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ARTICLE

Cumulative success rates following mild IVF in unselected infertile patients: a 3-year, single-centre cohort study

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Daniel Bodri studied medicine and specialized in obstetrics and gynaecology in Hungary. After initial assisted reproduction training in Paris (2002–2003), he worked in a large infertility centre in Barcelona (2004–2011) and subsequently conducted research at two branches of Kato Ladies Clinic in Japan (2011–2012). He was awarded an MSc in clinical embryology from Leeds University (2008) and a PhD from the Autonomous University of Barcelona (2011). He has served as an Associate Editor for *Human Reproduction* since 2012. Current research interests include ovarian stimulation (GnRH antagonists, GnRH agonist triggering, minimal stimulation, natural-cycle IVF), oocyte donation, embryo-transfer procedures and evidence-based medicine.

Abstract A 3-year, retrospective, single-centre cohort study was conducted in a private infertility centre to determine cumulative live birth rates (LBR) per scheduled oocyte retrieval following minimal ovarian stimulation/natural-cycle IVF in unselected infertile patients. A total of 727 consecutive infertile patients were analysed who underwent 2876 (median 4) cycles with scheduled oocyte retrieval from November 2008 to December 2011. Natural-cycle IVF or clomiphene-based minimal ovarian stimulation was coupled with single-embryo transfer and increased use of delayed vitrified–warmed blastocyst transfer. Main outcome measures were crude and expected age-specific cumulative LBR per scheduled oocyte retrieval. Crude cumulative LBR were 65%, 60%, 39%, 15% and 5% in patients aged 26–34, 35–37, 38–40, 41–42 and 43–44 years, respectively. No live births occurred in patients aged ≥45 years. Drop-out rates per cycle were 13–25%. Success rates gradually reached a plateau, with few additional live births after six cycles. Most of the expected success rate was reached within 6 months with almost maximal rates within 15 months of the first oocyte retrieval. Acceptable cumulative LBR are reached with an exclusive minimal ovarian stimulation/single-embryo transfer policy especially in patients aged <38 years but also in intermediate aged patients (38–40 years).

KEYWORDS: cumulative live birth, minimal ovarian stimulation, natural-cycle IVF, poor responder, single-embryo transfer, in-vitro fertilization

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Introduction

In the 21st century, women are having fewer children and they are delaying births to a later age than in previous centuries. As a result, first childbearing has been postponed considerably by many women (te Velde and Pearson, 2002). This trend can cause serious issues since a lot of women are not aware of potential difficulties when having children later in life (DeCherney and Berkowitz, 1982). However, an age-related decrease in success rates of infertility treatments is well documented (van Noord-Zaadstra et al., 1991). Therefore, it is important for both candidate couples and fertility specialists to predict the probability for success after a defined number of treatment cycles in function of female age. In this perspective, providing cumulative chances of achieving a live birth after a given number of cycles is more meaningful than live birth per cycle. This is of extreme importance in treatments with lower expected success rates such as natural-cycle IVF or mild ovarian stimulation IVF.

Since the inception of IVF, there has been a constant interest in mild approaches to IVF treatment (Edwards, 2007; Nargund et al., 2007). Since 1994, the Kato Ladies Clinic (KLC) in Tokyo, Japan has pioneered the development of mild IVF approaches. At KLC and at its other branches throughout Japan (including the current study centre), minimal ovarian stimulation and natural-cycle IVF quickly became the mainstream treatment by completely replacing conventional IVF protocols. In other parts of the world, the uptake of minimal stimulation IVF in everyday clinical practice is still slow, which might be related to various factors such as lower expected success rates compared with conventional IVF and the lack of robust scientific evidence supporting the large-scale use of mild approaches (Fauser et al., 2010; Verberg et al., 2009).

To date, there are only three studies which have presented cumulative success rates in normal responders following natural-cycle or mild stimulated IVF: two were based on a (modified) natural-cycle IVF approach (Nargund et al., 2001; Pelinck et al., 2007); another was a randomized clinical trial based on mild ovarian stimulation with gonadotrophin-releasing hormone (GnRH) antagonist co-treatment combined with single-embryo transfer (SET) (Heijnen et al., 2007). These series showed encouraging results; however, they involved a selected infertile population of typically <38-year-old patients with favourable infertility diagnoses and no previous IVF treatment.

A number of previous studies from the current study group presented the outcome of a large series of unselected infertile patients giving an insight into the overall efficiency of minimal (mainly clomiphene-citrate based) stimulation protocols and natural-cycle IVF (Kato et al., 2012; Kawachiya et al., 2012; Teramoto and Kato, 2007; Zhang et al., 2010). However, in these studies success rates were calculated on a 'per transfer' or 'per oocyte retrieval' basis and no attempt was made to define cumulative success rates. Therefore the aim of this single-centre retrospective review was to present crude and expected cumulative live birth rates per scheduled oocyte retrieval following a natural cycle and minimal stimulation approach in an unselected infertile population.

Materials and methods

Study patients

This retrospective review included all consecutive patients from a single centre (Kobe Motomachi Yume Clinic, Kobe, Japan) who were scheduled to have oocyte retrieval between November 2008 and December 2011. Cycles cancelled before oocyte retrieval scheduling were not included in the centre's database. Cancellation rate was estimated to be nearly 10%. Most of the cancelled cycles were found in poor responders with high basal FSH concentrations (>20 IU/ml). A total of 727 consecutive infertile women were included, undergoing a total of 2876 treatment cycles (median four) which represented the total activity of the study centre since its inception. All women had a normal basic fertility work up, including hysterosonography, hysterosalpingography or laparoscopy in most. Since minimal ovarian stimulation and natural-cycle is the mainstream treatment in this clinic, patients were counselled as such.

Fresh embryo transfers performed during the study period, as well as delayed cryopreserved embryo transfers (CPET) performed up until July 2012, were analysed. All CPET were linked with the original oocyte retrievals from where the transferred cryopreserved embryos originated. These CPET were usually performed within the 3-month period following the original oocyte retrieval. Live birth was the main outcome measure. Live birth was defined as a child born after 22 weeks or weighing at least 500 g. Patient cycles that were performed after achieving a first live birth were not included. All patients without a live birth in a treatment 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.

In Japan, ethical committees that review drug-related clinical trials (usually at medical universities and large university-affiliated hospitals) are supervised by the Ministry of Health, Labor and Welfare. Other ethical committees not involved in trials for commercial products are primarily self-governing bodies established by each institution and not government regulated (Akabayashi et al., 2007). Institutional Review Board and ethical committee approval was not required for the present study due to its retrospective nature.

Natural-cycle IVF and minimal ovarian stimulation protocols

Unstimulated natural-cycle IVF (55%) or clomiphene citrate-based minimal stimulation (38%) was used in the majority of cycles, whereas other mild stimulation protocols using letrozole (Femara; Novartis, Japan) or low-dose human menopausal gonadotrophin (HMG; Ferring, Japan) represented only a smaller proportion (7%) of cases (Kato et al., 2012). Details of the natural-cycle IVF and clomiphene citrate-based minimal stimulation protocol are described here.

Briefly, clomiphene citrate 50 mg/day (Serofene, Merck Serono, Japan) was administrated orally with an extended regimen from cycle day 3 until the day before inducing final

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oocyte maturation. GnRH antagonists were not used because LH suppression was already obtained by the extensive clomiphene citrate regimen. HMG or recombinant FSH (Follistim, MSD or Gonal-f, Merck Serono, Japan) was added in injections (75–150 IU/every other day) in 53% of clomiphene citrate-based stimulation protocols in order to obtain between one and four mature follicles (Teramoto and Kato, 2007). In the natural-cycle IVF protocol, no GnRH antagonists or FSH add-back was used.

Monitoring involving ultrasound scan and hormonal profile (oestradiol, LH and progesterone) was usually started on day 8 and continued every other day until triggering day. Instead of human chorionic gonadotrophin, ovulation triggering was routinely performed with 600 μg GnRH agonist (Suprecure nasal solution, Sanofi, Japan), administered in a nasal spray form. In a proportion of natural-cycle IVF treatments, oocyte retrieval was scheduled based on the occurrence of the spontaneous LH surge. Nonsteroidal anti-inflammatory drugs (Voltaren; Novartis) were also used to reduce the rate of premature ovulation in natural-cycle IVF (Kawachiya et al., 2012).

Oocyte retrieval, fertilization, embryo culture and cryopreserved embryo-transfer cycles

Oocyte retrieval was performed using an extra-thin 22G needle (Kitazato, Japan) without follicular flushing. Patients returned home after a 20-min observation period. Conventional insemination or intracytoplasmic sperm injection (ICSI) was performed approximately 3 and 5 h after oocyte retrieval, respectively. Normally fertilized zygotes with two pronuclei were cultured individually from days 1 to 3 and in a majority of cases subsequently cultured from days 4 to 6 until blastocyst stage in small multigas incubators (Astec, Japan).

Since the inception of this study centre, only SET has been performed and a universal SET policy has been strictly observed. This was in line with recommendations of Japanese professional societies encouraging the use of SET. In this cohort, 21% of the embryo transfers were performed at day 2 or 3 with a fresh cleavage-stage embryo, whereas 70% involved a vitrified blastocyst. In the remaining 9% of cases, embryos were transferred as fresh blastocysts or vitrified cleavage-stage embryos. Details of the vitrification method using the Cryotop (Kitazato) have been described previously (Kuwayama, 2007).

In the presence of tubal factor infertility (tubal obstruction, hydrosalpinx or the history of extrauterine pregnancy) or previous implantation failures with cleavage-stage embryos, elective vitrified–warmed blastocyst transfer was preferred. These delayed CPET were usually performed within the 3-month period following the oocyte retrieval from where embryos originated. CPET were performed in spontaneous (without drugs only dydrogesterone as luteal support) or hormonal replacement cycles (using oral oestradiol tablets and dydrogesterone) (Kato et al., 2012).

All embryo-transfer procedures were performed under vaginal ultrasound guidance using a specially designed soft catheter (Kitazato) by placing a single embryo in minimal volume to the mid-uterine cavity (Bodri et al., 2011).

Data analysis

For each group of interest, categorical variables are presented as number of cases, including nominator and denominator values, and percentages. The primary outcome of this retrospective cohort study was cumulative live birth rate. The live birth of more than one child was given the same weight as the live birth 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 a previous report, this study provides two approaches frequently employed to estimate the effectiveness of assisted reproduction treatment according to the number of cycles (De Brucker et al., 2009). The first method calculates outcome by dividing the number of women achieving live birth to a predetermined number of cycles (numerator) by the total number of women who were scheduled for oocyte retrieval (denominator). Once follicular development was observed, patients were already entered into the database even before they reached the triggering stage and were considered as 'scheduled for oocyte retrieval'. The only reason why a cycle would be cancelled is absence of follicular development (<10% per started cycle). The outcome measure associated with this method is referred to as 'crude live birth rate'.

The other method estimates the cumulative live birth rate after a specified number of cycles using life table analysis, by taking into account the effect of censoring (drop out) (De Brucker et al., 2009). The outcome measure associated with this method is referred to as 'expected live birth 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 drop out (censoring) into account and provides a conservative estimate of outcome.

Expected cumulative success rates (curves) were compared by log-rank tests. A P-value ≤ 0.05 was considered as statistically significant. Cumulative delivery rates were compared for six subgroups according to patient's age (i.e. 20–34, 35–37, 38–40, 41–42, 43–44, and ≥45 years) at the first IVF treatment, according to the definition of the Society for Assisted Reproductive Technology (Luke et al., 2012). Age at first cycle determined which group the patients belonged to. Computational procedures were performed using Statistical Package for Social Sciences for Windows version 16 (SPSS, Chicago, IL, USA).

Results

Baseline characteristics

About 60% of the patients were older than 38 years at the start of treatment. Body mass index was low (20.8 ± 2.7 kg/m^2) as expected in the Japanese population. Most patients had primary infertility (64%) and were nulliparous (87%). Among infertility causes, Bologna poor responders (29%) were overrepresented. Only a few patients (20%) had not had any previous fertility treatment, and most of them (59%) had already undergone conventional and/or minimal IVF treatment cycles at other centres. Baseline

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patient characteristics at the time of the first oocyte retrieval are summarized in Table 1.

Treatment characteristics and overall success rates

During the study period, a total of 727 infertile patients were scheduled to have 2876 oocyte retrievals, with a yield of (mean ± SD) 1.7 ± 2 oocytes (range 0–22). The median number of scheduled oocyte retrievals per patient was four (range 1–26). The time interval between successive oocyte retrievals was 53 ± 55 days (range 18–712 days). The time interval between the first and last scheduled oocyte retrieval (patient follow up) was 155 ± 194 days (range 19–1097 days). In total, 966 (fresh or vitrified) SET were performed, and in 181 patients, vitrified embryo(s) remained which could potentially serve for additional CPET. Finally this resulted in 273 live births: 270 singletons and three pairs (1%) of monozygotic twins (Figure 1). For singletons, the gestational age at delivery and birthweight was 39.1 ± 1.7 weeks and 3075 ± 432 g, respectively (premature delivery rate was 11/270 = 4%). For monozygotic twins the gestational age at delivery and birthweight was 36 ± 1 weeks and 2439 ± 282 g, respectively. Overall, in all age groups, a cumulative live birth rate of 38% was reached.

Table 1 Baseline patient characteristics.

Characteristic	*Patients (n = 727)*
Woman's age (years)	38.4 ± 4.5
26–34	148 (20)
35–37	144 (20)
38–40	181 (25)
41–44	202 (28)
45–52	52 (7)
Body mass index (kg/m^2)	20.8 ± 2.7
Female infertility	
Primary	465 (64)
Nulliparous	629 (87)
Bologna poor responders	214 (29)
Tubal	84 (12)
Endometriosis	34 (4.7)
PCOS	36 (5.0)
Uterine	19 (2.6)
Mixed	38 (5.2)
Basal FSH (IU/ml)	
≥12	244 (34)
≥20 IU/ml	87 (12)
Duration of marriage (years)	6.7 ± 4.2
Treatment history	
None	145 (20)
IUI (No. of cycles)	446 (61), 4.9 ± 3.5
Conventional IVF (No. of cycles)	319 (44), 2.8 ± 2.2
Minimal IVF (No. of cycles)	220 (30), 4.4 ± 4.8
Total IVF (No. of cycles)	431 (59), 4.3 ± 4.1
Partner's age (years)	40.7 ± 6

Values are *n* (%) and/or mean ± SD.
IUI = intrauterine insemination; PCOS = polycystic ovary syndrome.

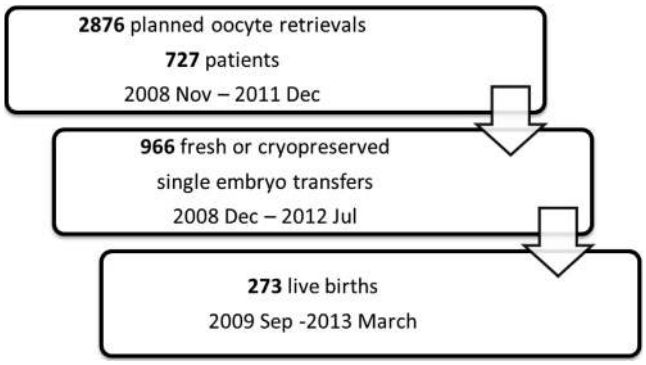

Figure 1 Study and follow-up periods.

Although the proportions of cycles with retrieved (85%), inseminated (76%) and fertilized (66%) egg(s) remained remarkably stable in each cycle rank, there was a progressive decrease in the proportion of cycles reaching embryo transfer (from 47% to 7%) and especially with live births (from 15% to 1%) (Figure 2A). Whereas during the first attempt, natural-cycle IVF was predominant (78%), in subsequent cycles its proportion decreased (to 41–60%) in favour of clomiphene-citrate based minimal stimulation (28–54%) (Figure 2B). With each successive cycle, the proportion of poor-prognosis patients (>40 years old, elevated basal FSH and Bologna poor responders) increased steadily from 30–35% to 66–86% (Figure 2C).

Age and success rate

Crude and expected cumulative live birth rates according to age are presented in Figure 3. Table 2 provides crude and expected cumulative delivery rates with 95% confidence intervals, as well as more detailed data on dropout and delivery rates per cycle. Maximal crude cumulative live birth rates decreased with progressing female age (log-rank test $P < 0.001$) and were 65%, 60%, 39%, 15% and 5% in patients aged 26–34, 35–37, 38–40, 41–42 and 43–44 years, respectively (Figure 3A). A plateau in success rates was reached after approximately six cycles. About 85% and 95% of the overall crude cumulative success rate was reached after four and six cycles, respectively. In 52 patients aged ≥45 years, 256 cycles were performed but no live births occurred. A time-based analysis showed that, in the overall cohort, 82% of the expected success rate was reached within 6 months and almost maximal rates (98%) within 15 months of the first oocyte retrieval. A plateau in success rates was reached gradually after 6 months. Dropout rates per cycle varied between 13–25% (Table 2). Maximal expected cumulative live birth rates decreased with progressing female age (log-rank test $P < 0.001$) and were 93%, 92%, 55%, 20% and 6% in patients aged 26–34, 35–37, 38–40, 41–42 and 43–44 years, respectively (Figure 3B).

Discussion

This 3-year cohort showed that acceptable crude cumulative success rates can be achieved in a programme based

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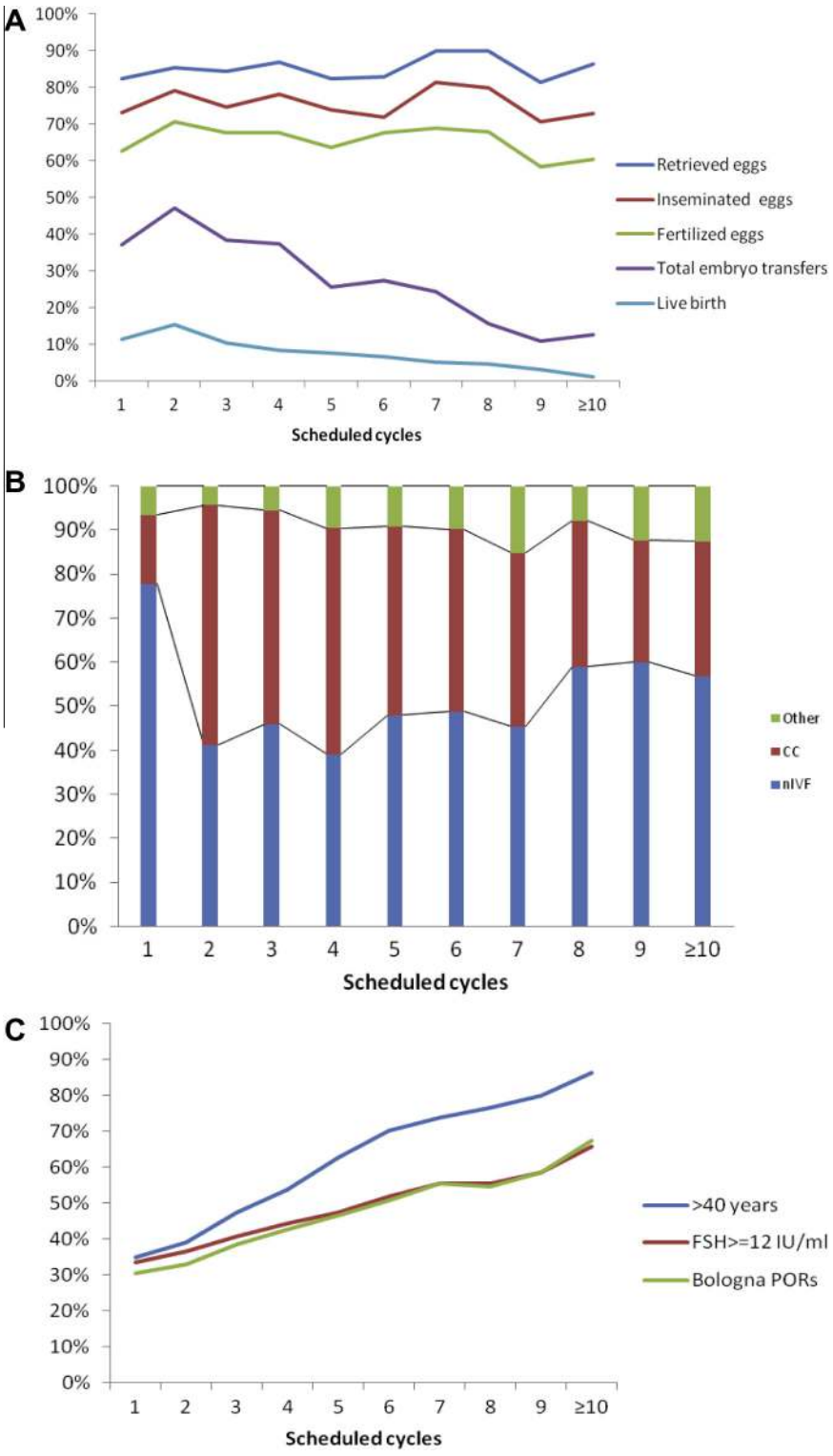

Figure 2 Treatment efficiency (A), type of stimulation protocol (B) and poor-prognosis patients (C) of scheduled cycles (initiated cycles scheduled for oocyte retrieval). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

on the exclusive use of minimal stimulation protocols and SET, especially in women aged <38 years but also those aged 38–40 years. A plateau in success rates was observed and there was little additional benefit from performing more than six treatment cycles.

In contrast with the two European studies which presented cumulative success following mild IVF, this study used live birth in an unselected infertile population as a robust outcome measure. In a Dutch study (Pelinck et al., 2007), a cumulative clinical pregnancy rate of 44%

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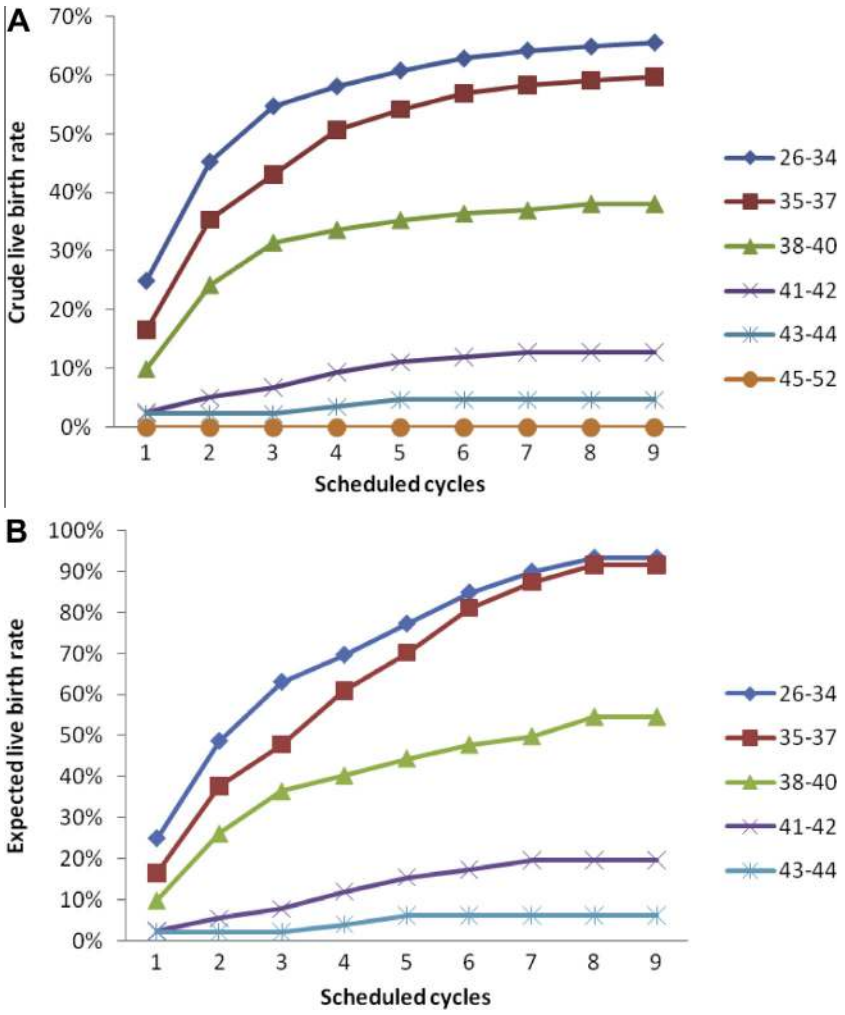

Figure 3 Crude (A, conservative estimate) and expected (B, optimistic estimate) live birth rates of scheduled cycles (initiated cycles scheduled for oocyte retrieval) according to age. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

was reached after nine cycles (256 patients performing 1048 cycles) which is very similar (46%) to the success reached in an earlier smaller UK study where 52 patients underwent 181 natural-cycle IVF cycles (Nargund et al., 2001). The current study has furthered knowledge in relation to previous published papers from this study group where no cumulative success rates have so far been presented. In two of the largest single-centre series ever published which used a minimal stimulation approach in a Japanese setting, overall live birth rates per oocyte retrieval cycle were 11.1% and 12.2%, respectively (Kato et al., 2012; Teramoto and Kato, 2007). This was comparable with live birth rates achieved during the initial cycles in the current series but, as highlighted, a plateau was reached after a number of cycles that limited further increase in cumulative live birth rates.

Expected success rates were considerably higher than crude live birth rates especially in patients aged <41 years. Although this optimistic calculation hugely overestimates the expected success, it gives an estimation what could be expected if no patient drop out would occur up until nine treatment cycles. In this series, dropout rates (13–25% per cycle and 56% after nine cycles) were fairly low and similar to those reported (3–19% per cycle and 48% cumulative) by the aforementioned Dutch study, where enrolled patients were offered a maximum of nine modified natural-cycle IVF treatments (Pelinck et al., 2007). In contrast, following conventional IVF, discontinuation rates are considerably higher (usually well above 50% per cycle) even in countries where treatment is reimbursed (Malizia et al., 2009; Schroder et al., 2004; Soullier et al., 2011). In the setting of a well-controlled randomized clinical trial, it was found that, compared with conventional IVF, a mild treatment strategy was associated with a significant reduction in dropout rates (Verberg et al., 2008). This is particularly important because reduced patient discontinuation might compensate for the lower per-cycle success rate associated with mild ovarian stimulation. The reasons for an apparently low dropout rate in this study are difficult to determine but might be related to socioeconomic characteristics of Japanese infertile patients, the lack of active censoring by the medical team and the fact that minimal stimulation might be perceived by patients as a more cost-effective and less-invasive approach than conventional IVF.

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Table 2 Cumulative delivery rates for the total cohort and stratified according to prespecified age groups, for the first nine cycles.

	Treatment cycle number								
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
All ages									
No. of patients	727	558	389	284	196	154	119	90	65
No. of nonpregnant	644	472	349	260	181	144	113	86	63
No. of discontinued	86	83	65	64	27	25	23	21	10
Dropout rate (%)	13	18	19	25	15	17	20	24	16
No. of deliveries	83	86	40	24	15	10	6	4	2
Crude cumulative LBR (%)	11	23	29	32	34	35	36	37	37
95% CI (%)	9–14	20–26	26–32	29–36	31–38	32–39	33–40	33–40	34–41
Expected cumulative LBR (%)	12	25	33	39	43	47	50	52	53
95% CI (%)	9–14	22–28	29–36	35–42	39–47	43–51	45–54	47–57	48–59
LBR per cycle (%)	11	15	10	8	8	6	5	4	3
Age 26–34 years									
No. of patients	148	95	50	28	16	9	6	3	1
No. of nonpregnant	112	65	36	23	12	6	4	2	0
No. of discontinued	17	15	8	7	3	0	1	1	0
Dropout rate (%)	15	23	22	30	25	0	25	50	0
No. of deliveries	36	30	14	5	4	3	2	1	1
Crude cumulative LBR (%)	24	45	54	57	60	62	64	64	65
95% CI (%)	18–32	37–53	46–62	49–65	52–68	54–70	56–71	56–71	57–72
Expected cumulative LBR (%)	25	49	63	70	77	85	90	93	93
95% CI (%)	19–31	42–56	56–71	62–77	69–85	77–93	83–97	87–100	87–100
LBR per cycle (%)	24	32	28	18	25	33	33	33	100
Age 35–37 years									
No. of patients	144	106	68	44	21	11	6	3	1
No. of nonpregnant	120	79	57	33	16	17	4	2	0
No. of discontinued	14	11	13	12	5	1	1	1	0
Dropout rate (%)	12	14	23	36	31	14	25	50	0
No. of deliveries	24	27	11	11	5	4	2	1	1
Crude cumulative LBR (%)	17	35	43	51	54	57	58	59	60
95% CI (%)	11–23	28–43	35–51	43–59	46–62	49–65	50–66	51–67	52–68
Expected cumulative LBR (%)	17	38	48	61	70	81	87	92	92
95% CI (%)	11–22	31–45	40–56	53–69	61–79	72–90	79–96	84–99	84–99
LBR per cycle (%)	17	25	16	25	24	36	33	33	100
Age 38–40 years									
No. of patients	181	144	93	66	43	33	25	21	15
No. of nonpregnant	163	118	80	62	40	31	24	19	15
No. of discontinued	19	25	14	19	7	6	3	4	7
Dropout rate (%)	12	21	18	31	18	19	13	21	47
No. of deliveries	18	26	13	4	3	2	1	2	0
Crude cumulative LBR (%)	10	24	31	34	35	36	37	38	38
95% CI (%)	6–14	18–31	25–38	27–41	28–42	29–43	30–44	31–45	31–45
Expected cumulative LBR (%)	10	26	37	40	45	48	50	55	55
95% CI (%)	6–14	20–32	29–44	33–48	36–53	39–57	41–59	44–65	44–65
LBR per cycle (%)	10	18	14	6	7	6	4	10	0
Age 41–42 years									
No. of patients	117	97	82	66	51	44	37	30	22
No. of nonpregnant	114	94	80	63	49	43	36	30	22
No. of discontinued	17	12	14	12	5	6	6	8	5
Dropout rate (%)	15	13	18	19	10	14	17	27	23

(*continued on next page*)

Table 2 Cumulative delivery rates for the total cohort and stratified according to prespecified age groups, for the first nine cycles.

	Treatment cycle number								
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
No. of deliveries	3	3	2	3	2	1	1	0	0
Crude cumulative LBR (%)	3	5	7	9	11	12	13	13	13
95% CI (%)	0–5	1–9	2–11	4–15	5–17	6–18	7–19	7–19	7–19
Expected cumulative LBR (%)	3	6	8	12	16	17	20	20	20
95% CI (%)	0–5	1–10	3–13	5–19	8–23	9–26	10–29	10–29	10–29
LBR per cycle (%)	3	3	2	5	4	2	3	0	0
Age 43–44 years									
No. of patients	85	74	63	53	44	38	29	21	16
No. of nonpregnant	83	74	63	52	43	38	29	21	16
No. of discontinued	9	11	10	8	5	9	8	5	5
Dropout rate (%)	11	15	16	15	12	24	28	24	31
No. of deliveries	2	0	0	1	1	0	0	0	0
Crude cumulative LBR (%)	2	2	2	4	5	5	5	5	5
95% CI (%)	0–6	0–6	0–6	0–7	0–9	0–9	0–9	0–9	0–9
Expected cumulative LBR (%)	2	2	2	4	6	6	6	6	6
95% CI (%)	0–6	0–6	0–6	0–9	0–13	0–13	0–13	0–13	0–13
LBR per cycle (%)	2	0	0	2	2	0	0	0	0
Age 45–52 years									
No. of nonpregnant	52	42	33	27	21	19	16	12	10
No. of patients	52	42	33	27	21	19	16	12	10
No. of discontinued	10	9	6	6	2	3	4	2	1
Dropout rate (%)	19	21	18	22	10	16	25	17	10
No. of deliveries	0	0	0	0	0	0	0	0	0
Crude cumulative LBR (%)	0	0	0	0	0	0	0	0	0
LBR per cycle (%)	0	0	0	0	0	0	0	0	0

LBR = live birth rate.

Moreover, this time-based analysis showed that a large part of the expected success can be reached within 6 months (especially in patients aged <41-years), which might suggest an easier patient tolerance of mild compared with conventional IVF.

With the exception of a Dutch RCT (Heijnen et al., 2007), there is a lack of properly controlled prospective studies comparing the efficiency of mild versus conventional IVF approaches (Gleicher et al., 2012). Also, comparison with published observational cohort studies is fairly difficult due to a different case-mix of infertile patients in each study (Malizia et al., 2009; Pouly et al., 2012; Schroder et al., 2004; Witsenburg et al., 2005). In this aspect cumulative success rates probably allow better comparison between different centres (Gnoth et al., 2011). In comparison with a recent registry-based US study (which is the largest dataset presenting cumulative success following conventional IVF rates published in the literature; Luke et al., 2012), the current series shows comparable overall cumulative success in patients aged <41 years (**Figure 4**). Also in this series, no live births were observed in patients aged ≥45 years. This is very much in line with an Israeli study which concluded that IVF treatment should be limited to patients no older than 43 (Hourvitz et al., 2009). In a recent study from the Tokyo branch of the current group, with a much larger sample (>7000 patients), there were occasional live births achieved in patients aged ≥45 years (with the oldest patients aged 48), but the probability of live birth per started cycle was only 0.46% (Kato et al., 2012).

This study has several limitations. Firstly, cycles which were cancelled before oocyte retrieval were not registered, therefore the denominator was 'planned scheduled retrieval' and not 'started cycle'. This might lead to a slight overestimation of cumulative success rates. Secondly, most patients underwent previous IVF treatments in other centres, but in the current evaluation only cycles performed at this centre were taken into account. This means that 59% of patients underwent previous IVF cycles (4.3 ± 4.1, range 1–30) although it was not possible to adjust for it. Thirdly, the unselected infertile population was particularly biased towards poor-prognosis patents (>40 years and Bologna poor responders), which might limit generalizability to other less infertile populations. Finally, there was a considerable heterogeneity due to different treatment protocols (natural-cycle IVF versus clomiphene-citrate minimal stimulation) or embryo-transfer strategies used (fresh cleavage versus cryopreserved blastocyst) in each cycle rank.

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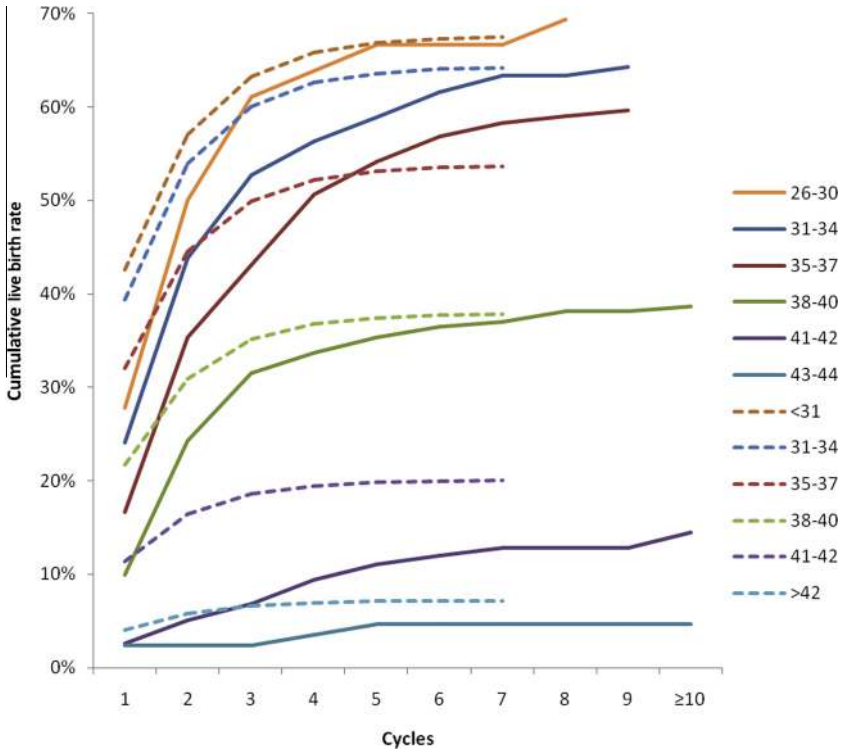

Figure 4 Comparison of age-specific cumulative live birth rates (using a conservative estimate) of the current series (Japanese cohort; solid lines) and that of Luke et al. (2012; US cohort; dotted lines). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The strength of this large series is that it gives a more precise picture on overall efficacy of mild IVF treatments in each age-specific group. Interestingly, the approach described here (which might be labelled as unconventional or experimental by some observers) fully complies with the goal of an 'ovarian hyperstimulation syndrome-free' and/or 'singleton-only IVF clinic', two recent concepts which have also been advocated by Western opinion leaders (Devroey et al., 2011; Kresowik et al., 2011).

In conclusion, this 3-year series shows that acceptable cumulative live births rates can be achieved in a programme based on the exclusive use of mild ovarian stimulation protocols and SET (ESHRE Campus Report, 2001). Although these results are encouraging, more research is needed to better define those patient groups who would benefit the most from mild IVF approaches.

Presentation

The data in this study were presented orally at the 29th Annual ESHRE Meeting, London, 7—10 July 2013.

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