the success rates in ART are particularly low for women 40 or older, the cutoff age after which no pregnancies are observed with ART remains elusive and controversial, since there are still acceptable chances for pregnancy in women of this age group [11]. Only recently the SART registry has been providing rates of pregnancy and live births for women 43 years of age and older (pregnancy rates of 10.8 % and 7.4 % for women at ages 43 and 44, with a live birth of 5.1 % and 3.0 %, respectively) but these data are still limited. As a consequence it is difficult to provide proper counseling to this group of patients.

In this study we showed that pregnancy and live birth rates per initiated cycle in women older than 42 years old undergoing ART with their own oocytes, were 10.9 % and 9.6 % for 43 years old and 10.9 % and 3.6 % for 44 years old patients, respectively. There was only one positive pregnancy test at age 45, however no gestational sac was visualized (biochemical pregnancy).

These findings are consistent with other studies reporting no live births beyond the forty-third year [12] or live birth

Table 2 Outcomes by age groups

Age	43	44	≥ 45	Overall
Patients	41	35	33	109
Cycles	73	55	40	168
Retrievals	68	37	18	123
Transfers	61	33	14	108
Mean number of oocytes	10.1 ± 6.4	7.6 ± 4	6.2 ± 5.2	8.8 ± 5.98
Mean Number of 2pn	5.60 ± 4.07	4.55 ± 3.21	3.94 ± 3.07	5.23 ± 3.73
Mean number of transferred embryos ^a	2.1 ± 2.1	2.5 ± 1.90	1.58 ± 1.89	$2.2 \pm 2.0.4$
Cancellation rate per cycle ^b	5 (6.8 %)	18 (32.7 %)	22 (55 %)	45 (26.7 %)
Chemical pregnancy rate per cycle ^c (%)	6 (8.2 %)	5 (9 %)	1 (2.5 %)	12 (7.1 %)
Clinical pregnancy rate per cycle ^d (%)	8 (10.9 %)	6 (10.9 %)	–	14 (8.3 %)
Spontaneous abortion rate per pregnancy (%)	1 (12.5 %)	4 (66.4 %)	–	5 (35.7 %)
Live birth rate per cycle (%)	7 (9.6 %)	2 (3.6 %)	0	9 (5.3 %)

^a Between 43 and ≥ 45 years old ($P < 0.05$), ^b Cancellation rates were different among groups ($P < 0.001$), ^c Positive HCG values, ^d Fetal Cardiac Activity observed

Table 3 Cumulative clinical pregnancy rates in women ≥ 43 years of age*

	Overall	Attempt number			
		1	2	3	4
No. of patients (n)	67	28	11	3	
No. of clinical pregnancies (n)	4	3	6	1	
Cumulative clinical pregnancy rate (%)	5.9	10.4	19.4	20.9	
Expected cumulative clinical pregnancy rate (%)	5.9	19.2	47.7	65.2	
Confidence interval % (CI)	2.2–9.6	4.1–22.4	13.8–49.5	15.1–69.3	

*Not including women in whom ART treatments cancelled due to the poor or no response to the therapy

rate between 0 and 3.2 % for women beyond their forty-fourth birthday [6,12,19]. The low live birth rate for women 44 years old (3.6 %) is also in agreement with another recently published report of only 2.3 % live birth rate in women 44 years or older [11]. There is no age matched data on natural birth rate after 45 years old; however natural birth rate has been reported as 0.2–0.38 % of total deliveries in exceptionally fertile populations [5,13]. A recent Chinese study reported that 1.8 % of women between the age of 41–49 had a natural pregnancy [27].

It has been reported that, women 40 years old with adequate follicular development may represent a subgroup of patients with higher chances of conception [6,18]. In one of the earlier studies reporting ART success rates in advanced age groups, Bopp et al. [1] emphasized the negative effect of maternal age on GIFT and IVF outcome. They found a progressive decline in delivery rates with aging and also found significant differences in cancellation rates per initiated cycle between women aged 44–45 years (69.5 %), than those in women 25–39 years (38.2 %) [1]. Although in later studies cancellation rates declined, obviously higher pregnancy rates could not be achieved per cycle (Table 5).

Orvieto et al. [16] reported that the number of transferred embryos and the number of good quality embryos were significant between pregnant and non pregnant patient. On the contrary in our study, women who achieved pregnancy did not show any statistical difference from non-pregnant women when cycle characteristics were compared. In that point there may be other factors that can affect success rates in ART, besides number of collected oocytes and the number of transferred embryos in advanced age group.

Some authors suggested that cumulative delivery rates could be increased in all age groups except older than 40 years or in those with four or fewer retrieved oocytes [3]. Similarly, it has been reported that the pregnancy rate and the cumulative conception rate were also lower after multiple attempts [21]. On the contrary in the latter study authors reported the cumulative conception rate is greater in older women who respond to gonadotropins. In our study cumulative pregnancy and delivery rates were not higher despite adequate oocytes picked up and embryo transfer. This can be interpreted as the lack of ability of FSH measurement and embryo quality to predict chance of live birth in this group, which seems somewhat counterintuitive and should be explored. Unfortunately by increasing the selection criteria for older women, you risk to exclude most aged women seeking fertility in their forties, from attempting infertility treatment.

This study is the first report that investigates cumulative pregnancy rates and repetitive cycle characteristics of women above 43 years old who meet the criteria for ovarian stimulation. Although IVF is an effective treatment for infertility, multiple cycles can be required for some cases. Previous studies have reported that cumulative conception rates of up to 61 % can be achieved with five IVF cycles [7,23]. More recently, Malizia et al. [14] published that among patients who were 40 years of age or older, the cumulative live-birth rate after 6 cycles was 42 % (95 % CI, 37 to 47) with an optimistic analysis and 23 % (95 % CI, 21 to 25) with a conservative analysis. In the present study we have shown that in older patients (>43) the cumulative live birth rate went from 1.1 % at the 1st cycle to 9.1 % after three cycles. Due to the possibility of achieving a consistent

Table 4 Cycle characteristics for pregnant and non-pregnant women ≥ 43 years old

	Basal FSH (mIU/ml)	E2 on day of hCG (pg/ml)	Endometrial thickness (mm)	Number of oocytes	Number of transferable embryos	Embryo grade (Median, Range)
*Positive β -hCG	7.9 \pm 3.9	1680 \pm 751	10.1 \pm 3.3	11.3 \pm 6.9	2.7 \pm 2.2	3 (2–4)
Negative β -hCG	9.0 \pm 4.5	1678 \pm 867	11.1 \pm 1.6	8.8 \pm 5.6	2.4 \pm 1.9	2 (2–4)

*None of the parameters were statistically different between pregnant and non-pregnant cycles ($P > 0.05$)

Table 5 Summary of cycle outcomes from different studies in patients 43 years of age and older

Age	Cycles			Cancel (n)			CP's (n)			SAB (n)			LB (n)		
	43	44	≥45	43	44	≥45	43	44	≥45	43	44	≥45	43	44	≥45
[6]	80	62	96	NA	NA	NA	9	3	3	5	2	2	4	1	–
[11]	380	230	69	67	51	14	48	14	3	18	7	NA	29	6	1
[24]	199	150	192	34	25	13	14	6	4	NA	NA	NA	8	4	1
[19]	68	33	23	NA	NA	NA	13	1	–	NA	NA	NA	5	–	–
[12]	91	74	51	25	19	17	6	3	1	4	1	1	NA	NA	–
*Present Study	73	55	40	5	18	22	8	6	–	1	4	–	7	2	–
Overall	891	604	471	17.6 %	22.2 %	18.7 %	10.9 %	5.4 %	2.3 %	39.4 %	53.8 %	75 %	6.6 %	2.4 %	<1 %

CP clinical pregnancy, SAB spontaneous abortion, LB live birth, NA non applicable

*Clinical pregnancy and live birth rates of our study did not show any difference from the other studies

ovarian response in repeated cycles, some authors have recommended at least four cycles of IVF in women of all ages. But there is no data examining cumulative clinical pregnancy or cumulative live birth rates for women beyond 43 years old in the literature [2,21]. We attempted to calculate the cumulative conception rate up to 4 cycles in women older than 43 years. Depending on the outcome of the first treatment cycle using life table analysis with the Kaplan Meier method we aimed to estimate more accurately the probability of achieving a pregnancy in each attempt. As expected, the overall cumulative conception rate is dramatically lower in these advanced age groups (Table 3).

In light of this information, there still might be an acceptable chance of pregnancy in IVF indicated for women in the age group between 43 and 44 years, if selection of couples is carried out appropriately according to a sufficient ovarian reserve, as was performed in the patients treated in this study. Although there was a significant decrease in live birth rates between the age groups, no significant decrease was found between the first and the subsequent attempts in the present study. These findings indicate that infertility care providers can recommend repeating up to 3 IVF cycles, if transferable embryos could be obtained in women up to 44 years old.

The results of this study may be significant for being one of the few reports of the outcomes for IVF/ICSI in women aged 43 and over. To the best of our knowledge, in only one study from a large IVF center in the USA, a reasonable pregnancy and delivery rate has been reported in a series of women 43 years old and beyond [11]. The study by Klipstein et al. [11] included a larger cohort of patients 43 years or older compared to our study. One possible reason for our case limitation is that the Connecticut State restricts coverage for infertility treatment for women 40 years or older (Connecticut Hospital association, CHIME data fact sheet. Infertility Coverage and Multiple Births, Dec. 2005), in contrast to the large number of ART cycles in the study of Klipstein et al. [11]

in which their state offers infertility coverage for all couples who meet specific criteria. This concept is also supported by the study by Jain and colleagues, showing that the percentage of cycles resulting in pregnancy and live births was significantly higher in states requiring partial or complete coverage, as opposed to states with no mandated insurance coverage for IVF. Interestingly, states that do not require insurance coverage also have the highest number of embryos transferred per cycle and the highest rates of live births with multiple infants [9,10]. This data has also been more recently validated by Martin et al. [15] in the USA using the 2006 SART data.

One valid approach for increasing clinical pregnancy rates in advanced maternal aged women is offering preimplantation aneuploidy testing [20]. In a previous report, we reported that 77.1 % (13/57) of embryos displayed a chromosomal abnormality for the advanced maternal age group (above 35 years old) [17]. The chromosomal abnormality rate for women 43 years or beyond in our own analysis was found to be 80.6 %. However, the main challenge for aged women seeking infertility treatment, are higher cancellation rates and difficulties in getting enough available embryos which makes it more difficult for them to succeed when using embryo biopsy and chromosomal testing for their ART treatment. A possible deleterious effect when stimulating older women could also further compound their treatment [8].

Based on the results of this study, it is reasonable to suggest that, to avoid age discrimination, the law mandating infertility coverage in some states should be amended to include women up to the age of 44 years. But it should place some limitations for ART cycles, even if adequate ovarian response could be achieved. In fact, an evaluation of a total of 736 ICSI cycles, which were performed in 443 women >39 years old concluded that no viable pregnancies ensued in women from 45 years old onwards [6]. Similarly Lass and colleagues reported no live births after 44 years old [12]. Only in two recent studies, have pregnancies been reported after 44 years old [6,11]. In our literature search we failed to

identify any study reporting cumulative pregnancy data only for women above 42 years old to compare cycle characteristics and pregnancy rates.

Conclusions

In the management of infertile couples, chronological age alone should not be the only factor determining access to fertility treatment, since individual variations in the quality of the aging oocytes can produce different outcomes [25]. The present study is consistent with previous reports which emphasize that standardization of patient selection without arbitrary age limits, can result in cost-effective management [9–11,24]. Our own data also support that offering up to 3 IVF attempts may be a reasonable option before oocyte donation for women who are 43 and 44 years old. Based on our outcomes, women 45 years and beyond will not benefit from ART procedures using their own oocytes. A chance for conceiving has been estimated to be almost zero in women at the age of 45 and over and therefore these women have been excluded from the majority of IVF programs.

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