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Original article

Live birth rates are satisfactory following multiple IVF treatment cycles in poor prognosis patients

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ABSTRACT

This seven-year retrospective study analysed the live birth rate (LBR) for women undergoing IVF treatment with various antral follicle counts (AFC). The LBR decreased with lower AFC ratings, and in 290 treatment cycles for women in the poorest AFC category, ≤4 follicles (group E), the LBR was the lowest at 10.7%. The pregnancy loss rate (PLR) significantly increased with poorer AFC categories, from 21.8% in AFC group A (≥20 follicles), to 54.4% in AFC group E ($p < 0.0001$). This trend was repeated with advancing age, from 21.6% for younger women (< 35 years), to 32.9, 48.5 and 100% for ages 35–39, 40–44 and ≥45 years, respectively ($p < 0.0001$). However, LBR within the specific AFC group E cohort was also age-dependent and decreased significantly from 30.0% for <35 years old, to 13.3, 3.9 and 0% for patients aged 35–39, 40–44 and ≥45 years, respectively. Most, importantly, LBR rates within these age groups were not dependent on the number of IVF attempts (1st, 2nd, 3rd or ≥4 cycles), which indicated that cycle number should not be the primary deciding factor for cessation of IVF treatment in responding women <45years old.

1. Introduction

The management of poor ovarian responders (PORs) poses a serious dilemma for fertility clinicians, yet the main issue remains in defining the condition. Various criteria were previously used [1] until the European Society of Human Reproduction and Embryology (ESHRE) attempted to provide a strong definition based on the Bologna criteria [2,3]. This definition of PORs requires the presence of at least two of the following three criteria: (i) advanced maternal age (≥40 years) or any other risk factor such as previous ovarian surgery, (ii) a prior poor ovarian response (cycles cancelled or ≤3 oocytes with a conventional stimulation protocol) or (iii) an abnormal ovarian reserve test (ORT) consisting of an AFC of <5–7 antral follicles or a serum anti-Mullerian hormone (AMH) of <0.5–1.1 ng/mL (3.6–7.9 pmol/L).

Recently, it has been suggested that Bologna POR patients should not pursue further IVF-ET treatment, if they have failed to succeed within the first three treatment regimens [4]. Live birth rates (LBR) for this type of patient is approximately 6% per cycle [5,6]. Furthermore, a sub-population of very poor prognosis patients exists, who are deemed to have a LB chance of between 1 and 5%. [7], while treatment cycles in patients with ≤1% chance are considered futile [8]. However, when to cease treatment of Bologna criteria, very poor prognosis, or indeed patients with no chance of achieving a LB, is hotly debated by fertility specialists [9].

What is clear, is it that the decision to preclude treatment in the case of "futility", or to stop further treatment in the case of poor prognosis patients who have undergone multiple unsuccessful attempts, has to be consensually made by both patients and clinicians together [8]. However, this decision should be patient-centred and in the case of "futility", the decision not to treat should not be made to protect the clinic success rates, while treatment should not be encouraged for pecuniary interests of the clinic. Instead, the option to treat, or continue treating in the case of multiple failures, is chosen once the clinician has assessed all the risks and benefits associated with continued treatment, and once the patients are fully informed of the significantly low chance of

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success. In some situations, the benefits to treat or continue to treat may be psychological, in that the patient knows that every avenue was explored to achieve a favourable outcome. Nonetheless counselling should be provided throughout the decision-making process, the clinical treatment, and in the aftermath, where alternative options may be explored such as using donor embryos or adoption. Overall, patients in POR categories need to be fully aware and realistic regarding their chances.

However, in the clinic, the option to stop or refuse treatment may contravene the right of informed patients for self-determination [7]. In addition, the current LBR observed for POR patients (1–6%), are not too different from those for patients in the early years

PIVET Medical Centre Database
1 April 2008-30 April 2015

		AFC Grade				
		A's	B&C	D	E	Total
Initial IVF Cycle No.		**978**	**1273**	**865**	**579**	**3695**
	Exclude:					
	Oocyte/ embryo recipient/donor, surrogacy	**37**	**34**	**16**	**49**	**136**
IVF Cycles No.		**941**	**1239**	**849**	**530**	**3559**
	Exclude:					
	1. Cancelled cycle	52	68	92	116	**328**
	2. No Oocyte/ no mature oocyte	4	15	22	22	**63**
	3. Freeze all (embryo/oocyte) or no outcome	125	93	62	58	**338**
	4. Failed fertilisation/ embryo discarded	15	35	55	44	**149**
	Total	**196**	**211**	**231**	**240**	**878**
	% of cycles not having ET	**(20.8%)**	**(17.0%)**	**(27.2%)**	**(45.2%)**	**(24.7%)**
Embryo Transfer Cycles No.		**745**	**1028**	**618**	**290**	**2681**
	NOT PREGNANT	**429**	**688**	**481**	**233**	**1831**
	PREGNANT	**316**	**340**	**137**	**57**	**850**
	PR / IVF-ET cycle	**(42.4%)**	**(33.1%)**	**(22.2%)**	**(19.7%)**	**(31.7%)**
	1. Twin/ multiple	11	19	5	2	**37**
	2. Singleton	232	227	72	29	**560**
	3. FDIU	1	0	0	0	**1**
	4. Termination	3	1	2	0	**6**
	5. Miscarriage	45	53	34	16	**148**
	6. Ectopic	1	10	5	1	**17**
	7. Biochemical	23	30	19	9	**81**
	Live Birth	**243**	**246**	**77**	**31**	**597**
	LBR / IVF-ET Cycle	**32.6%**	**23.9%**	**12.5%**	**10.7%**	**22.3%**

FDIU = Fetal death in utero **PR = Pregnancy rate** **LBR = Live Birth rate**

Fig. 1. Flow Chart of IVF-ET cycle outcomes based on AFC category.

of IVF, who would now be considered "best prognosis" patients [7]. Therefore, is it now correct to refuse treatment based on the extremely low success rate for patients who are fully aware of their live birth prospects?

While this debate will continue, one of the key issues is that data to define when consecutive treatment should be stopped is very limited. Consequently, the aim of the current study was to determine the LBR and Cumulative LBR (CLBR) for all patients who underwent IVF-ET procedures, with specific focus on Bologna criteria POR patients, with a low AFC (≤4 follicles) and who had 4 or more treatment cycles. Such cases are associated with poor pregnancy results with reported LBR per cycle of less than 10% (ranging from 2.6–8.3%) and LBR per woman around 14% (ranging from 7.4–20.5%) [5,10–12]. The inclusion of CLBR also known as productivity rate (PR) [13], is important as it encompasses the total birth outcomes from a single stimulation and transvaginal oocyte aspiration (TVOA), incorporating the associated fresh IVF-ET treatment outcome, along with all frozen embryo transfers (FETs) linked to that treatment. Considering the increased focus on single embryo transfers (SETs), and the continued advancements in cryopreservation technologies in the current era, this is an important outcome and provides an appropriate reference for comparing treatment outcomes, particularly for subsequent multiple transfer cycles, some of which fail.

2. Materials and methods

2.1. Patient selection

The data was retrospectively collected and analysed from the PIVET Medical Centre database in April 2016 and covered a 7-year period (1 April 2008 to 30 April 2015). The data includes all IVF cycles with a fresh embryo transfer (IVF-ET), along with any related frozen cycles (FET). Donor/recipient treatments, PGD/PGS, as well as surrogacy were all excluded from analysis (Fig. 1). "Freeze-all embryos" usually occurred due to various factors such as excessive ovarian response (unlikely to occur in low AFC patients), patient unavailability for ET, or PGD screening, and were excluded (Fig. 1).

2.2. Ovarian stimulation for IVF cycles

Various ovarian stimulation regimens were used in this study including long down-regulation, flare cycle and an antagonist protocol, all described previously [14–16]. Whilst stimulation protocol selection was at clinician discretion, the preference was usually the antagonist protocol for younger women with a higher AFC rating, and the flare regimen for older women with a low AFC rating. A specialised dosing algorithm was used to select the rFSH starting dose [15,16], and this flexible system incorporates maternal variables that are predictive of ovarian response including AFC and AMH, along with other important parameters such as age, BMI, smoking status and basal serum FSH level. Patients identified as PORs based on the algorithm invariably received a high rFSH dosage of either 450 or 600 IU (currently capped at 450 IU). The algorithm incorporates a range of patients, including those with potential risk of ovarian hyper stimulation syndrome (OHSS), along with those who are potential PORs. The main dictating parameter for dosage selection was AFC grade, while AMH category was used as a modifying parameter, reducing dosage if it was higher than AFC grading [16]. The AFC grade was based on the total number of day 5 follicles noted on the transvaginal scan (TVS) during the assessment cycle and patients grouped as follows (Group A, ≥20/30/40 follicles; group B, 13–19 follicles; group C, 9–12 follicles; group D, 5–8 follicles; group E, ≤4 follicles). Groups B and C were combined (B/C, 9–19 follicles) to obtain a group that was of similar size to the others.

2.3. Ovulation induction and luteal support for IVF

Ovulation was initiated with a single dose of rhCG (Ovidrel: Merck, Serono Australia, 2 ampoules equating to approximately 13,000 IU hCG) for patients with at least 2 leading follicles ≥18 mm in diameter. For patients with <4 follicles and a previous poor recovery despite maximal rFSH, 3 Ovidrel ampoules (19,500 IU) were used as the trigger. Our perception is that these patients have diminished ovarian vasculature and therefore higher serum concentrations of hCG trigger are required to promote *in vivo* oocyte maturation. In antagonist cycles with excessive follicle recruitment (> 12 follicles over 12 mm), gonadotrophin-releasing hormone agonist (Lucrin: Abbott, Australia) trigger approximating to 2.5 mg was used. Oocyte recovery was performed at 35–37 h post trigger. Luteal support for IVF-ET cycles was based on the number of oocytes recovered and has been fully described [15]. Post ovulatory support involved rhCG injections, as well as oestrogen (E2) and progesterone (P4) pessaries, particularly in the case of FET [17].

2.4. Embryo culture and transfer

Embryo transfers were conducted using either day 3 (cleavage stage) or day 5 (blastocyst stage) embryos. Blastocysts were graded based on Gardner's classification and cleavage stage embryos were graded as previously published [18–21]. Most POR cases received day 3 transfers as internal clinical protocols required 3 good quality embryos on day 3 to allow further culture to blastocyst stage. Primarily, single embryo transfer (SET) is performed in Australia and New Zealand (86.9% autologous cases) [22], but exceptions were made when a written request was submitted in cases of multiple IVF failures (≥3). All frozen embryos were cryopreserved by vitrification using the Cryotop, mostly at blastocyst stage [23–25].

2.5. Pregnancies and live birth

Pregnancy blood test (βhCG, E2, P4) was performed at approximately 4-weeks gestation or 19 days post-trigger for IVF-ET [26]. Weekly blood test for βhCG, E2 and P4 was performed until 8 weeks gestation to ascertain the progress of pregnancy, giving hormonal support when deemed necessary [17]. TVS for fetal viability was performed at 7-weeks gestation, and detection of an intrauterine gestational sac with fetal heart beat confirmed clinical pregnancy. Pregnancy loss rate (PLR) was recorded after this scan and included miscarriage, ectopic pregnancy, failed pregnancies of unknown location and early resorbing biochemical pregnancies. These cases were all included in calculating PLR, being all first trimester losses per total pregnancies generated. Mid-trimester losses and terminations (<20 weeks) were examined separately and combined with the few cases of fetal deaths in utero (FDIU) (>20 weeks). Live birth outcomes were recorded after the expected delivery date. CLBR was calculated using the total number of live birth outcomes from a single IVF-ET treatment cycle, but included all fresh and frozen embryo transfers associated with that initial treatment.

2.6. Ethical consideration

The PIVET clinic is accredited with the Reproductive Technology Accreditation Committee (RTAC) and the Reproductive Technology Council (RTC) of Western Australia. Reporting of the data was approved under Curtin University Ethics Committee approval no. RD_25-10 general approval for retrospective data analysis 2011, updated 2015.

2.7. Statistical analysis

IBM SPSS Statistics 22.0 Software was used for the statistical analysis. Means were compared by two sample *t*-test and ratios by X^2. Multiple group comparisons and trends were analysed by one–way ANOVA. Statistical significance was set at p-value < 0.05.

3. Results

From a total of 3695 initiated cycles during the 7-year study period, there were 3559 autologous IVF cycles (Fig. 1). This resulted in 2681 IVF-ET cycles with fresh embryo transfer performed. Clinical pregnancies were achieved in 769 cycles (28.7%) with 597 (22.3%) live birth deliveries (Fig. 1). The LBR for IVF-ET cycles dropped gradually according to AFC grading, group A (32.6%), B/C (23.9%), D (12.5%) and E (10.7%) (Fig. 1). Just under half of IVF cycles in AFC group E (45.3%) had no fresh ET performed, primarily due to cancelled cycles (21.9%), no oocytes or no mature oocytes collected (4.2%), failed fertilization or due to poor quality embryos not suitable for transfer (8.3%) (Fig. 1). Freeze-all (10.9%) of embryos was performed mainly due to inability of patient to attend fresh ET, PGD screening or elective FET to improve outcome (Fig. 1).

The mean age of patients in all cycles was 36.0 ± 5.2 years (range: 21–51), and there was no significant difference in the mean age or BMI among the various AFC groups (Table 1). However, when the age group was divided into <40 and ≥40 years old, there was a significant difference between the groups (Table 1), with AFC group E having the highest percentage of advanced aged patients and consequently a higher proportion of Bologna criteria women ($p < 0.001$) (Table 1). Over half of the total cycles in AFC group E patients (54.1%) were from those aged ≥40 years (Table 1).

Both the LBR per IVF-ET and LBR per pregnancy were significantly lower in the AFC groups D & E ($p < 0.001$) (Table 2). A similar trend was observed for PLR per pregnancy, yet the PLR per IVF-ET was not significantly different among AFC groups (Table 2). In relation to the influence of age, both the LBR per IVF-ET and LBR per pregnancy were significantly lower for older women ($p < 0.0001$) (Table 3) as expected, while the PLR per pregnancy increased with advancing age, from 21.6% for <35 years, 32.9% for 35–39 years, 48.5% for 40–44 years and 100% for the 2 pregnancies ≥45 years ($p < 0.001$) (Table 3). A similar trend for PLR was observed per IVF-ET (Table 3).

When the impact of IVF attempt number was investigated, the LBR per IVF-ET cycle within AFC group E patients showed no significant difference from the first IVF-ET cycle (12.6%) for up to and including ≥4 cycles (13.6%) ($p > 0.05$) (Table 4). The same trend occurred in AFC groups A and D (Table 4). Conversely, patients belonging to AFC group B/C combined, showed a significant difference in LBR per IVF-ET cycle for increasing number of IVF attempts, being lowest at cycle number 3 (13.6%), but rising to 17.1% at ≥4 cycles (Table 4). Furthermore, the CLBR per woman was highest in AFC group A with a total of 45.4% following ≥4 cycles, with a decreasing trend observed according to AFC grouping. However, although those in AFC group E had the lowest CLBR per woman of 9.2% in the first cycle, this was not significantly different from the CLBR in subsequent cycles, and peaked after ≥4 cycles with an acceptable rate of 18.4% (Table 4).

The clinical outcomes of multiple IVF cycles in patients with specific Bologna criteria parameters including advanced maternal age (≥40 years), those with poor ovarian response (≤3 oocytes retrieved at TVOA) and those with low AFC (group E) was investigated (Table 5). The LBR per cycle for each IVF attempt (1, 2, 3, ≥4) was not significantly different for each individual Bologna parameter analysed (i.e. advanced age, previous POR or low AFC group E). However, it was at the lowest for IVF-ET cycle number 3 and 4 (4.5 and 6.1%, respectively) for women who were 40 years or more (Table 5). Interestingly, across the three Bologna parameters and focusing on 4 or more IVF-ET attempts, the CLBR per woman was lowest for older women (≥40 years) (13.6%), as compared to those with POR (14.9%) or low AFC (18.4%). However, a CLBR of 13.6% would still be deemed acceptable in this older group of patients (Table 5). Moreover, each of the CLBR doubled in the ≥4 cycles compared to their first cycle for each of the three Bologna parameters, indicating the benefit of multiple IVF attempts ≥4 (Table 5).

Finally, when the focus was shifted to AFC group E only cycles (≤4 follicles), a clear influence of age within this group was observed (Table 6). Women aged ≤35 years, had the highest first cycle LBR (29.0%), when compared to older patient groups (Table 6). Although the number of women in this group requiring additional cycles tended to decrease with increasing cycle number, the LBR for ≥4 cycles was maximum for the entire group E cohort at 80%, but with a small number of cases (n = 5). Importantly, the LBR per cycle for women aged 35–39 years and 40–44 years did not change significantly as subsequent cycle number increased, which indicated that the LBR was maintained up to and including more the 5 IVF-ET cycles. Specifically, for poor prognosis patients with a low AFC (≤4 follicles) and aged between 40 and 44, there were 2 live births from 33 ET which resulted from 4 or more IVF attempts. This LBR of 6.1% is greater than that deemed to be fitting for a very

Table 1
Demographics for IVF-ET cycles with regards to AFC category.

	A's	%	B & C	%	D	%	E	%	Total	p
Age (years)										
Mean ± SD	32.6 ± 4.4		36.0 ± 4.8		38.4 ± 4.4		39.2 ± 4.9		36.0 ± 5.2	**0.9019**[a]
Range	[22–46]		[21–47]		[23–48]		[21–51]		[21–51]	
<35	480	64.4	368	35.8	127	20.6	50	17.2		
35–39	230	30.9	396	38.6	199	32.2	83	28.6		
40–44	33	4.4	247	24.0	268	43.4	128	44.1		
≥45	2	0.3	17	1.6	24	3.9	29	10.0		
Total	745		1028		618		290			
<40	710	95.3	764	74.3	326	52.8	133	45.8		<**0.0001**[b]
≥40	35	4.7	264	25.7	292	47.3	157	54.1		
BMI										
Mean ± SD	25.1 ± 5.2		24.4 ± 4.2		24.6 ± 4.6		24.6 ± 4.8		24.7 ± 4.5	**0.9024**[a]

SD = Standard deviation.
[a] One way ANOVA.
[b] X^2 test.

Table 2
Live birth and pregnancy loss rate according to AFC category.

AFC	A's	B & C	D	E	Total	p[a]
Number of IVF-ET cycles	745	1028	618	290	2681	
NOT PREGNANT	429	688	481	233	1831	
PREGNANT	316	340	137	57	850	
• PR/IVF-ET cycle (%)	42.4	33.1	22.2	19.7	31.7	<0.0001
1. Live Birth	243	246	77	31	597	
• LBR/IVF-ET cycle (%)	32.6	23.9	12.5	10.7	22.3	<0.0001
• LBR/pregnancy (%)	76.9	72.4	56.2	54.4	70.2	<0.0001
2. Pregnancy loss	69	93	58	26	246	
• PLR/IVF-ET cycle (%)	9.3	9.0	9.4	9.0	9.2	0.9930
• PLR/pregnancy (%)	21.8	27.4	42.3	54.4	28.9	<0.0001
3. FDIU/termination	4	1	2	0	7	
• Rate/IVF-ET cycle (%)	0.5	0.1	0.3	0.0	0.3	
• Rate/pregnancy (%)	1.3	0.3	1.5	0	0.8	

PR = Pregnancy rate.
LBR = Live Birth rate.
Pregnancy loss = miscarriage + ectopic + biochemical.
PLR = Pregnancy Loss rate.
FDIU = Fetal death in utero > 20 weeks.
[a] X^2 test.

Table 3
Live birth and pregnancy loss rate according to age groups.

Age (years)	<35	35–39	40–44	≥45	Total	p[a,b]
Number of IVF-ET cycles	1025	908	676	72	2681	
NOT PREGNANT	572	616	573	70	1831	
PREGNANT	453	292	103	2	850	
• PR/IVF-ET cycle (%)	44.2	32.2	15.2	2.8	31.7	<0.0001
1. Live Birth	350	194	53	0	597	
Singleton	330	179	51	0	560	
Twin/multiple	20	15	2	0	37	
• LBR/IVF-ET cycle (%)	34.1	21.4	7.8	0	22.3	<0.0001
• LBR/pregnancy (%)	77.3	66.4	51.5	0	70.2	<0.0001
2. Pregnancy loss	98	96	50	2	246	
Miscarriages	56	56	35	1	148	
Ectopic pregnancy	8	8	1	0	17	
Biochemical	34	32	14	1	81	
• PLR/IVF-ET cycle (%)	9.6	10.6	7.4	2.8	9.2	0.0367
• PLR/pregnancy (%)	21.6	32.9	48.5	100	28.9	<0.0001
4. FDIU/termination	5	2	0	0	7	
• Rate/IVF-ET cycle (%)	0.5	0.2	0	0	0.3	
• Rate/pregnancy (%)	1.1	0.7	0	0	0.8	

PR = Pregnancy rate.
LBR = Live Birth rate.
Pregnancy loss = miscarriage + ectopic + biochemical.
PLR = Pregnancy Loss rate.
FDIU = Fetal death in utero.
[a] X^2 test.
[b] All the p values were still the same (<0.0001) even when the age group 40–44 was combined with the ≥45 group. The p value for PLR/IVF-ET cycle was 0.0327 when the two age groups combined.

Table 4
Live birth and cumulative live birth rates according to IVF-ET cycle number and AFC category.

IVF-ET Cycles		1	2	3	≥4	Total	p[a]
AFC Grade							
	Total Cycles	448	171	60	66	745	
A	Live births	152	61	17	13	243	
	LBR/cycle (%)	33.9	35.7	28.3	19.7	32.6	0.0862
Women No. = 534	Cumulative LB	152	213	230	243		
	CLBR/woman (%)	28.5	39.9	43.1	45.5		
	Total Cycles	515	242	125	146	1028	
B & C	Live births	139	63	17	25	244	
	LBR/cycle (%)	27.0	26.0	13.6	17.1	23.7	0.0025
Women No. = 630	Cumulative LB	139	202	219	244		
	CLBR/woman (%)	22.1	32.1	34.8	38.7		
	Total Cycles	232	144	88	154	618	
D	Live births	31	15	16	15	77	
	LBR/cycle (%)	13.4	10.4	18.2	9.7	12.5	0.2204
Women No. = 320	Cumulative LB	31	46	62	77		
	CLBR/woman (%)	9.7	14.4	19.4	24.1		
	Total Cycles	127	66	38	59	290	
E	Live births	16	4	3	8	31	
	LBR/cycle (%)	12.6	6.1	7.9	13.6	10.7	0.4258
Women No. = 185	Cumulative LB	17	22	25	34		
	CLBR/woman (%)	9.2	11.9	13.5	18.4		

LBR = Live Birth rate.
LB = Live Birth.
CLBR = Cumulative Live Birth rate.
[a] X^2 test.

poor prognosis patient (1–5%). However, patients aged ≥45 years did not yield any successful live births regardless of how many autologous cycles were attempted (Table 6).

4. Discussion

In 2009, Homburg and colleagues demonstrated that although the pregnancy rate significantly reduced after the third cycle attempt in women aged 20–46 years, no statistically significant decrease was observed between cycles 4–20 [27]. The pregnancy rate per cycles 7–20 remained at an acceptable 15%. They concluded that limiting the number of treatment cycles for patients who are responding to ovarian stimulation "unjustly denies" women the right to the possibility of having a child. However, in 2016, a report from China focused on those patients classified as being PORs by the Bologna criteria and drew a conclusion with an opposing view. Yang et al. reported that extremely low LBR could be anticipated following three unsuccessful cycles and it therefore may not be appropriate to suggest more IVF-ET cycles for POR patients with repetitive failure [4]. However, very little data is available to conclusively advise patients and clinicians not to proceed with additional autologous cycles beyond three attempts. The data presented in the current study adds further evidence to demonstrate that LBR can be sustained or indeed improved past four IVF attempts in poor prognosis patients. This information is important for the field not only because data is currently limited, but because the proportion of "difficult to treat" patients seeking IVF is increasing, characterized by those with advanced maternal age or those with endocrine and metabolic disorders causing premature depletion of the ovarian reserve [28].

The current study analysed the LBR as well as the CLBR, also known as PR [13], across different AFC categories and patient age groups, with a key focus on women with a low AFC of ≤4 follicles (Group E) most of which are likely to meet other poor prognosis characteristics according to the Bologna criteria [2]. Despite no significant difference in mean age or BMI for various AFC groups, the proportion of patients aged ≥40 significantly increased as AFC decreased, consistent with expectation. Intuitively, LBR per IVF-ET cycle was also reduced as AFC diminished, but those with lower counts (group D and E), had a reasonable LBR of 12.5% and 10.7%, respectively. Simultaneously, PLR significantly increased with the decreasing AFC as well as with advancing age.

More surprisingly, the LBR and CLBR improved substantially with increasing IVF-ET cycle number for the worst AFC category, group E (up to 13.6% and 18.4%, respectively for ≥4 cycles) contrary to recent publications [4]. These values were clearly better than other previous data with values ranging from 2.6–6.3% for LBR per cycle [5,10–12]. For those with advanced age (40–44 years), similar low LBR was noted in patients within AFC group E (6.1% with cycle attempts ≥4), consistent with earlier reports with a range of 4.5% to 9.7% [29–31]. Considering that those with a LB chance of between 1 and 5% are considered very poor prognosis [7,8], the data from the current study indicate that it is still worthwhile undergoing more IVF-ET cycles, especially for those patients still aged <45 years [27]. Continuing beyond cycle number three could also be the only option for couples who are against receiving

Table 5
Live birth and cumulative live birth rates according to IVF-ET cycle number for poor prognosis factors.

IVF-ET Cycles		1	2	3	≥4	Total	p[a]
	Total Cycles	127	66	38	59	290	
AFC category E	Live births	16	4	3	8	31	
	LBR/cycle (%)	12.6	6.1	7.9	13.6	10.7	0.4258
Women, n = 185	Cumulative LB	17	22	25	34		
	CLBR/woman (%)	9.2	11.9	13.5	18.4		
	Total Cycles	160	103	50	106	419	
Oocyte No.≤3 at TVOA	Live births	22	8	4	11	45	
	LBR/cycle (%)	13.8	7.8	8.0	10.4	10.7	0.4124
Women, n = 301	Cumulative LB	22	30	34	45		
	CLBR/woman (%)	7.3	9.9	11.3	14.9		
	Total Cycles	240	170	110	228	748	
Age of woman ≥40	Live births	24	10	5	14	53	
	LBR/cycle (%)	10.0	5.9	4.5	6.1	7.1	0.1800
Women, n = 391	Cumulative LB	24	34	39	53		
	CLBR/woman (%)	6.1	8.7	10.0	13.6		

LBR = Live Birth rate.
LB = Live Birth.
CLBR = Cumulative Live Birth rate.
TVOA = Transvaginal Oocyte Aspiration.
[a] X^2 test.

Table 6
Live birth and cumulative live birth rates for AFC group E patients stratified by age and IVF-ET cycle number.

No. of IVF-ET cycles		1	2	3	≥4	Total	p[a]
Age (year)							
	Total Cycles	31	10	4	5	50	
<35	Live births	9	1	1	4	15	
	LBR/cycle (%)	29.0	10.0	25.0	80.0	30.0	0.0477
	Total Cycles	43	17	12	11	83	
35–39	Live births	6	2	1	2	11	
	LBR/cycle (%)	14.0	11.8	8.3	18.2	13.3	0.9109
	Total Cycles	41	35	19	33	128	
40–44	Live births	1	1	1	2	5	
	LBR/cycle (%)	2.4	2.9	5.3	6.1	3.9	0.8401
	Total Cycles	12	4	3	10	29	
≥45	Live births	0	0	0	0	0	
	LBR/cycle (%)	0.0	0.0	0.0	0.0	0.0	

LBR = Live Birth rate.
LB = Live Birth.
CLBR = Cumulative Live Birth rate.
[a] X^2 test.

oocyte and embryo donations due to religious or cultural factors, or adamantly require genetic maternity [7]. However, the modest LBR should be taken into consideration by patients and they should be provided with clear information to understand the LBR figure realistically. For those aged ≥45 years there is strong evidence to indicate IVF-ET should not be encouraged unless patients are willing to be an oocyte or embryo donor recipient. Although for patients aged ≥43 years, there is evidence to show that transfer of more embryos may lead to acceptable LBR (7.4%) [7]. However, in Australia and New Zealand, the field is increasingly moving towards elective SETs to minimise multiplicity and pregnancy complications [32].

In our experience, women in this age range request one opportunity with stimulation of own ovarian follicles before reaching the decision to accept an oocyte or embryo donation. Oocyte and embryo donation is an effective tool in assisted reproduction, for not only women who have recovered from cancer treatment and ovarian dysfunction, but also for women of advanced reproductive age with repeated IVF cycle failures [33]. However, despite the success rates of oocyte donation, availability of donors is often limited or attitudes towards donation are negative, therefore new treatment options are required to combat these issues [34]. Studies have shown that few women are willing to donate oocytes, with ethnic differences and lack of knowledge on the matter impacting on individual's willingness to donate their reproductive material [35,36]. However, as the field of assisted reproduction advances, the LBR in older, POR patients may indeed improve and exceed the current rates. These rates are remarkably similar to those for patients in the early years of IVF, who would now be considered "best prognosis" patients [7].

The precise reasons for our equivalent or better rates in more than three IVF-ET cycles is not immediately obvious. However, our clinic's specific rFSH dosing algorithms enable optimum rFSH dosing based on AFC, with modulation by AMH and various parameters (age, BMI, smoking status) and may have an impact [16]. The algorithm successfully eliminates the estimation for the best tailored rFSH dosage for individual patients. It also ensures clinicians do not rely on previous cycles to determine the optimal dosage. In addition, approximately 75% of group E patients avail of the option to use adjuvant therapy such as growth hormone (GH) or dehydroepiandrosterone (DHEA) prior to their IVF-ET. To provide this analysis on LBR is beyond the scope of the current study. However, although LBR appear to be higher for those utilizing adjuvant therapy in group E or in groups D and E combined, there was no statistically significant difference (data not shown).

In conclusion, when financial concerns are not the deciding issue, fully informed women aged <45 years should not be deprived of the opportunity to undergo more autologous IVF attempts. Our data, in contrast to the aforementioned studies who have reported low success rates, suggests these patients have a reasonable chance of achieving a successful outcome represented by live birth, regardless of cycle number and repeat IVF cycle failure. Ultimately, future advances in technological, pharmaceutical, and nutraceutical interventions may lead to increased LBR for these POR and very poor prognosis patients. However, this is based on the fact that the assisted reproduction industry continues to treat and explore treatment options for these patients, without relying solely on egg donation as the primary treatment option [7].

Author roles

KBM, KNK and JLY conceived the idea and study design. KBM and PMH performed the data extraction and KBM performed the initial analyses. KNK, NLW and KIM provided additional data analysis. KBM, KNK and JLY prepared the first manuscript draft, which was revised by all authors.

Declaration

The authors report no financial or commercial conflicts of interest.

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