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ORIGINAL ARTICLE *Infertility*

Cumulative delivery rates in different age groups after artificial insemination with donor sperm

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BACKGROUND: Although the age-effect on *in vitro* fertilization outcomes has been well documented, data on donor insemination are scarce hampering accurate patient counseling. This cohort study therefore aims at analyzing cumulative delivery rates after donor insemination for various indications.

METHODS: A large retrospective analysis was performed on 6630 insemination cycles in 1654 women. Delivery rates were calculated by life-table analysis after a maximum of 12 cycles in five subgroups of age when starting inseminations. Multivariable modeling was used to explore the effects according to age, indication (male infertility, lesbian couple or single-parent request) and ovarian stimulation protocol (none, clomiphene citrate or gonadotrophins).

RESULTS: Overall, 928 deliveries were observed, i.e. a delivery rate of 14% per cycle and an expected cumulative delivery of 77% after 12 cycles. Subgroup analysis showed an expected cumulative delivery after 12 cycles of 87% for the group aged 20–29, 77% for ages 30–34, 76% for ages 35–37, 66% for ages 38–39 and 52% for ages 40–45. Drop-out analysis in the latter subgroup showed that only one patient discontinued treatment because of medical reasons. In contrast to age, neither indication nor ovarian stimulation protocol had any significant effect on the delivery rate.

CONCLUSIONS: Our study corroborates the impact of age on donor insemination outcome. Nevertheless, even in some older age subgroups, acceptable expected cumulative delivery rates were observed. Despite this, the main reason for discontinuing treatment, however, was the anticipated low success rate. Women, up until 42 years of age, could be encouraged to continue treatment.

Key words: age / donor insemination / cumulative delivery rates / AID / pregnancy

Introduction

Postponing childbearing is a social trend and has led to an increase in treatments for age-related female subfertility (Broekmans *et al.*, 2007). However, there is an age-related decrease in success rates of these treatments (van Noord-Zaadstra *et al.*, 1991; Hull *et al.*, 1996). Patients undergoing fertility treatments need to be clearly informed about their chances of having a baby. Therefore, it is important for both candidate couples and fertility specialists treating them to know the probability for delivery after a defined number of treatment cycles. The cumulative chances of achieving a live birth after a given number of cycles are obviously more meaningful than the live birth rate per cycle.

Although this information is currently available for assisted reproduction by *in vitro* fertilization and intra-cytoplasmic sperm injection (Osmanagaoglu *et al.*, 1999, 2002; Elizur *et al.*, 2006), only limited data are available for intrauterine insemination with donor insemination (CECOS, 1982; Barret and Cooke, 1993; Botchan *et al.*, 2001; Custers *et al.*, 2008; Dovey *et al.*, 2008).

There have been many reports about the success rates per cycle, but cumulative delivery rates in different age groups for artificial insemination with donor sperm (AID) have never been studied on large patient populations. Especially for older patients, these data are very important. Therefore, the aim of this study was to analyze the cumulative delivery rates on patients undergoing donor insemination according to their age and to analyze whether ovarian stimulation treatment and indication for AID had any effect on the success rates.

Materials and Methods

Insemination

In this retrospective study, we examined the outcome of insemination using cryopreserved donor semen in 1654 women who started their first treatment cycle between January 2000 and December 2005. They underwent a total of 6630 donor insemination cycles. None of these patients had had a previous delivery and <10% had been pregnant in the past. The indications for donor insemination were severe male infertility, requests from lesbian couples and single-parent requests. All women were assumed to be normally fertile, since they had a normal fertility work-up including either hysterosonography or hysterosalpingography or laparoscopy. Although patients had normal menstrual cycles, some patients did receive mild ovarian hyperstimulation (MOH) either with clomiphene citrate 50–100 mg from Day 3 till Day 7 of the menstrual cycle or human menopausal gonadotrophins 75–150 U from Day 3 of their cycle onwards. Although there is no evidence that adding MOH to otherwise normally cycling patients will increase the success rates in intrauterine insemination (IUI) using frozen-thawed donor sperm, patients receiving MOH did so because their referring physician opted to apply MOH. All patients received one single IUI performed 36–44 h after injecting 5000 U hCG (Pregnyl, Organon, Oss, The Netherlands) whenever ultrasound showed the presence of one to a maximum three follicles measuring at least 17 mm in diameter. IUI was performed using frozen-thawed donor sperm with a minimum of 1×10^6 progressively motile spermatozoa being inseminated using a Frydman catheter (Laboratoires CCD, Paris, France). Sperm for insemination was prepared by a two-layer density gradient (Pure sperm™, Nidacon, Mölndal, Sweden) after thawing. From the evening of the day of insemination, patients were advised to use intravaginal micronized progesterone 3 × 200 mg (Utrogestan, Besins, Paris France). Our patients received blocks of four cycles of donor insemination before returning to their doctor.

Pregnancies were diagnosed by a standard serum assays for hCG showing levels of >10 IU/l on at least two consecutive occasions. Clinical pregnancies were evidenced by the presence of an intrauterine gestational sac at ultrasound. Pregnancy follow-up was done by sending questionnaires to patients and their doctor or by telephone queries whenever questionnaires were incomplete. Live birth delivery after 25 weeks of gestation was the main outcome measure of our study.

Patients who did not return their questionnaire or who discontinued their treatment without further notice were contacted by phone in order to obtain the following information: their status with regard to treatment (no further treatment or still continuing treatment), occurrence with or without infertility treatment of a pregnancy outside our department and reasons for discontinuing treatment.

Data analysis

For each group of interest, categorical variables are presented as number of cases including nominator and denominator values and percentages. Comparisons of percentages among groups were performed by using the Fisher's exact probability for each comparison made.

The primary outcome of this retrospective cohort study was delivery resulting in at least one live birth. The delivery of more than one child was given the same weight as the delivery of a singleton. Patients were not re-enrolled after having a first delivery. Each miscarriage was included in the count of the cycles, until the patients reached the final outcome.

In line with previous reports from our institution, we provide two approaches frequently employed to estimate the effectiveness of assisted reproduction technology (ART) treatment according to the number of cycles. The first method calculates outcome by dividing the number of women achieving live birth delivery up to a predetermined number of cycles (numerator) by the total number of women who started treatment with AID (denominator). The outcome measure associated with this method is referred to as '*Crude* cumulative delivery rate'. The other method estimates the cumulative live birth delivery rate after a specified number of cycles using life-table analysis, by taking into account the effects of censoring (drop-out). The outcome measure associated with this method is referred to as '*Expected* cumulative delivery rate'. As these outcome measures cannot be transformed to a similar unit, the outcomes of both methods cannot be readily compared. Basically, the first method does not take into account drop-out (censoring) and provides a conservative estimate of outcome.

Expected cumulative delivery rates (curves) were compared by log-rank tests. Cox's proportional hazard model was used to perform a multivariate analysis. A *P*-value of 0.05 or less is considered as statistically significant. Apart from comparisons according to indication and controlled ovarian stimulation protocol, cumulative delivery rates were compared for five subgroups according to patient's age, i.e. 20–29, 30–34, 35–37, 37–39 and 40–45 years old, at the first insemination of the treatment course. Age at first insemination treatment determined the group to which our patients belonged, i.e. if a patient was 29 years old at her first insemination cycle, she was allocated to the 20–29 age group. The last age group was further subdivided for further analysis into four subgroups: 40, 41, 42 and 43 years or older. For the controlled ovarian stimulation protocol, only the last cycle of the woman was taken into account, i.e. time-dependent covariates in Cox regression or other methods to examine the effect of stimulation treatments which change from cycle to cycle were not used in the current analyses.

Computational procedures were performed using Statistics Package for Social Sciences for Windows version 16 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

Tables I and II provide information about the background of the 1654 patients treated, including the numbers with the different reasons for donor insemination, the different stimulation protocols and the different age groups. Overall, in our series, the most frequent indication for AID came from lesbian couples, clomiphene citrate was most frequently used for controlled ovarian stimulation, and most patients belonged to the 30–34 age group.

Several statistically significant and clinically relevant between-group differences were observed. With advancing age, there was a gradual increase in the proportion of single-parent requests and a decline in the proportion of lesbian women undergoing donor insemination (Table I). Clomiphene citrate was more frequently used in lesbian women (Table II).

Overall success rates

There were 1654 women who underwent a total of 6630 treatment cycles. The number of cycles ranged from 1 to 24. We were unable to collect information on outcome in only <3% of the women. Overall, 928 deliveries were recorded (14% per cycle). In the first cycle, the average delivery rate was 19% and thereafter rates varied between 9% and 14% per cycle. The *crude* and *expected* cumulative delivery rates for the whole group were 56% and 77%, respectively (Table III, upper panel). After the fifth cycle, the accrual in delivery rates became less pronounced and reached a plateau at the eighth cycle in all age groups below 40. There was no change in the pregnancy rate over the course of the study (data not shown).

Table I Detailed patient characteristics for indication for AID (left panel) and controlled ovarian stimulation protocol (right panel), for the total group and stratified according to pre-specified age groups*

Age group	Indication for artificial insemination with donor sperm**			Controlled ovarian stimulation protocol***		
	Lesbian couple	Single parent request	Male infertility	No medication	Clomiphene citrate	Gonadotrophins
Total group	913	378	363	295	1151	206
20–29 years	227 (24.9%)	11 (2.9%)	93 (25.6%)	94 (31.9%)	220 (19.1%)	16 (7.7%)
30–34 years	321 (35.2%)	87 (23.0%)	131 (36.1%)	107 (36.3%)	377 (32.8%)	55 (26.6%)
35–37 years	189 (20.7%)	97 (25.7%)	78 (21.5%)	46 (15.6%)	267 (23.2%)	51 (24.6%)
38–39 years	96 (10.5%)	74 (19.6%)	27 (7.4%)	28 (9.5%)	140 (12.2%)	29 (14.0%)
40–45 years	80 (8.8%)	109 (28.8%)	34 (9.4%)	20 (6.8%)	147 (12.8%)	56 (27.1%)

*Data represent number of cases (%).
**P-value for χ^2 test <0.001.
***P-value for χ^2 <0.001.

Table II Detailed patient characteristics for indication for AID stratified according to controlled ovarian stimulation protocol*

Age group	Indication for artificial insemination with donor sperm**		
	Lesbian couple	Single parent request	Male infertility
Total group	913	378	363
No medication	161 (17.7%)	70 (18.5%)	64 (17.6%)
Clomiphene citrate	672 (73.7%)	242 (64.0%)	237 (65.3%)
Gonadotrophins	79 (8.7%)	66 (17.5%)	62 (17.1%)

*Data represent number of cases (%).
**P-value for χ^2 test <0.001.

A total of 1020 babies were born, of which 89 were twins. Of the 89 twins, 75 patients took clomiphene citrate, 11 women used gonadotrophins and only 3 used no medication. In the oldest group, none of the women had twins. Intrauterine death occurred in two pregnancies. Three women delivered triplets.

Among 912 pregnancies during the first six cycles, there were 103 miscarriages (11.9%). Miscarriage rates after six cycles were 6.4% for the 20–29 years age group, 8.0% for the 30–34 years age group, 10.4% for the 35–37 years age group, 20.8% for the 38–39 years age group and 31.9% for the 40–45 years age group. In the oldest group, there were 23 miscarriages in 72 pregnancies. There were 11 ectopic pregnancies (1.3%) in the 912 pregnancies after six cycles.

We noted no complications related to treatment or artificial insemination. The prematurity rate (<37 weeks) was 5.1%. The mean infant weight at birth for single pregnancies was 3310 g (standard deviation 478 g) and the incidence of children born weighing <2500 g was 4.8%.

Age and success rates

Figure 1 shows the *expected* cumulative delivery rates for the total patient group stratified according to age, whereas Table III provides more detailed data (including 95% confidence intervals). The lower panels of Table III show the *crude* and *expected* cumulative delivery rates stratified according to age together with the drop-out rates and delivery rates per cycle up to 12 cycles after starting treatment. As expected, delivery rates decreased significantly with increasing female age (log-rank test $P < 0.001$).

Subgroup analysis in the oldest group (40–45 years; $n = 223$ patients) revealed a *crude* and *expected* cumulative delivery rates of 26% and 52% after 12 cycles, respectively, despite the drop-outs occurring mainly as a result of discouraging patients to continue their treatment for the reason of their advanced age (Table IV). Only one patient discontinued treatment because of medical reasons.

In the group starting treatment at age 40, the *crude* and *expected* cumulative delivery rates were 35% and 55%, respectively, after nine cycles, after which a plateau was reached. In the group starting treatment at age 41, the cumulative delivery rates reached a plateau after six cycles.

In the group starting treatment at age 42, both the *crude* and the *expected* cumulative delivery rates reached a plateau at 9% from cycle 2 till cycle 11. One additional delivery in one patient occurred after cycle 12, increasing the *expected* cumulative delivery rate from 9% to 32%.

In the group starting treatment at age 43 or later, a plateau was reached after three cycles, but one delivery occurred after the sixth cycle. As indicated in Table IV, only a small number of women aged 43 years or over were available.

Figure 2 shows the *expected* cumulative delivery rates among patients aged 40 years or older when starting treatment.

Effects of age, indication and stimulation protocol on success rate

Overall, our Cox regression analysis on the total group, with live birth delivery as the outcome (dependent) variable and age group indication, and controlled ovarian stimulation protocol as explanatory (independent) variables, indicated that age was the only factor that had a significant and independent effect on success (Tables V and VI). Overall, older women are less likely to achieve a successful delivery. Adjustment for the indication for donor insemination had no effect on the cumulative delivery rates. Likewise, there was no effect

Table III Cumulative delivery rates for the total group (upper panel) and stratified according to pre-specified age group (next panels)*

	Treatment cycle number											
	1	2	3	4	5	6	7	8	9	10	11	12
All ages												
Number of patients	1654	1275	1019	726	571	435	282	207	161	89	69	51
No. of non-pregnant and discontinued	60	79	149	53	70	115	44	26	60	12	10	24
No. of deliveries	319	177	144	102	66	38	31	20	12	8	8	5
No. of non-pregnant	1335	1098	875	624	505	397	251	187	149	81	61	46
Drop-out rate	4%	7%	17%	8%	14%	29%	18%	14%	40%	15%	16%	52%
Crude cumulative delivery rate**	19%	30%	39%	45%	49%	51%	53%	54%	55%	55%	56%	56%
Lo 95% CI	17%	28%	36%	42%	46%	49%	51%	52%	53%	53%	54%	54%
Hi 95% CI	21%	32%	41%	47%	51%	54%	55%	57%	57%	58%	58%	59%
Expected cumulative delivery rate***	19%	31%	40%	49%	55%	59%	63%	67%	69%	72%	75%	77%
Lo 95% CI	18%	29%	38%	46%	52%	56%	60%	64%	66%	69%	72%	74%
Hi 95% CI	21%	32%	42%	51%	57%	61%	66%	69%	72%	75%	79%	81%
Delivery rates per cycle	19%	14%	14%	14%	12%	9%	11%	10%	7%	9%	12%	10%
Age 20–29 years												
Number of patients	331	237	174	121	93	64	41	24	14	7	4	1
No. of non-pregnant and discontinued	12	15	15	6	10	14	11	3	6	2	3	0
No. of deliveries	82	48	38	22	19	9	6	7	1	1	0	1
No. of non-pregnant	249	189	136	99	74	55	35	17	13	6	4	0
Drop-out rate	5%	8%	11%	6%	14%	25%	31%	18%	46%	33%	75%	-
Crude cumulative delivery rate**	25%	39%	51%	57%	63%	66%	68%	70%	70%	70%	70%	71%
Lo 95% CI	20%	34%	45%	52%	58%	61%	63%	65%	65%	65%	65%	66%
Hi 95% CI	29%	45%	56%	63%	68%	71%	73%	75%	75%	75%	75%	76%
Expected cumulative delivery rate***	25%	40%	53%	62%	70%	74%	78%	84%	85%	87%	87%	87%
Lo 95% CI	21%	35%	48%	57%	65%	69%	73%	79%	80%	82%	82%	82%
Hi 95% CI	29%	45%	58%	67%	74%	79%	83%	89%	90%	93%	93%	93%
Delivery rates per cycle	25%	20%	22%	18%	20%	14%	15%	29%	7%	14%	0%	100%
Age 30–34 years												
Number of patients	539	402	320	223	171	133	93	67	53	28	20	13
No. of non-pregnant and discontinued	12	23	44	10	20	25	12	7	20	7	3	5
No. of deliveries	125	59	53	42	18	15	14	7	5	1	4	3
No. of non-pregnant	414	343	267	181	153	118	79	60	48	27	16	10
Drop-out rate	3%	7%	16%	6%	13%	21%	15%	12%	42%	26%	19%	50%
Crude cumulative delivery rate**	23%	34%	44%	52%	55%	58%	60%	62%	63%	63%	64%	64%
Lo 95% CI	20%	30%	40%	48%	51%	54%	56%	58%	59%	59%	60%	60%
Hi 95% CI	27%	38%	48%	56%	59%	62%	65%	66%	67%	67%	68%	68%
Expected cumulative delivery rate***	20%	31%	42%	50%	55%	59%	64%	65%	67%	71%	75%	77%
Lo 95% CI	16%	27%	37%	44%	50%	54%	59%	59%	61%	64%	68%	70%
Hi 95% CI	24%	35%	46%	55%	60%	64%	70%	71%	73%	77%	82%	85%
Delivery rates per cycle	23%	15%	17%	19%	11%	11%	15%	10%	9%	4%	20%	23%
Age 35–37 years												
Number of patients	364	279	228	162	129	100	62	48	39	25	22	17
No. of non-pregnant and discontinued	13	12	31	11	14	30	6	8	12	0	2	7
No. of deliveries	72	39	35	22	15	8	8	1	2	3	3	0
No. of non-pregnant	292	240	193	140	114	92	54	47	37	22	19	17
Drop-out rate	4%	5%	16%	8%	12%	33%	11%	17%	32%	0%	11%	41%

Continued

Table III *Continued*

	Treatment cycle number											
	1	2	3	4	5	6	7	8	9	10	11	12
Crude cumulative delivery rate**	20%	30%	40%	46%	50%	52%	55%	55%	55%	56%	57%	57%
Lo 95% CI	16%	26%	35%	41%	45%	47%	50%	50%	50%	51%	52%	52%
Hi 95% CI	24%	35%	45%	51%	55%	58%	60%	60%	61%	61%	62%	62%
Expected cumulative delivery rate***	20%	31%	42%	50%	55%	59%	64%	65%	67%	71%	75%	76%
Lo 95% CI	16%	27%	37%	44%	50%	54%	59%	59%	61%	64%	68%	70%
Hi 95% CI	24%	35%	46%	55%	60%	64%	70%	71%	73%	77%	82%	85%
Delivery rates per cycle	20%	14%	15%	14%	12%	8%	13%	2%	5%	12%	14%	0%
Age 38–39 years												
Number of patients	197	163	133	100	75	58	41	31	25	13	8	6
No. of non-pregnant and discontinued	9	13	20	15	9	14	8	2	12	2	2	5
No. of deliveries	25	17	13	10	8	3	2	4	0	3	0	0
No. of non-pregnant	172	146	120	90	67	55	39	27	25	10	8	6
Drop-out rate	5%	9%	17%	17%	13%	25%	21%	7%	48%	20%	25%	83%
Crude cumulative delivery rate**	13%	21%	28%	33%	37%	39%	40%	42%	42%	43%	43%	43%
Lo 95% CI	8%	16%	22%	26%	30%	32%	33%	35%	35%	36%	36%	36%
Hi 95% CI	17%	27%	34%	40%	44%	45%	46%	49%	49%	50%	50%	50%
Expected cumulative delivery rate***	13%	22%	29%	37%	43%	46%	49%	55%	55%	66%	66%	66%
Lo 95% CI	8%	16%	23%	30%	36%	39%	41%	46%	46%	54%	54%	54%
Hi 95% CI	17%	27%	36%	43%	51%	54%	57%	64%	64%	77%	77%	77%
Delivery rates per cycle	13%	10%	10%	10%	11%	5%	5%	13%	0%	23%	0%	0%

*Data represent number of cases (%).
**Calculated by dividing the number of women achieving live birth delivery up to a pre-determined number of cycles (numerator) by the total number of women who started treatment with AID (denominator).
***Estimated according to the life table methodology.

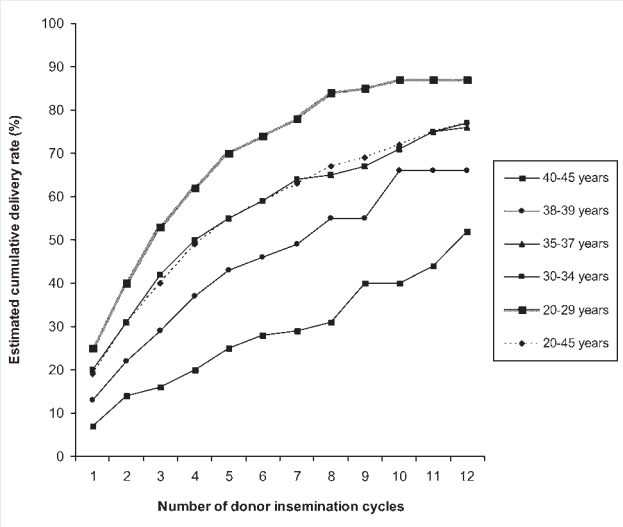

Figure 1 Cumulative live birth delivery rates after donor insemination in five pre-specified age groups, i.e. 20–29, 30–34, 35–37, 38–39, 40–45 years and in all age groups (20–45 years).Note: except for cycle 12, the data points for ages 30–34 and 35–37 are the same.

of adjustment for controlled ovarian stimulation on the cumulative delivery rates.

For the subgroup of patients aged 43 or over, our Cox regression analysis should be interpreted with some caution given the small number of women starting treatment and the small number of deliveries, especially among women over the age of 43 (Table VI).

Discussion

Although our study confirms the impact of age on donor insemination outcome in terms of live birth delivery, we observed acceptable cumulative delivery rates after donor insemination, even in older age subgroups.

Many women in industrialized societies want to delay reproduction because they give priority to their careers or simply did not meet the right partner. This trend is also present in women seeking treatment with donor insemination. Knowing the probability of delivering a baby after fertility treatment is important for both the candidate mother and her fertility specialist.

The effect of age on the success rate of infertility treatments has been well documented. Increasing age is associated with a decrease in pregnancy rate and the eventual delivery rate. This applies to either natural conception (Dunson *et al.*, 2004) or ART (Federation CECOS, 1982; Van Noord-Zaadstra *et al.*, 1991; Scott *et al.*, 1995). Ovarian reserve decreases with advancing age, leading to a decrease

Table IV Cumulative delivery rates for the oldest groups stratified according to four pre-specified age group*

	Treatment cycle number											
	1	2	3	4	5	6	7	8	9	10	11	12
Age 40–45 years												
Number of patients	223	194	164	120	103	80	45	37	30	16	15	14
No. of non-pregnant and discontinued	14	16	39	11	17	32	7	6	10	1	0	7
No. of deliveries	15	14	5	6	6	3	1	1	4	0	1	2
No. of non-pregnant	208	180	159	114	97	77	44	36	26	16	14	12
Drop-out rate	7%	9%	25%	10%	18%	42%	16%	17%	38%	6%	0%	58%
Crude cumulative delivery rate**	7%	13%	15%	18%	21%	22%	22%	23%	25%	25%	25%	26%
Lo 95% CI	3%	9%	11%	13%	15%	17%	17%	17%	19%	19%	19%	20%
Hi 95% CI	10%	17%	20%	23%	26%	27%	28%	28%	30%	30%	31%	32%
Expected cumulative delivery rate***	7%	14%	16%	20%	25%	28%	29%	31%	40%	40%	44%	52%
Lo 95% CI	4%	9%	11%	15%	19%	21%	22%	23%	30%	30%	32%	38%
Hi 95% CI	10%	18%	21%	26%	31%	35%	37%	39%	51%	51%	57%	66%
Delivery rates per cycle	7%	7%	3%	5%	6%	4%	2%	3%	13%	0%	7%	14%
Age 40 years												
Number of patients	82	69	58	50	40	29	20	15	14	7	7	6
No. of non-pregnant and discontinued	5	5	7	5	8	8	4	0	4	0	0	5
No. of deliveries	8	6	1	5	3	1	1	1	3	0	1	0
No. of non-pregnant	74	63	57	45	37	28	19	14	11	7	6	6
Drop-out rate	7%	8%	12%	11%	22%	29%	21%	0%	36%	0%	0%	83%
Crude cumulative delivery rate**	10%	17%	18%	24%	28%	29%	30%	32%	35%	35%	37%	37%
Lo 95% CI	3%	9%	10%	15%	18%	19%	21%	22%	25%	25%	26%	26%
Hi 95% CI	16%	25%	27%	34%	38%	39%	40%	42%	46%	46%	47%	47%
Expected cumulative delivery rate***	10%	18%	19%	27%	33%	35%	38%	42%	55%	55%	61%	61%
Lo 95% CI	4%	10%	11%	17%	22%	24%	26%	29%	39%	39%	44%	44%
Hi 95% CI	16%	26%	27%	37%	43%	46%	51%	56%	70%	70%	78%	78%
Delivery rates per cycle	10%	9%	2%	10%	8%	3%	5%	7%	21%	0%	14%	0%
Age 41 years												
Number of patients	71	63	56	39	34	26	14	13	10	4	3	3
No. of non-pregnant and discontinued	4	2	14	4	5	11	1	3	5	1	0	1
No. of deliveries	4	5	3	1	3	1	0	0	1	0	0	1
No. of non-pregnant	67	58	53	38	31	25	14	13	9	4	3	2
Drop-out rate	6%	3%	26%	11%	16%	44%	7%	23%	56%	25%	0%	50%
Crude cumulative delivery rate**	6%	13%	17%	18%	23%	24%	24%	24%	25%	25%	25%	27%
Lo 95% CI	0%	5%	8%	9%	13%	14%	14%	14%	15%	15%	15%	16%
Hi 95% CI	11%	20%	26%	27%	32%	34%	34%	34%	35%	35%	35%	37%
Expected cumulative delivery rate***	6%	13%	18%	20%	27%	30%	30%	30%	40%	40%	40%	58%
Lo 95% CI	0%	5%	9%	10%	16%	18%	18%	18%	30%	30%	30%	28%
Hi 95% CI	11%	21%	27%	30%	38%	42%	42%	42%	51%	51%	51%	87%
Delivery rates per cycle	6%	8%	5%	3%	9%	4%	0%	0%	10%	0%	0%	33%
Age 42 years												
Number of patients	34	30	24	17	16	14	9	8	5	4	4	4
No. of non-pregnant and discontinued	3	4	7	1	2	5	1	3	1	0	0	1
No. of deliveries	1	2	0	0	0	0	0	0	0	0	0	1
No. of non-pregnant	33	28	24	17	16	14	9	8	5	4	4	3
Drop-out rate	9%	14%	29%	6%	13%	36%	11%	38%	20%	0%	0%	33%
Crude cumulative delivery rate**	3%	9%	9%	9%	9%	9%	9%	9%	9%	9%	9%	12%

Continued

Table IV *Continued*

	Treatment cycle number											
	1	2	3	4	5	6	7	8	9	10	11	12
Lo 95% CI	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1%
Hi 95% CI	9%	18%	18%	18%	18%	18%	18%	18%	18%	18%	18%	23%
Expected cumulative delivery rate***	3%	9%	9%	9%	9%	9%	9%	9%	9%	9%	9%	32%
Lo 95% CI	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Hi 95% CI	9%	19%	19%	19%	19%	19%	19%	19%	19%	19%	19%	66%
Delivery rates per cycle	3%	7%	0%	0%	0%	0%	0%	0%	0%	0%	0%	25%
Age 43–45 years												
Number of patients	36	32	26	14	13	11	2	1	1	1	1	1
No. of non-pregnant and discontinued	2	5	11	1	2	8	1	0	0	0	0	1
No. of deliveries	2	1	1	0	0	1	0	0	0	0	0	0
No. of non-pregnant	34	31	25	14	13	10	2	1	1	1	1	1
Drop-out rate	6%	16%	44%	7%	15%	80%	50%	0%	0%	0%	0%	100%
Crude cumulative delivery rate**	6%	8%	11%	11%	11%	14%	14%	14%	14%	14%	14%	14%
Lo 95% CI	0%	0%	1%	1%	1%	3%	3%	3%	3%	3%	3%	3%
Hi 95% CI	13%	17%	21%	21%	21%	25%	25%	25%	25%	25%	25%	25%
Expected cumulative delivery rate***	6%	9%	12%	12%	12%	20%	20%	20%	20%	20%	20%	20%
Lo 95% CI	0%	0%	1%	1%	1%	3%	3%	3%	3%	3%	3%	3%
Hi 95% CI	13%	18%	23%	23%	23%	37%	37%	37%	37%	37%	37%	37%
Delivery rates per cycle	6%	3%	4%	0%	0%	9%	0%	0%	0%	0%	0%	0%

*Data represent number of cases (%).
**Calculated by dividing the number of women achieving live birth delivery up to a pre-determined number of cycles (numerator) by the total number of women who started treatment with AID (denominator).
***Estimated according to the life table methodology.

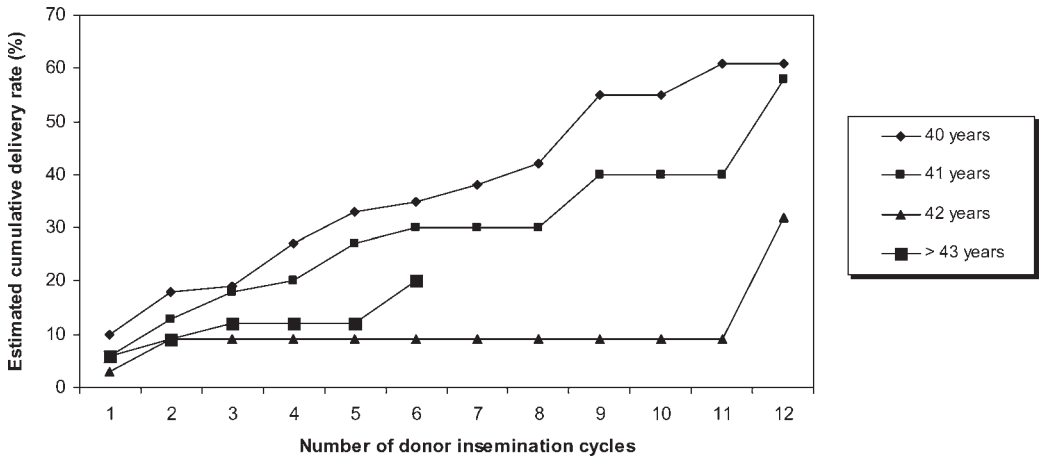

Figure 2 Cumulative live birth delivery rates after donor insemination in four pre-specified age subgroups of the oldest patients, i.e. 40, 41, 42 and the >43 years age groups.

in the numbers of oocytes obtained (Faddy and Gosden, 1996), to an increase in the incidence of aneuploidy in oocytes (Munné *et al.*, 1995) and to poor oocyte quality (Navot *et al.*, 1991). Age is therefore the most important limiting factor for the success of reproductive treatments.

Unfortunately, in the literature, few reports deal with the effect of age on the outcome of donor insemination. Botchan *et al.* (2001) described the results of 6139 artificial insemination cycles with donor spermatozoa. The author investigated only the cumulative pregnancy rates but not the cumulative delivery rates. They described

Table V Hazard ratio (HR) for live birth delivery for the total group, stratified according to pre-specified age groups*

Age group	Unadjusted (crude) hazard ratio (95% CI)	*P*-value	Adjusted hazard ratio (95% CI)**	*P*-value
20–28 years (referent category)	—	—	—	
30–34 years	0.818 (0.693 to 0.966)	0.018	0.816 (0.689 to 0.966)	0.018
35–37 years	0.698 (0.579 to 0.842)	<0.001	0.695 (0.572 to 0.845)	<0.001
38–39 years	0.497 (0.387 to 0.637)	<0.001	0.495 (0.383 to 0.641)	<0.001
40–45 years	0.279 (0.209 to 0.372)	<0.001	0.278 (0.206 to 0.376)	<0.001

*Cox regression analysis with live birth delivery as the outcome (dependent) variable and age group as explanatory (independent) variables.
**HR simultaneously adjusted for indication for AID (three categories: male infertility, lesbian couple or single-parent request) and controlled ovarian stimulation protocol (three categories: no medication, clomiphene citrate or human menopausal gonadotrophins).

Table VI Hazard ratio (HR) for live birth delivery in the oldest age group (40–45 years), stratified according to pre-specified age groups*

Age at first insemination cycle	Unadjusted (crude) hazard ratio (95% CI)	*P*-value	Adjusted hazard ratio (95% CI)**	*P*-value
40 years (referent category)	—	—	—	
41 years	0.758 (0.426–1.347)	0.345	0.718 (0.401–1.284)	0.264
42 years	0.314 (0.111–0.892)	0.030	0.316 (0.110–0.906)	0.032
43–45 years	0.471 (0.182–1.221)	0.121	0.429 (0.163–1.133)	0.088

*Cox regression analysis with live birth delivery as the outcome (dependent) variable and age group as explanatory (independent) variables.
**HR simultaneously adjusted for indication for AID (three categories: male infertility, lesbian couple or single-parent request) and controlled ovarian stimulation protocol (three categories: no medication, clomiphene citrate or human menopausal gonadotrophins).

cumulative pregnancy rates after 3, 6 and 12 months but not after each cycle as in this study.

The CECOS 1982 study reported on 2193 women who were receiving AID and whose husbands were totally sterile. Outcome in four age groups was reported as pregnancy and not as delivery after 25 weeks, as in our study. The CECOS 1982 study included only 144 patients in the oldest group and only 14 patients older than 40 years. They reported a cumulative success rate of 53.6% after 12 cycles in the group of patients aged 35 years and more. We included 784 patients aged 35 years or more, reaching an expected cumulative delivery rate of up to 76%. As a general rule, providing an accurate answer about the success rates for elderly women remains hampered by a lack of power related to the small number of women included and the low number of delivery events observed. Barrett and Cook reported a cumulative pregnancy rate of 54% after 12 cycles of AID treatment above the age of 36. Unfortunately, their report provides no details about the number of patients treated in specific age groups.

In line with a report published by Lansac and Royère (2001), we observed a prematurity rate (<37 weeks) of 5.1%. Our data on mean infant weight also confirm the results published by Schoysman *et al.* (1981) and Hoy *et al.* (1999) showing that, compared with the general population, AID is not associated with a significant difference in the prevalence of preterm birth, low birthweight or perinatal mortality.

In the current study, we aimed at analyzing delivery rates after donor insemination according to different age groups using life-table analyses. Methodological strengths of our study include the large sample size, the consecutive recruitment of unselected patients, a virtually complete patient follow-up, the choice of live birth delivery as the outcome event of primary interest and the use of well-validated methods to present both *crude* and *expected* cumulative delivery rates and to model cumulative delivery using a standard (Cox regression) technique.

This cohort study, being retrospective in nature, has some weaknesses as well. In order to minimize age-bias, we analyzed a large consecutive series which was divided into six age groups. The drop-out rate in the older groups was much higher than in the younger groups, however, not because of medical reasons or absence of follicular development. The most important reason was the advice of the treating doctor to refrain from any further treatment because of his anticipation of low success rates associated with advancing age. Only in the 42-year-old age group was there one patient who did not have adequate follicular development.

Life-table analysis has been used to estimate the success rates of various techniques of reproductive surgery and assisted reproduction (Hull *et al.*, 1992). Life-table analysis assumes that those patients who continue their treatment and those who quit their treatment for non-medical reasons have the same probability of achieving the defined event (e.g. delivery) (Stolwijk *et al.*, 1996). Some authors argue that patients who discontinue the treatment may have done so because of poor treatment prognosis (Doody, 1993; Walters, 1994). However, another study (Haan *et al.*, 1991) found no over-representation of patients with a poor prognosis in the group of drop-outs. It has been suggested (Engmann *et al.*, 1999) that when calculating cumulative delivery rates by life-table analysis, the age of each woman should be recorded at the start of her first treatment cycle, even though this can cause an underestimation of age-related cumulative delivery rates. For example, when a woman starts her first cycle at 32 years, her second at 39 years and her third at 42 years, calculation

of the cumulative delivery rate will consider her to be 32 years. This calculation method thus introduces a biased decline due to advancing female age (Engmann *et al*., 1999). Life-table analysis also tends to overestimate the estimated cumulative delivery rates when the group is too small. Although we included a large total number of patients, fewer patients of advanced age asked for AID, and hence the older age groups included limited numbers of patients. This is quite well illustrated by our data: after the ninth cycle in the 40–45 years group, for example, the *expected* cumulative delivery rate of 40% increases up to 52% due to three additional deliveries in a subgroup of 16 women. In the current series, all cumulative delivery rates are presented with corresponding 95% confidence intervals. In doing so, we provide information to the reader on magnitude and precision of cumulative delivery rates at each cycle, as well as the role that chance may play in the observed study results.

Finally, we can conclude that age was the only factor that had a significant and independent effect on success of the donor insemination. Neither indication nor ovarian stimulation had any effect on the delivery rates. However, since we did not use time-dependent covariates in Cox regression or other methods to examine the effect of stimulation treatments which change from cycle to cycle, the last stimulation in a patient being used to represent the overall effect of stimulation may not be sensitive to detect the effects of stimulation on pregnancy rates.

Overall, and despite some methodological limitations, the data of this cohort study show that up to 42 years, the cumulative delivery rates after donor insemination are acceptable. Patients can be counseled according to these data regarding their chances of obtaining a delivery. Although based on retrospective data, we could not establish a role for controlled ovarian stimulation in order to improve the success rate in these otherwise normally cycling women, not even in the advanced age groups.

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