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ARTICLE

Assisted reproduction using donor spermatozoa in women aged 40 and above: the high road or the low road?

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Abstract The effect of age on outcome is one of the most intriguing areas in the assisted reproduction field. In older patients using donor spermatozoa to reproduce, it remains undefined as to which is the treatment of choice: intrauterine insemination (IUI) or IVF/intracytoplasmic sperm injection (ICSI). Since life-table analysis provides data that are easy to use for patient counselling, this study analysed cumulative delivery rates (CDR) in patients using donor spermatozoa undergoing either primarily IUI or IVF/ICSI and patients who eventually switched from IUI to IVF/ICSI. Crude and expected CDR after six IUI cycles and three primary ICSI cycles (no previous IUI) were similar in both groups (24% versus 26% and 29% versus 35%, respectively). Since time-to pregnancy is an important factor in these older patients, ICSI treatment is advised to be started immediately, since a single cycle of ICSI will achieve the same success rate as a much longer period with at least six IUI cycles. If patients switch to ICSI after failed IUI, this only adds marginal benefit in CDR. Nearly all deliveries in the primary ICSI group were achieved in the first cycle.

KEYWORDS: age, cumulative delivery rate, delivery, ICSI, IUI, life-table analysis

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Introduction

Female fertility starts to decline at least 10 years prior to the onset of menopause (Broekmans et al., 2007). Although there is no strict definition of advanced reproductive age in women, subfertility becomes more pronounced after the age of 35 years. The effect of female age on fertility was reported more than 20 years ago (Menken et al., 1986). Over the past few decades, postponing childbirth has become a social trend as more women have pursued higher education and careers. This has led to an increase in treatments for age-related female subfertility (Broekmans et al., 2007). However, an age-related decrease in success rates of these treatments has been well documented (Hull et al., 1996; van Noord-Zaadstra et al., 1991). Therefore, it is important for both candidate couples and fertility specialists to describe the probability of delivery after a defined number of treatment cycles. In this perspective, providing the cumulative chances of achieving a live birth after a given number of cycles is more meaningful than live birth rates per cycle. As important as success rate is the choice of treatment to achieve success. Should clinicians opt for intrauterine insemination (IUI) or for IVF/intracytoplasmic sperm injection (ICSI) as primary treatment in women with advanced age requiring donor spermatozoa to reproduce?

Only limited data are available for IUI (CECOS, 1982; Barratt and Cooke, 1993; Botchan et al., 2001; Custers et al., 2008; Dovey et al., 2008). Previously, the present study group reported on a large study describing the cumulative delivery rate (CDR) in different age groups after artificial insemination with donor spermatozoa and this study revealed crude and expected CDR of 26% and 52% after 12 cycles in older age subgroups (40–45 years; De Brucker et al., 2009).

The most common indications for using donor spermatozoa are severe male infertility including azoospermia, lesbian couples and single-parent requests. While for husband spermatozoa, life-table data are available in literature for IVF and ICSI (Elizur et al., 2006; Malizia et al., 2009; Osmanagaoglu et al., 1999, 2002), no study in the literature reports cumulative data for IVF/ICSI with donor spermatozoa. While most women undergoing assisted reproduction treatment with donor spermatozoa have patent tubes, aged women may opt for IVF/ICSI because of an anticipated decline in ovarian reserve after age 40. Indeed, ovarian reserve determines the number of oocytes that can be obtained after hormonal stimulation, and this is more important for IVF than IUI outcome. Hence, in a setting where both IUI and IVF are reimbursed, women may prefer IVF/ICSI over IUI, hoping to 'buy time'.

Thus, an important factor for these older patients not covered in the current literature, apart from the question whether IVF/ICSI has a role, is the question of when to refrain from IUI and switch to IVF/ICSI. Various recommendations for all ages have been made about the maximum number of IUI cycles that should be performed, but good data is lacking (Custers et al., 2008). Therefore, this study analysed CDR in patients using donor spermatozoa undergoing IUI or IVF/ICSI. Moreover, IVF/ICSI CDR after failed IUI was analysed.

Materials and methods

Patients

A retrospective study was performed on patients enrolled in our programme between January 2003 and December 2007. All patients were treated with frozen–thawed donor spermatozoa. In total, 173 patients aged ≥40 years at the time of their first assisted reproduction cycle were included; the oldest patient was 45 years old. This study analysed 764 IUI cycles in 150 patients and 46 primary ICSI cycles in 23 patients. Since 63 patients opted for ICSI after failed IUI treatment, this group will be referred to as 'switchers'. Switchers underwent 129 ICSI cycles. Switchers were further divided into three subgroups: 1–3 IUI cycles; 4–6 IUI cycles; and 7–12 IUI cycles prior to their switch (**Figure 1**).

Ovarian reserve was assessed by measurement of FSH concentration on day 3 of the menstrual cycle and by antral follicle count. Tubal patency was examined by hysterosalpingography.

Live birth after 25 weeks of gestation was taken as the primary endpoint. All patients without a delivery after 25 weeks in an IUI or ICSI cycle were eligible for a subsequent cycle, including patients with cancelled cycles and those with a pregnancy that did not result in a live birth.

Follow up was ensured by sending questionnaires to patients and their doctor or by telephone queries whenever questionnaires were incomplete or in case of missing data. The following information was obtained from patients that stopped their treatment: status with regards to treatment (no further treatment or still continuing treatment); occurrence of a pregnancy with or without infertility treatment outside of the study clinic; and reasons for discontinuing treatment.

Clinical and laboratory procedures

Intrauterine insemination

Although patients had normal menstrual cycles, some patients received mild ovarian stimulation either using clomiphene citrate 50–100 mg from day 3 until day 7 of their menstrual cycle or human menopausal gonadotrophin 75–150 U from day 3 of their cycle onwards. Although there is no evidence that adding mild ovarian stimulation to

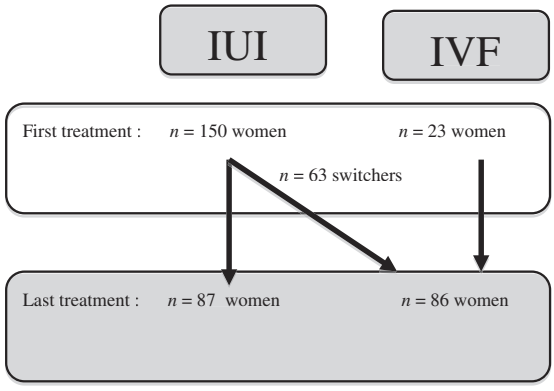

Figure 1 Treatment groups.

otherwise normally cycling patients will increase the success rates in IUI, these patients were receiving mild ovarian stimulation on the decision of their referring physician. All patients received single IUI 36–44 h after injecting 5000 U human chorionic gonadotrophin (Pregnyl; MSD) whenever ultrasound showed the presence of one follicle measuring at least 17 mm in diameter. Treatment was cancelled if more than three follicles measuring 14–17 mm were observed.

IUI was performed using frozen–thawed donor spermatozoa, with a minimum of 1×10^6 progressively motile spermatozoa being inseminated using a Frydman catheter (Laboratoires CCD, Paris, France). After thawing, spermatozoa used for insemination was prepared by a two-layer density gradient (PureSperm; Nidacon, Mölndal, Sweden). From the evening of the day of insemination, patients were advised to use intravaginal micronized progesterone 3×200 mg (Utrogestan; Besins, Paris France). Patients received blocks of three cycles of donor insemination before returning to their doctor.

IVF/ICSI

A combination of long-term desensitizing gonadotrophin-releasing hormone agonist in association with human menopausal gonadotrophin was used in most cases. In order to avoid fertilization failure due to cryodamage to the spermatozoa to be used, ICSI was used in all cycles. The details of spermatozoa and oocyte assessment and handling have been extensively described elsewhere (Van Steirteghem et al., 1996). Forty-eight hours after sperm injection, up to three embryos, or in exceptional cases four, were transferred into the uterine cavity. Frozen–thawed embryo transfers were included. Embryos were cryopreserved by slow freezing. Micronized progesterone (600 mg/day) was administered intravaginally in three separate doses for luteal-phase supplementation with or without human chorionic gonadotrophin (Smitz et al., 1988).

Statistical analysis

The primary outcome of this retrospective cohort study was delivery. 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. A miscarriage was included in the count of the cycles until the patients reached the final outcome. Miscarriage was defined as the spontaneous loss of a clinical pregnancy before 12 weeks of gestation.

In line with previous reports from this institution, this article presents two approaches frequently employed to estimate the effectiveness of assisted reproduction technology treatment according to the number of cycles. The first method calculates outcome by dividing the number of women achieving live birth up to a predetermined number of cycles (numerator) by the total number of women who started treatment with IUI or ICSI with donor spermatozoa (denominator). The outcome measure associated with this method is referred to as the crude or real CDR. The second 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 the expected CDR. As these outcome measures cannot be transformed to a similar unit, the outcomes of both methods cannot be readily compared. However, since the first method does not take drop out into account, it provides a conservative estimate of outcome. For each CDR the corresponding 95% confidence intervals (CI) were calculated. Crude and expected CDR are presented for the primary IUI group and the total ICSI group.

Data for the ICSI patients were stratified according to primary ICSI or ICSI after IUI (switchers). In addition, crude and expected CDR after ICSI were analysed for three subgroups of the switchers group: 1–3, 4–6 and 7–12 previous IUI cycles. CDR curves among groups of interest were compared by log-rank tests. *P*-values ≤ 0.05 were considered statistically significant.

Finally, this study also calculated crude CDR in the switchers group. This was done by dividing the number of women achieving live birth delivery up to the number of IUI and ICSI cycles (numerator) by the total number of women who started treatment with IUI (denominator).

Computational procedures were performed using Excel 2003 (Microsoft) and IBM SPSS Statistics version 20 (IBM Corporation).

Retrospective studies performed on anonymous patient's data are not required to be reviewed by the local ethical committee according to Belgian legislation and the guidelines of this institution.

Results

Baseline characteristics

Age between the 150 IUI starters (41.9 years, 95% CI 41.6–42.2) and the 23 primary ICSI starters (41.4 years, 95% CI 40.7–41.9) was similar. In the primary ICSI group, 16 patients out of 23 (69.6%) had tubal factor. The other seven patients (30.4%) preferred to opt for IVF/ICSI immediately.

IUI delivery rates

In total, 150 women aged $\geq$40 years underwent a total of 764 treatment cycles. Overall, 45 deliveries were recorded after 12 cycles. None of them were twins. The prematurity rate (<37 weeks) was 6.6%. A few patients ($n = 2$) underwent more than 12 IUI cycles, but without success. The crude and expected CDR for the whole group were 30% (95% CI 23–37%) and 56% (95% CI 41–71%), respectively, with a plateau being reached after nine cycles. The CDR, including drop-out rate, until 12 IUI cycles are shown in **Table 1**. The miscarriage rate after six cycles was 31.6% (18 miscarriages in 57 pregnancies).

IVF/ICSI delivery rates

Overall, 175 ICSI cycles were recorded among 86 patients. The average number of cycles per patient was 2.03. Overall, there were 25 deliveries including three deliveries of <37 weeks of gestation (12%). There were no twin pregnancies. The crude and expected CDR for the overall ICSI group were 29% (95% CI 19–39%) and 47% (95% CI 30–65%) after six

Table 1 Cumulative delivery rates after IUI with donor spermatozoa in 150 women aged ≥40 years.

Outcome	*Treatment cycle number (n = patients)*											
	1 (n = 150)	*2* (n = 130)	*3* (n = 112)	*4* (n = 87)	*5* (n = 77)	*6* (n = 64)	*7* (n = 38)	*8* (n = 31)	*9* (n = 26)	*10* (n = 14)	*11* (n = 13)	*12* (n = 12)
Non-pregnant	140	119	107	83	74	61	37	30	22	14	12	10
Deliveries	10	11	5	4	3	3	1	1	4	0	1	2
Non-pregnant and discontinued	10	7	20	6	10	23	6	4	8	1	0	6
Drop-out rate	7	6	19	7	14	38	16	13	36	7	0	60
Crude CDR	7	14	17	20	22	24	25	25	28	28	29	30
95% CI	3–11	8–20	11–23	14–26	15–29	17–31	18–32	18–32	21–35	21–35	21–36	30
Expected CDR	7	15	18	22	25	29	31	33	43	43	48	56
95% CI	3–11	9–20	12–25	15–29	18–33	21–37	22–39	23–42	31–55	31–55	34–61	41–71
Delivery rate per cycle	7	8	4	5	4	5	3	3	15	0	8	17

Values are *n*, % (95% CI) or (%). Crude CDR is calculated 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 IUI or ICSI with donor spermatozoa (denominator). Expected CDR is estimated according to the life-table methodology.
CDR = cumulative delivery rate.

cycles with a plateau being reached after three cycles (**Table 2**). Only one delivery was obtained after more than three cycles.

Similar results were seen after three cycles in the primary ICSI group (23 patients, 46 cycles) and the switchers group (63 patients, 129 cycles) (**Table 2**). The crude and expected CDR for the primary ICSI group were 26% (95% CI 8–44%) and 35% (95% CI 10–59%) after three cycles, respectively. The crude and expected CDR for the switchers group were 29% (95% CI 17–40%) and 42% (95% CI 26–57%) after three cycles, respectively. **Table 2** also describes the drop-out rates per cycle. Only one patient in the switchers group underwent seven ICSI cycles, but without any success. Only one patient in the primary ICSI group stopped after a poor ovarian response during the first cycle.

Primary treatment choice

IUI versus primary ICSI

To explore the question whether patients ≥40 years old should start with IUI rather than with ICSI, the CDR of both groups were plotted according to the number of cycles (**Figure 2**) and formally compared using the log-rank test. In the primary ICSI group (no previous IUI), nearly all deliveries were achieved in the first cycle with no further deliveries beyond three ICSI cycles; the delivery rates were 22% (95% CI 5–39%) after one cycle and 26% (95% CI 8–44%) after six cycles (**Figure 2**). In the IUI group, the delivery rate was only 7% (95% CI 3–11%) after one cycle, and a delivery rate of 24% (95% CI 17–31%) was only achieved after six IUI cycles. The CDR after six IUI cycles is thus comparable with the result of one ICSI cycle. With the numbers available, there was no statistically significant difference between the IUI and primary ICSI groups (log-rank test).

?A3B2 twb=.26w?>Mean time to a clinical pregnancy leading to a live birth after IUI was 194 days. This was the mean time to complete six IUI cycles and to ascertain if a pregnancy had been achieved. Mean time to pregnancy after one IVF cycle was 44 days.

Primary ICSI versus ICSI after failed IUI

There were no statistical differences when comparing results observed for primary ICSI and ICSI switchers after failed IUI (**Table 2**; log-rank test).

To explore the question if and when patients aged ≥40 years who initially start with IUI should switch to ICSI, this study compared three subgroups of ICSI switchers stratified according to number of previous IUI cycles and calculated the crude and expected CDR for the each subgroup: 1–3 previous IUI cycles (19 patients), 4–6 previous IUI cycles (22 patients) and 7–12 previous IUI cycles (22 patients). Due to the small numbers of patients available in each subgroup, data for per-cycle delivery rates were inconsistent. For this same reason, this study only discusses the crude CDR, which is more conservative than the expected rate. Crude CDR after three ICSI cycles were 21%, 27% and 36% for 1–3, 4–6 and 7–12 previous IUI cycles, respectively. There were no statistically significant differences between the three subgroups of switchers and the primary ICSI group (log-rank test). Nearly all deliveries were achieved in the first cycle and only one delivery was

Table 2 Cumulative delivery rates after ICSI with donor spermatozoa in 86 women aged ≥40 years.

	Overall treatment cycle number						*Primary ICSI treatment cycle number*						*Switchers treatmentcycle number*					
	1 (n = 86)	*2* (n = 45)	*3* (n = 21)	*4* (n = 11)	*5* (n = 8)	*6* (n = 3)	*1* (n = 23)	*2* (n = 10)	*3* (n = 6)	*4* (n = 3)	*5* (n = 3)	*6* (n = 1)	*1* (n = 63)	*2* (n = 35)	*3* (n = 15)	*4* (n = 8)	*5* (n = 5)	*6* (n = 2)
Non-pregnant	70	41	17	11	7	3	18	10	5	3	3	1	52	31	12	8	4	2
Deliveries	16	4	4	0	1	0	5	0	1	0	0	0	11	4	3	0	1	0
Non-pregnant and discontinued	25	20	6	3	4	2	8	4	2	0	2	1	17	16	4	3	2	1
Drop-out rate	36	49	35	27	57	67	44	40	40	0	67	100	33	52	33	38	50	50
Crude CDR	19	23	28	28	29	29	22	22	26	26	26	26	17	24	29	29	30	30
95% CI	10–27	14–32	18–37	18–37	19–39	19–39	5–39	5–39	8–44	8–44	8–44	8–44	8–27	13–34	17–40	17–40	19–41	19–41
Expected CDR	19	26	40	40	47	47	22	22	35	35	35	35	17	27	42	42	53	53
95% CI	15–22	22–30	35–45	35–45	30–65	30–65	7–37	7–37	10–59	10–59	10–59	10–59	9–26	16–38	26–57	26–57	31–76	31–76
Delivery rate per cycle	19	9	19	0	13	0	22	0	17	0	0	0	17	11	20	0	20	0

Values are *n*, % (95% CI) or (%). Crude CDR is calculated 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 IUI or ICSI with donor spermatozoa (denominator). Expected CDR is estimated according to the life-table methodology.
CDR = cumulative delivery rate.

seen after three ICSI cycles. This same trend was seen in the primary ICSI group.

Potential benefit of ICSI after failed IUI

Estimating the potential benefit of ICSI after failed IUI is more complex. **Figure 3** presents the calculated crude CDR for patients who switched to ICSI after failed IUI. Deliveries achieved after IUI were taken into account in the switchers' group. For graphical presentation, the switch to ICSI was made after the average of the previous IUI cycles (e.g. switch at cycle 2 for patients with 1–3 previous IUI cycles). The data in **Figure 3** suggest that switching to ICSI after failed IUI added only a marginal increase in CDR compared with continuation of IUI. The reason for this marginal increase in success rates is probably that patients with a failed IUI attempt are also those patients for whom even IVF/ICSI is not the solution to become pregnant quickly and easily.

Discussion

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 both natural conception (Dunson et al., 2004) or assisted reproduction treatment (Swartz et al., 1982; Scott et al., 1995; Van Noord-Zaadstra et al., 1991). Ovarian reserve decreases with advancing age, leading to a decrease in the numbers of oocytes obtained (Faddy and Gosden, 1996) and increases in the incidence of aneuploidy in oocytes (Munne et al., 1995) and poor oocyte quality (Navot et al., 1991). Age is an important limiting factor for the success of reproductive treatment. The treatment of choice, i.e. IUI or IVF/ICSI, remains undefined. In a retrospective study in 1654 women, this study centre reported CDR after donor insemination in all ages (De Brucker et al., 2009). Subgroup analysis in the oldest age group (40–45 years) revealed success rates in IUI similar to those in this study, despite the drop outs in both studies, occurring mainly as a result of discouraging patients to continue their treatment for the reason of their advanced age. Only a few other reports in the literature describe outcome after IUI with donor spermatozoa; however, CDR are not reported. Some of these cohort studies include only a small number of women aged over 40 (Schwartz et al., 1982; Barret and Cooke, 1993); other studies describe cumulative pregnancy rates but not CDR (Botchan et al., 2001). In their review, De Brucker and Tournaye (2010) conclude that above the age of 37, the success rate after IUI declines, but despite this fact, women aged up to 42 years should be encouraged to continue IUI when donor spermatozoa is used for insemination.

The current study investigated whether IVF/ICSI may be beneficial in women aged ≥40 years using donor spermatozoa to reproduce. Life-table analysis was used estimate this success. Life-table analysis has been used to estimate the success rates of various techniques of reproductive surgery and assisted reproduction (Hull et al., 1992). It assumes that those patients who continue their treatment and those who quit their treatment for non-medical reasons have the same

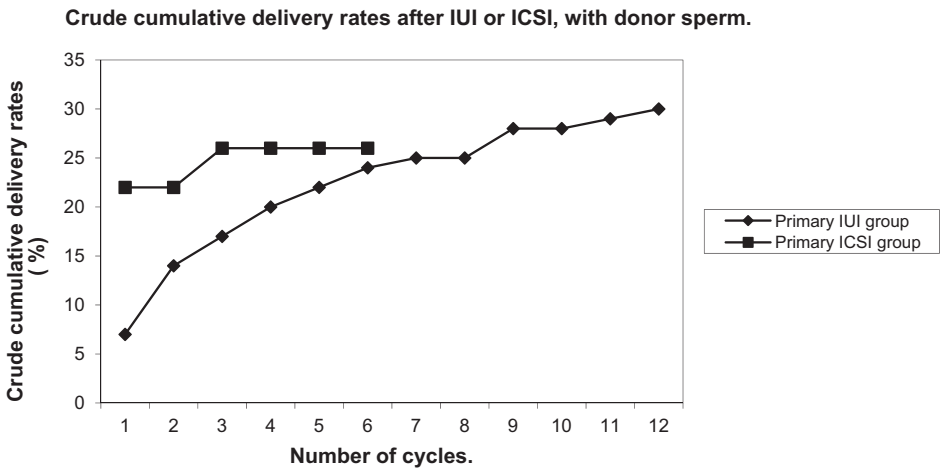

Figure 2 Crude cumulative delivery rates after IUI or primary ICSI with donor spermatozoa.

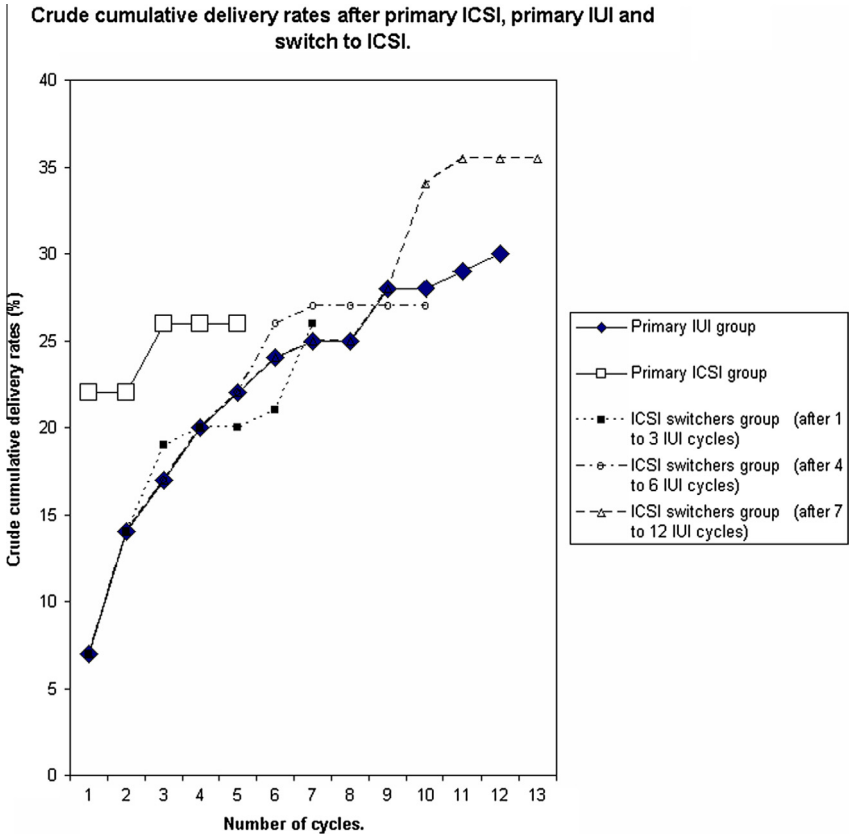

Figure 3 Crude cumulative delivery rates after IUI, primary ICSI and switching to ICSI after failed IUI. The switchers group was divided into three subgroups: 1—3, 4—6 and 7—12 IUI previous cycles. For graphical presentation, the switch to ICSI was made after the average of the previous IUI cycles (e.g. switch at cycle 2 for patients with 1—3 previous IUI cycles, at cycle 5 for patients with 4—6 previous IUI cycles and switch at cycle 9 for patients with 7—12 previous IUI cycles).

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. Life-table analysis also tends to overestimate the estimated CDR when the group is too small, so the current series presents all CDR with corresponding 95% confidence intervals; doing so provides information on the magnitude and precision of the CDR at each cycle, as well as the role that chance may play in the observed results. The CDR in this study obtained after ICSI are difficult to compare with other published data. Therefore data obtained

after ICSI using husband's spermatozoa are available for further comparison. Malizia et al. (2009) performed a retrospective analysis on a cohort of 6164 patients undergoing a total of 14,248 IVF cycles. In total, 1290 women aged ≥40 years reached an expected CDR of 42% after six cycles and a crude CDR of 23% after six cycles; in the current study, the crude CDR was 29% (95% CI 19–39%) using donor spermatozoa. Malizia et al. (2009) concluded that IVF overcame infertility in younger women and that women aged ≥40 years should be informed that IVF does not completely reverse the age-dependent decrease in fertility. The fact that success rates in ICSI using husband spermatozoa are similar to those using frozen–thawed donor spermatozoa is not surprising. Sperm quality did not appear to influence CDR (Osmanagaoglu et al., 1999).

The question remains as to whether patients aged ≥40 years in whom the ovarian reserve is declining should start with IUI or ICSI. These results show that CDR after six IUI cycles is similar to the results of one ICSI cycle. Nearly all deliveries in the primary ICSI group were achieved in the first cycle (CDR 21.7%, 95% CI 5.0–39.1%), with no further deliveries beyond three ICSI cycles. In contrast, in the IUI group, a trend of rising CDR was observed. There are a few trials in the literature that have investigated this subject. Nearly all studies excluded women aged ≥40 years except the FORT-T trial, of which preliminary results have been presented (Reindollar et al., 2011). This three-arm randomized clinical trial compared two cycles of ovulation induction/IUI with immediate IVF for the treatment of unexplained infertility in couples of which the female partner was aged 38–42 years. It demonstrated that the per cycle pregnancy and live birth rates were superior in the immediate IVF arm. One randomized pilot trial (Custers et al., 2011) compared the effectiveness of one cycle of IVF with elective single-embryo transfer versus three cycles of IUI with ovarian stimulation in 116 couples with unexplained subfertility and an unfavourable prognosis. They concluded that one cycle of IVF/elective single-embryo transfer might be as effective as three cycles of IUI/ovarian stimulation as primary treatment. Furthermore, a randomized clinical trial in the Netherlands (Steures et al., 2006) of IUI/ovarian stimulation versus no treatment for 6 months showed that for good-prognosis couples (unexplained infertility), IUI/ovarian stimulation was no better than expectant management. An Australian cohort analysis (Chambers et al., 2010) found a cumulative live birth rate per couple for the IUI group of 27.6% compared with 39.2% for the IVF group ($P = 0.01$). The authors supported the view that IVF is more clinically effective than IUI as a first-line therapy for subfertility because of consistently higher success rates, shorter times to pregnancy and a trend to less multiple pregnancies. The IVF programme was costlier than the IUI programme (cost of two IVF cycles versus one IUI cycle). From a cost–benefit perspective, one can defend six unstimulated IUI cycles over one ICSI cycle, although six stimulated IUI cycles are much more expensive than one ICSI cycle. Pashayan et al. (2006) published a mathematical model to estimate cost-effectiveness ratios for IVF, unstimulated IUI (U-IUI) and stimulated IUI (S-IUI); the cost of one IVF cycle was estimated as £3217, of one U-IUI cycle as £449 and of one S-IUI cycle as £1005. But since time-to pregnancy is important for women aged ≥40 years, from a time-management viewpoint IVF/ICSI should be offered as the primary treatment. It is noteworthy that in some states in the USA, where there is mandated insurance coverage, there is a stipulation for a certain number of IUI cycles before patients are allowed to switch to IVF. In those situations, the cost of treatment is borne directly by the insurer which patients are more readily to accept rather than opting for 'premature' treatment which they may have to pay for. This is not the case in Belgium. Health insurance supplies reimbursement for both treatments, i.e. six cycles of IUI with gonadotrophins and up to six cycles of IVF/ICSI up to age 43 years.

Whether patients who do not became pregnant after a series of IUI cycles should switch to IVF/ICSI or should continue IUI to improve their success rates remains an unsolved question. In this study, deliveries after IUI were taken into account in the different switchers subgroups. Switching to ICSI after failed IUI added no more than only a marginal benefit in CDR. The Fast Track and Standard Treatment (FASTT) trial (Reindollar et al., 2010) compared conventional treatment pathway with an accelerated treatment pathway. The researchers found that continuing IUI/ovarian stimulation added no value in comparison with couples in the accelerated arm; in this arm, couples who did not become pregnant after three cycles of clomiphene/IUI omitted the gonadotrophin/IUI treatment and moved directly to IVF. Couples in the accelerated arm became pregnant at a faster rate and with fewer cycles. But, this study only included women younger than 40. In studies with husband spermatozoa, retrospective data on the optimal number of IUI cycles exists, however, recommendations on the number of treatment cycles that should be offered are inconsistent (Aboulghar et al., 2001; Custers et al., 2008; Chaffkin et al., 1991, Plosker et al., 1994; Agarwal and Buyalos, 1996; Campana et al., 1996; Berg et al., 1997; Yang et al., 1998; Nuojua-Huttunen et al., 1999; Sahakyan et al., 1999). Most authors recommend to refrain from IUI after three or four cycles (Aboulghar et al., 2001; Agarwal and Buyalos, 1996; Chaffkin et al., 1991; Nuojua-Huttunen et al., 1999; Plosker et al., 1994; Sahakyan et al., 1999; Yang et al., 1998), whereas others advise to pursue IUI even after six cycles (Berg et al., 1997; Campana et al., 1996; Custers et al., 2008). As mentioned already, only a few studies have reported on IUI with donor spermatozoa. None of these publications included a follow up on the outcome of IVF/ICSI cycles after failed IUI.

The methodological strengths of this study include a virtually complete patient follow up, live birth delivery as the outcome event of primary interest and the use of well-validated methods to present both crude and expected CDR. This cohort study, being retrospective in nature, has some limitations as well. Although the current study is one of the largest cohorts ever reported of women aged ≥40 years, no statistically significant differences were found. With the numbers available in this observational study, a two-sided log-rank test achieves 28% power at a 0.05 significance level to detect a difference between the IUI and primary ICSI groups. Within the context of a randomized controlled trial, power and sample calculations based on the numbers available, indicate that a sample size of 440 patients (220 in each treatment arm) would be required to detect a difference between the IUI and primary ICSI groups with 80% power at a 0.05 significance level. The drop-out rate in women

aged ≥40 years is much higher than in younger women and this treatment discontinuation trend can be observed in either IUI programmes (De Brucker et al., 2009) or IVF programmes (Soullier et al., 2011). Soullier et al. (2011) concluded that even when treatment is reimbursed, the discontinuation rate associated with age encourages older women to discontinue. However, the most important reason to refrain from any further treatment is the advice of the treating doctor and their anticipation of low success rates associated with advancing age. Time-to-pregnancy is an important issue in these older women. This study group can defend at the moment the choice to advise immediate ICSI treatment, since a single cycle of ICSI achieves the same success rate as a much longer period with IUI with all of the accompanying stress and expense.

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