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ORIGINAL ARTICLE *Reproductive epidemiology*

Cumulative live birth rates for women returning to ART treatment for a second ART-conceived child

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STUDY QUESTION: What are the success rates for women returning to ART treatment in the hope of having a second ART-conceived child.

SUMMARY ANSWER: The cumulative live birth rate (LBR) for women returning to ART treatment was between 50.5% and 88.1% after six cycles depending on whether women commenced with a previously frozen embryo or a new ovarian stimulation cycle and the assumptions made regarding the success rates for women who dropped-out of treatment.

WHAT IS KNOWN ALREADY: Previous studies have reported the cumulative LBR for the first ART-conceived child to inform patients about their chances of success. However, most couples plan to have more than one child to complete their family and, for that reason, patients commonly return to ART treatment after the birth of their first ART-conceived child. To our knowledge, there are no published data to facilitate patient counseling and clinical decision-making regarding the success rates for these patients.

STUDY DESIGN, SIZE, DURATION: A population-based cohort study with 35 290 women who commenced autologous (using their own oocytes) ART treatment between January 2009 and December 2013 and achieved their first treatment-dependent live birth from treatment performed during this period. These women were then followed up for a further 2 years of treatment to December 2015, providing a minimum of 2 years and a maximum of 7 years of treatment follow-up.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Cycle-specific LBR and cumulative LBR were calculated for up to six complete ART cycles (one ovarian stimulation and all associated transfers). Three cumulative LBR were calculated based on the likelihood of success in women who dropped-out of treatment (conservative, optimal and inverse probability-weighted (IPW)). A multivariable logistic regression model was used to predict the chance of returning to ART treatment for a second ART-conceived child, and a discrete time logistic regression model was used to predict the chance of achieving a second ART-conceived child up to a maximum of six complete cycles. The models were adjusted for patient characteristics and previous and current treatment characteristics.

MAIN RESULTS AND THE ROLE OF CHANCE: Among the women who had their first ART-conceived live birth, 15 325 (43%) returned to treatment by December 2015. LBRs were consistently better in women who recommenced treatment with a previously frozen embryo, compared to women who underwent a new ovarian stimulation cycle. After six complete cycles, plus any surplus frozen embryos, the cumulative LBR was between 60.9% (95% CI: 60.0–61.8%) (conservative) and 88.1% (95% CI: 86.7–89.5%) (optimal) [IPW 87.2% (95% CI: 86.2–88.2%)] for women who recommenced treatment with a frozen embryo, compared to between 50.5% (95% CI: 49.0–52.0%) and 69.8% (95% CI: 67.5–72.2%) [IPW 68.1% (95% CI: 67.3–68.9%)] for those who underwent a new ovarian stimulation cycle. The adjusted odds of a second ART-conceived live birth decreased for women ≥35 years, who waited at least 3 years before returning to treatment, or who required a higher number of ovarian stimulation cycles or double embryo transfer to achieve their first child.

LIMITATIONS, REASONS FOR CAUTION: Our estimates do not fully account for a number of individual prognostic factors, including duration of infertility, BMI and ovarian reserve.

WIDER IMPLICATIONS OF THE FINDINGS: This is the first study to report success rates for women returning to ART treatment to have second ART-conceived child. These age-specific success rates can facilitate individualized counseling for the large number of patients hoping to have a second child using ART treatment.

STUDY FUNDING/COMPETING INTEREST(S): No funding was received to undertake this study. R. Paul and O. Fitzgerald have nothing to declare. D. Lieberman reports being a fertility specialist and receiving non-financial support from MSD and Merck outside the submitted work. C. Venetis reports being a fertility specialist and receiving personal fees and non-financial support from MSD, personal fees and non-financial support from Merck Serono and Beisins and non-financial support from Ferring outside the submitted work. G.M. Chambers reports being a paid employee of the University of New South Wales, Sydney (UNSW) and Director of the National Perinatal Epidemiology and Statistics Unit (NPESU), UNSW. The Fertility Society of Australia (FSA) contracts UNSW to prepare the Australian and New Zealand Assisted Reproductive Technology Database (ANZARD) annual report series and benchmarking reports.

TRIAL REGISTRATION NUMBER: NA.

Key words: ART / IVF / cumulative live birth rates / IVF success rates / IVF pregnancy rates

Introduction

Approximately 15% of couples experience infertility, affecting over 180 million people worldwide (Mascarenhas *et al.*, 2012, Inhorn and Patrizio, 2015). ART, such as IVF, has revolutionized the treatment of infertility, with more than 2 million treatment cycles performed each year and an estimated 7 million children conceived since the first ART-conceived baby was born in 1978 (Adamson *et al.*, 2018).

Because the success of ART is generally well below 50% per cycle, most patients undertake multiple cycles to achieve a live birth, and many patients discontinue treatment before having a child (Gameiro *et al.*, 2012). For this reason, cumulative live birth rates (CLBRs) per patient over successive 'complete' ART cycles, which includes the outcomes from all fresh and frozen/thaw (cryopreserved) embryo transfers following an episode of ovarian stimulation, are the most relevant measure of ART treatment success (Smith *et al.*, 2015, Maheshwari *et al.*, 2015). A number of studies have reported the CLBR for the first live born baby to inform patients about their chances of success (Malizia *et al.*, 2009, Smith *et al.*, 2015, McLernon *et al.*, 2016, Chambers *et al.*, 2017). However, most couples plan to have more than one child to complete their family (Commonwealth of Australia, 2017), and for that reason, patients commonly return to ART treatment after the birth of their first ART-conceived child. To our knowledge, there are no published data to facilitate patient counseling and clinical decision-making regarding ART success rates for these patients.

The aims of this study were to identify factors associated with returning to ART treatment for a second ART-conceived child and to calculate the cycle-specific LBR and CLBR for up to six ART cycles for these women.

Materials and Methods

Study population

Data were extracted from the Australian and New Zealand Assisted Reproduction Database (ANZARD) for ART cycles performed in the 90 Australian and New Zealand clinics between January 2009 and December 2015. Fertility clinics in these countries must report all cycles to ANZARD as part of their licensing agreements, and therefore complete registration is assumed (Fitzgerald *et al.*, 2018).

The study cohort comprised 35 290 women who commenced autologous (using their own oocytes) ART treatment between January 2009 and December 2013 and achieved their first treatment-dependent live birth from treatment performed during this period. These women were then followed up for a further 2 years of treatment to December 2015, providing a minimum of 2 years and a maximum of 7 years of treatment follow-up. Live births up to October 2016 were included. Records of all frozen embryo transfers were linked to the associated episode of ovarian stimulation for each woman. This allowed each complete treatment cycle to be identified and the reproductive outcomes to be measured. The exclusion criteria included ART treatment using donated oocytes/embryos and treatment for the purpose of long-term egg/embryo storage only. A live birth was defined as the birth of at least one live infant of at least 20 weeks gestation or a minimum of 400 grams birthweight.

Analysis

Factors associated with returning to treatment

The demographic and treatment characteristics of women who returned to ART treatment for a subsequent child versus those who did not were compared. Demographic characteristics included age of women at first live birth, parity (number of pregnancies >20 weeks), infertility diagnosis and year of first ART-conceived live birth. The treatment characteristics of the cycle that resulted in the first live birth included number of previous complete cycles, number of oocytes collected, type of treatment (IVF or ICSI), number and stage of embryo transfer and type of embryo transfer (fresh or frozen). A complete cycle was defined as all fresh and frozen embryo transfer cycles resulting from a single ovarian stimulation.

Multivariable logistic regression models were used to identify factors independently associated with returning to ART treatment for a second baby. The variables that were significant with $P < 0.20$ in the bivariate analysis were selected to be included in the initial multivariable logistic regression model, followed by the backward selection process, which determined the variables with $P < 0.05$ for the final model (Hosmer and Lemeshow, 2000, Afifi *et al.*, 2011). The C-index was used to assess the goodness of fit of the models in predicting the chance of returning to ART treatment for a second baby (Hosmer *et al.*, 2013).

Cycle-specific LBR and CLBR for women who returned for treatment

Women who returned to ART treatment after their first live birth can recommence treatment using either surplus frozen embryos from the previous cycle or by starting a new ovarian stimulation ART cycle. Therefore, the CLBR for these two different populations were calculated to provide estimates for presenting cohorts of women. For each of these cohorts, three estimates of CLBR in up to six complete cycles were calculated based on differing assumptions about the prognosis of women who discontinued ART treatment, that is, who dropped-out of treatment without achieving a second ART-conceived child.

The conservative CLBR assumed that the women who discontinued treatment would have a zero probability of achieving a live birth if they had continued with treatment. For each successive complete cycle, the CLBR was calculated by dividing the number of women who achieved a second ART-conceived live birth up to and including that cycle by the total number of women who ever attempted ART treatment for a second ART-conceived baby. The 95% CIs of cycle-specific and conservative CLBR was calculated using standard errors from the binomial distribution.

The optimal CLBR were calculated by assuming that women who discontinued treatment would have had the same chance of a live birth in a particular cycle as those who continued. The Kaplan–Meier method was used with 95% CIs calculated using standard errors calculated by Greenwood's method (Kaplan and Meier, 1958).

Because the conservative and optimal estimates could be considered to provide an over pessimistic and over optimistic range of CLBR estimates, an inverse probability-weighted (IPW) approach was also used to account for the chance of continuing treatment based on the characteristics of women who continued or discontinued treatment (Modest *et al.*, 2018). Using this approach, a woman is assigned a higher weight if her characteristics are similar to women who do not return for treatment. Conversely, a woman is assigned a lower weight if her characteristics are similar to the women who continue treatment until a live birth is achieved. The time-variant covariates used to assign the weights included in the denominator were age of women, number of oocytes collected, any cycle cancellation and any pregnancy loss within a complete cycle. The time-invariant covariates included in the denominator and numerator were types of infertility in the initial attempt for the second baby through ART, parity at the time of initiating ART treatment, year of initiating ART treatment for the second baby, age of woman at the first birth, number of complete cycles to achieve the first birth and number of oocytes collected at the cycle that resulted in the first birth. The estimated IPWs were then used in the Kaplan–Meier method to estimate the CLBR corrected for women who discontinued treatment. For all analysis, women who achieved a second ART-conceived live birth through ART were not included in further analysis.

Factors predicting a live birth

We used a discrete time logistic regression model to predict the chance of a second ART-conceived live birth after a maximum of six complete cycles. We developed one model for the women who initiated for the subsequent baby with cryopreserved embryos and another one for the women who initiated for the subsequent baby with fresh embryos from a new ovarian stimulation cycle. Women remained in the cohorts in which they were assigned. We treated the complete cycle number as the time variable while predicting the chance of a subsequent live birth in a specific cycle conditional on no birth having occurred in the previous cycles.

We initially fitted univariable models with the following characteristics: female age and cause of infertility at the initial attempt for a second ART-conceived child, period of time between the first ART-conceived live birth and the initial attempt for the second ART-conceived live birth, parity and treatment characteristics at the time of initiating ART treatment for the first ART-conceived live birth. Among the available treatment characteristics at the first ART-conceived live birth, we considered the number of complete cycles to achieve the first ART-conceived live birth, number of oocytes retrieved, type of treatment (IVF or ICSI), type of embryo transfer (fresh or frozen), number of embryos transferred and stage of embryo transfer. Variables that were significantly associated with live birth ($P < 0.05$) in the univariable models were selected to be included in the discrete time logistic regression models, using a manual backward selection process to select the variables with $P < 0.05$ for inclusion in the final models. We used the C-index to assess the goodness of fit of the model in predicting the chance of a subsequent ART-conceived baby (Hosmer and Lemeshow, 2000). Analyses were conducted in StataCorp. 2015 Stata Statistical Software: Release 14 (StataCorp LP, College Station, TX, USA).

Ethical approval for the study was obtained from the UNSW Human Research Ethics Advisory Panel (reference, GHC16983).

Results

Just over 43% (15 325) of the 35 290 women who had their first ART-conceived live birth during 2009–2013 returned to treatment by December 2015. One in four women (24%) who returned to treatment did so within 1 year, 79% within 2 years and 95% within 3 years of the first baby. Of the 15 325 women who returned to ART treatment, the median age was 36 years (IQR: 32–38 years) at the initiation of ART treatment for the second child. About three-quarters of the women (73%) recommenced treatment using a surplus frozen embryo from the cycle that resulted in their first ART-conceived live birth. Women who returned to treatment underwent an average of 0.7 fresh embryo transfers (LBR per embryo transfer: 25.9%) and 1.4 frozen embryo transfers (LBR per embryo transfer: 27.8%). Single embryo transfers accounted for 74% of fresh cycles and 92% of frozen embryo transfers. The demographics of the women at the time of the initial attempt for an ART-conceived second baby and overall treatment characteristics of the 38 102 cycles undertaken over the 7-year study period are presented in Supplementary Table SI.

Factors associated with returning to ART treatment for a subsequent child

The demographic and treatment characteristics of the 35 290 women who achieved their first ART-conceived baby are described in Table I, stratified by whether or not they returned to treatment. After adjusting for covariates, women who returned to ART treatment were more likely to be younger (compared to women aged <30 years; adjusted odds ratio (aOR) = 0.78 for age group 35–39 years; aOR = 0.56 for age group 40–44 years) were more likely to have been nulliparous at the time of their first ART-conceived child (compared to nulliparous women: aOR = 0.39 for parous women), to have a higher number of oocytes retrieved in the cycle that achieved the first live birth, to have used ICSI rather than IVF, to have transferred a fresh rather than frozen embryo and to have conceived the first live birth after the transfer of a single blastocyst. Interestingly, women who took more than one complete ART cycle to achieve their first live birth were more likely to return to ART treatment for a subsequent child (three versus one complete cycle: aOR 1.20, 95% CI 1.10–1.31).

Table I Demographic and treatment characteristics of women who conceived their first ART-conceived child following ART treatment performed in 2009–2013, Australia and New Zealand.[†]

Characteristics	Returned to ART treatment for second ART-conceived child (women = 15 325)	%	Had not yet returned to ART treatment for second ART-conceived child (women = 19 965)	%	Adjusted odds ratio (95%CI lower + 95%CI upper)[¥]
Female age at first ART-conceived live birth (years); *median (IQR)*	*33 (30–36)*		*34 (31–37)*		
<30	3075	20.1	3219	16.1	Ref
30–34	6339	41.4	7244	36.3	0.95 (0.90-1.01)
35–39	4911	32.0	7312	36.6	0.78 (0.73-0.83)
40–44	993	6.5	2165	10.8	0.56 (0.51-0.62)
>44	7	0.0	25	0.1	0.42 (0.81-1.01)
Parity at the time of initiating ART treatment for first ART-conceived live birth					
Nulliparous	12 971	84.6	15 022	75.2	Ref
Parous	1462	9.5	4022	20.1	0.39 (0.36-0.41)
Unknown	892	5.8	921	4.6	0.99 (0.89-1.09)
Cause of infertility as diagnosed at the first ART treatment[*]					
Male-only	2608	17.0	3089	15.5	1.07 (1.00-1.14)
Female factor					
Tubal disease only[§]	614	4.0	911	4.6	
Endometriosis only	1103	7.2	1236	6.2	1.15 (1.05-1.25)
Combined tubal and endometriosis[§]	630	4.1	891	4.5	
Other female factor only[§]	2029	13.2	2840	14.2	
Combined male–female factors	3513	22.9	4132	20.7	1.10 (1.04-1.17)
Unexplained[§]	3534	23.1	4847	24.3	
Not stated[§]	1294	8.4	2019	10.1	
Year of treatment resulting in first ART-conceived live birth					
2009	2829	18.5	2842	14.2	Ref
2010	3308	21.6	3353	16.8	0.87 (0.80-0.93)
2011	3450	22.5	3609	18.1	0.82 (0.76-0.88)
2012	3348	21.8	4413	22.1	0.62 (0.58-0.97)
2013	2390	15.6	5748	28.8	0.33 (0.31-0.36)
Number of complete cycles to achieve the first ART-conceived live birth					
One	9814	64.0	12 880	64.5	Ref
Two	3304	21.6	4304	21.6	1.05 (1.00-1.12)
Three	1207	7.9	1553	7.8	1.20 (1.10-1.31)
Four or more	1000	6.5	1228	6.2	1.47 (1.33-1.62)
Oocytes collected at the cycle that resulted in the first ART-conceived live birth; *median (IQR)*	*11 (7–15)*		*10 (7–15)*		
1–4	1235	8.1	2305	11.5	0.69 (0.64-0.75)
5–9	4970	32.4	6835	34.2	0.92 (0.87-0.97)
10–14	4688	30.6	5678	28.4	Ref
15–24	3692	24.1	4342	21.7	1.03 (0.97-1.10)
>24	718	4.7	772	3.9	1.18 (1.05-1.33)
Unknown	22	0.1	33	0.2	

Continued

Table I Continued.

Characteristics	Returned to ART treatment for second ART-conceived child (women = 15 325)	%	Had not yet returned to ART treatment for second ART-conceived child (women = 19 965)	%	Adjusted odds ratio (95%CI lower + 95%CI upper)[¥]
Fertilization technique that resulted the first ART-conceived live birth					
IVF	5631	36.7	8081	40.5	0.90 (0.86-0.95)
ICSI	9666	63.1	11 846	59.3	Ref
Unknown	28	0.2	38	0.2	
Number and stage of embryo(s) transferred in the cycle that resulted in the first ART-conceived live birth					
Single cleavage	3357	21.9	4461	22.3	0.87 (0.82-0.92)
Single blastocyst	9034	58.9	10 797	54.1	Ref
Multiple cleavage	1621	10.6	2595	13.0	0.71 (0.66-0.76)
Multiple blastocyst	1313	8.6	2112	10.6	0.69 (0.63-0.74)
First live birth from frozen embryo transfer					
No	10 764	70.2	13 633	68.3	Ref
Yes	4561	29.8	6332	31.7	0.88 (0.83-0.92)

[†]Women who conceived their first ART-conceived live birth following ART treatment performed in 2009–2013, and treatment follow-up until 31 December 2015.
*The reference category for cause of infertility was 'not present', e.g. for male-only infertility, the reference category equated to 'male infertility not present'.
[¥]The backward selection process was used to determine the variables (with $P < 0.05$) included in the final model.
C index of the model = 0.65 (95% CI: 0.64–0.66)
[§]Variables that were excluded from the final model with the backward selection process.
IQR: interquartile range

Cycle-specific LBR and CLBR for second ART-conceived live birth

Table II presents the cycle-specific LBR and CLBR (conservative, optimal and IPW estimates) for the 15 325 women who returned to ART treatment, stratified by whether treatment recommenced with a fresh (4129) or frozen embryo (11 196).

The cycle-specific LBR in the first cycle that used surplus frozen embryos from the stimulation cycle that resulted in the first live birth was 43.4%, compared to 31.3% from a complete cycle that commenced with an ovarian stimulation cycle. The improved cycle-specific LBR and CLBR achieved with cycles that started with a frozen embryo were seen until at least the sixth complete cycle. For example, the CLBR was between 60.1% (conservative) and 81.4% (optimal) (IPW estimate 79.9%) after the third complete cycle, compared to 47.1% and 56.4% (IPW estimate 53.7%) for those who recommenced treatment with a new stimulation cycle.

The age-specific CLBR for the cohorts recommencing treatment using a frozen embryo or a new ovarian stimulation cycle are presented in Supplementary Tables SII and SIII and Supplementary Figs SI and SII, noting that cycles of less than 50 women were excluded due to unreliable estimates. Among women aged <30 years who returned to treatment for a second ART-conceived child, the live birth success rates were similar for those who recommenced treatment with either a fresh or frozen cycle. However, for older women recommencing treatment, the LBR for women who recommenced treatment with a frozen embryo were consistently better than for those who commenced with a new stimulated cycle.

Factors associated with a second ART-conceived live birth

The patient and treatment factors positively associated with achieving a second ART-conceived live birth included younger female age at the recommencement of ART treatment, commencing with a frozen embryo, having male-factor only infertility, requiring only one complete cycle to achieve the first live birth and achieving their first live birth with a single blastocyst transfer (Table III). Compared to women aged <30 years, the adjusted odds of a second ART-conceived live birth for women aged 35–39 years decreased by 22% among women who recommenced treatment with a frozen embryo (OR: 0.78; 95% CI: 0.70–0.88) and by 50% among women who recommenced treatment with a fresh embryo (OR: 0.50; 95% CI: 0.38–0.64). The C-index of the model was 0.65 (95% CI: 0.64–0.66) for predicting live birth for women who recommenced treatment using surplus frozen embryos and was 0.72 (95% CI: 0.70–0.73) for women who recommenced treatment with a new ovarian stimulation cycle, similar to other ART prediction models (Nelson and Lawlor, 2011, McLernon *et al.*, 2016).

Discussion

Most couples desire more than one child to complete their family, for example Australian women aged 20 years on average intend to have 2.0–2.1 children (Commonwealth of Australia, 2017), and a significant proportion of couples who need ART treatment to achieve the birth of their first child are likely to return to treatment (Malchau *et al.*, 2017). This is the first report to describe the characteristics of women who

Table II Cycle-specific live birth rates and cumulative live birth rates for women who returned to ART treatment for a second ART-conceived child, Australia and New Zealand.[†]

Complete cycle number	Number of women starting cycle	Number of live births	Live birth rate			
			Cycle-specific (95% CI)	Cumulative Conservative (95% CI)	Cumulative Optimistic (95% CI)	Cumulative IPW (95% CI)
Women who initiated treatment with a frozen embryo						
Remaining frozen*	11 196	4863	43.4% (42.2–44.7)	43.4% (42.5–44.4)	43.4% (42.5–44.4)	43.0% (42.3–43.7)
1¥	3418	1324	38.7% (36.7–40.9)	55.3% (54.3–56.2)	65.3% (64.3–66.4)	62.7% (61.9–63.6)
2	1317	396	30.1% (27.3–33.2)	58.8% (57.9–59.7)	75.8% (74.6–76.9)	74.1% (73.2–75.0)
3	632	148	23.4% (19.9–27.5)	60.1% (59.2–61.0)	81.4% (80.3–82.6)	79.9% (78.9–80.8)
4	313	55	17.6% (13.5–22.9)	60.6% (59.7–61.5)	84.7% (83.4–85.9)	83.3% (82.3–84.2)
5	189	23	12.2% (8.1–18.3)	60.8% (59.9–61.7)	86.6% (85.2–87.9)	84.9% (83.9–85.9)
6	104	12	11.5% (6.6–20.3)	60.9% (60.0–61.8)	88.1% (86.7–89.5)	87.2% (86.2–88.2)
Women who initiated treatment with a new ovarian stimulation cycle						
1¥	4129	1292	31.3% (29.6–33.0)	31.3% (29.9–32.7)	31.3% (29.9–32.7)	28.9% (28.4–29.5)
2	2022	450	22.3% (20.3–24.4)	42.2% (40.7–43.7)	46.6% (44.9–48.3)	43.9% (43.2–44.5)
3	1093	201	18.4% (16.0–21.1)	47.1% (45.5–48.6)	56.4% (54.6–58.2)	53.7% (53.0–54.4)
4	597	80	13.4% (10.8–16.7)	49.0% (47.5–50.5)	62.3% (60.3–64.2)	60.4% (59.7–61.2)
5	348	41	11.8% (8.7–16.0)	50.0% (48.4–51.5)	66.7% (64.5–68.9)	64.4% (63.7–65.1)
6	223	21	9.4% (6.1–14.4)	50.5% (49.0–52.0)	69.8% (67.5–72.2)	68.1% (67.3–68.9)

[†]Women who conceived their first ART-conceived live birth following ART treatment performed in 2009–2013, and treatment followed up until 31 December 2015.
*Cycle that initiated with frozen embryo/s created in the cycle that resulted in the first ART-conceived live birth.
¥Cycles 1–6 are complete cycles defined as all embryo transfers associated with an ovarian stimulation.
IPW: inverse probability-weighted

do and do not return to ART treatment after their first ART-conceived child and the chances of having a second ART-conceived baby for those women who do return.

The perspective of a complete cycle, which links all fresh and frozen embryo transfers to the associated ovarian stimulation, allows cycle-specific LBR and CLBR to be calculated. The cycle-specific rates inform patients about their chances of a live birth from one course of ovarian stimulation followed by all embryo transfers, while the CLBR informs patients about their chances of a live birth after a given number of repeated ovarian stimulation cycles.

In our study of 35 290 women who had their first ART-conceived live birth from treatment performed between 2009 and 2013, 43% returned to ART treatment in the hope of achieving a second ART-conceived child. Women who were nulliparous at the time of their first ART-conceived child and younger women were more likely to return, as were women who needed three or more complete cycles to achieve their first live birth, to have used a fresh embryo to achieve their first live birth and to have conceived using a single blastocyst.

In line with the relatively good prognosis of patients returning to treatment with surplus frozen embryos, the success rates for these patients were relatively high compared to the overall CLBR reported in Australia (Chambers *et al.*, 2017). The LBR in the first complete cycle for the 15 325 patients who recommenced treatment was 43.4% in those who used a frozen embryo from their previous treatment and 31.3% in women who recommenced a new stimulation cycle. For those who recommenced treatment with a frozen cycle, the CLBR for up to six complete cycles, plus any surplus embryos, over the 2 to 7-year follow-up period was between 60.9% and 88.1%. For those who recommenced treatment with a new stimulated cycle, the CLBR rate for up to six complete cycles was between 50.5% and 69.8%. The overall CLBR to the first ART-conceived live birth for women who undertook ART treatment in Australia during a similar time period but

Table III Association between patient and treatment characteristics and having a second ART-conceived child, Australia and New Zealand.[†]

Characteristics	Women started with frozen embryo/s[*] (N = 11 196)	Women started with a new ovarian stimulation cycle (N = 4129)
	Adjusted odds ratio (95%CI lower + 95%CI upper)[¥]	Adjusted odds ratio (95%CI lower + 95%CI upper)[¥]
No. of complete cycles attempted to achieve a second ART-conceived live birth		
Remaining frozen[*]	1.15 (1.06-1.24)	
1	**Ref**	**Ref**
2	0.74 (0.64-0.85)	0.74 (0.60-0.91)
3	0.56 (0.46-0.69)	0.67 (0.48-0.94)
4	0.41 (0.30-0.56)	0.52 (0.33-0.82)
5	0.28 (0.18-0.44)	0.50 (0.28-0.88)
6	0.29 (0.16-0.54)	0.42 (0.21-0.83)
Women's age in years at initial attempt for second ART-conceived live birth		
<30	**Ref**	**Ref**
30–34	1.03 (0.92-1.16)	0.80 (0.63-1.01)
35–39	0.78 (0.70-0.88)	0.50 (0.38-0.94)
40–44	0.43 (0.37-0.49)	0.13 (0.09-0.20)
>44	0.13 (0.05-0.34)	0.03 (0.01-0.12)
Cause of male-only infertility as diagnosed at the initial attempt for a second ART-conceived live birth		
No	**Ref**	**Ref**
Yes	1.12 (1.03-1.22)	1.20 (1.04-1.38)
Period of time (in years) between the first live birth and initial attempt for second ART-conceived live birth		
<1 year	1.01 (0.94-1.09)	1.09 (0.95-1.25)
≥1 year but <2 years	**Ref**	**Ref**
≥2 years but <3 years	1.01 (0.91-1.11)	0.88 (0.74-1.04)
≥3 years	0.71 (0.60-0.84)	0.79 (0.59-1.06)
Treatment characteristics at first ART-conceived live birth		
Number of complete cycles to achieve the first ART-conceived live birth		
One	**Ref**	**Ref**
Two	0.85 (0.79-0.92)	0.82 (0.71-0.95)
Three	0.81 (0.71-0.92)	0.77 (0.63-0.94)
Four or more	0.78 (0.67-0.92)	0.58 (0.47-0.73)
Oocytes collected at the cycle that resulted the first ART-conceived live birth		
1–4	0.58 (0.49-0.69)	0.77 (0.63-0.93)
5–9	0.80 (0.74-0.87)	0.95 (0.83-1.10)
10–14	**Ref**	**Ref**
15–24	1.23 (1.13-1.33)	1.23 (1.02-1.49)
> 24	1.29 (1.11-1.50)	1.68 10.06-2.67)
Unknown	1.51 (0.65-3.48)	-

Continued

Table III Continued.

Characteristics	Women started with frozen embryo/s* (N = 11 196)	Women started with a new ovarian stimulation cycle (N = 4129)
	Adjusted odds ratio (95%CI lower + 95%CI upper)¥	Adjusted odds ratio (95%CI lower + 95%CI upper)¥
Number and stage of embryos transfer at the cycle that resulted the first ART-conceived live birth		
Single cleavage	0.70 (0.65-0.76)	0.82 (0.70-0.95)
Single blastocyst	**Ref**	**Ref**
Multiple cleavage	0.60 (0.53-0.68)	0.82 (0.69-0.97)
Multiple blastocyst	0.64 (0.56-0.73)	0.96 (0.81-1.15)

†Women who conceived their first ART-conceived live birth following ART treatment performed in 2009–2013, and treatment follow-up until 31 December 2015.
*Cycle that initiated with the frozen embryos created in the cycle that resulted in the first ART-conceived live birth.
¥The backward selection process was used to determine the variables (with $P < 0.05$) included in the final model. C index of the model was 0.65 (95% CI: 0.64–0.66) for women who started with frozen embryo/s and was 0.72 (95% CI: 0.70–0.73) for women who started with fresh embryo/s from a new ovarian stimulation cycle.

with a maximum of 6 years follow-up was between 53.9% and 73.1% (conservative and optimal estimates, respectively) (Chambers *et al.*, 2017). Although cycle-specific rates declined with successive cycles, the CLBR increased for all age groups up to six cycles. For example, for women with surplus frozen embryos, after three complete cycles, plus the transfer of frozen embryos, the conservative and optimal rates reached 68% and 90% for women aged <35 years, 59.7% and 79.8% for women aged 35–40 years and 38.4% and 54.8% for women aged 40–44 years, respectively. The CLBR for women who recommenced treatment with a new stimulation cycle were substantially less, but still one in two women aged 35–39 years (49.2–59.4%) and one in five women aged 40–44 years (19.9–24.8%) had a second ART-conceived live birth over the 2 to 7-year follow-up period. A lack of excess embryos in storage, older female age, if more than two embryo transfers were needed to achieve the first live birth and if other than a single blastocyst resulted in the first live birth, were all indications of a poorer prognosis for achieving a second child through ART.

The higher CLBR in the women who were able to use stored frozen embryos from the cycle that resulted in their first birth reflects the overall better prognosis for this group; that is, there was a higher chance of excess embryos for cryopreservation because of a higher number of oocytes retrieved and fewer embryo transfer cycles were needed to achieve the first live birth. Furthermore, women who use stored embryos have a biological advantage over those that started a new stimulated cycle, because embryos were frozen on average 1.5 years earlier than when they are used for the attempt to have the second ART-conceived child. The success of ART is highly dependent on the woman's biological age, with inferior outcomes after the mid-30s (Fitzgerald *et al.*, 2018). With 59% of women returning to treatment aged over 35 years, this is likely to have conferred a significant advantage on women who had stored embryos.

This report provides important information for counselling patients about their chances of achieving a second ART-conceived baby. However, a limitation of our study is that our estimates are based on population estimates and do not fully account for individual prognostic factors that affect a woman's chance of ART success, including duration of infertility, BMI and ovarian reserve. When and whether ART treatment should be recommenced or continued should ultimately be a decision for the fertility clinician and the patient, taking into account all medical and non-medical factors. Furthermore, it is likely that some women would have a natural conception after an ART-conceived child and thus have no desire to return to treatment. Although these natural conceptions are not recorded in the ANZARD, our live birth estimates reflect women who returned to treatment hoping for second ART-conceived child and thus are very relevant for counselling patients who desire another child (ElMokhallalati *et al.*, 2019). These estimates are based on patients undergoing treatment in Australia. Unlike most other countries, Australia has supportive funding for ART treatment through its universal health insurance scheme, Medicare, with no restrictions on reimbursement based on female age, number of ART cycles undertaken, number of previous children or factors such as BMI and smoking. Medicare reimburses ~60% of the AUD 10 000 (USD 7000) cost of an ART cycle, with patients required to pay the balance as an out-of-pocket expense (Chambers *et al.*, 2014). Largely because of the supportive funding environment, Australia has one of the highest ART utilisation rates in the world (Adamson *et al.*, 2018). While this may reduce the generalizability of the results to other countries with more restrictive access, the data provide unique insights into success rates among all patient groups, particularly women over 40 years who are usually not eligible for government or third-party funding. Indeed, in women aged 40–44 years the results were very reassuring: the conservative and optimal CLBR were 38.4% and 54.8%, respectively, after three complete cycles (plus surplus embryos) in women who commenced with a frozen embryo and 19.9% and 24.8%, respectively, in women who in commenced with a new ovarian stimulation cycle.

Conclusion

This study provides cycle-specific LBR and CLBR for women returning to ART treatment after their first ART-conceived child. These age-specific optimal and conservative success rates can facilitate individualized counselling for the large number of patients hoping to achieve a second ART-conceived child.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Authors' roles

R. Paul conceived research question, assisted with study design and interpretation, undertook analysis and edited the manuscript. O. Fitzgerald assisted with study design and interpretation, analysis and edited the manuscript. D. Lieberman assisted with study design and interpretation and edited the manuscript. C. Venetis assisted with study design and interpretation and edited the manuscript. G.M. Chambers assisted with study design, interpretation and drafted and finalised the manuscript.

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Conflict of interest

R. Paul and O. Fitzgerald have nothing to declare. D. Lieberman reports being a fertility specialist and receiving non-financial support from MSD and Merck outside the submitted work. C. Venetis reports being a fertility specialist and receiving personal fees and non-financial support from MSD, personal fees and non-financial support from Merck Serono and Beisins and non-financial support from Ferring outside the submitted work. G.M. Chambers reports being a paid employee of the University of New South Wales, Sydney (UNSW) and Director of the National Perinatal Epidemiology and Statistics Unit (NPESU), UNSW. The Fertility Society of Australia (FSA) contracts UNSW to prepare the Australian and New Zealand Assisted Reproductive Technology Database (ANZARD) annual report series and benchmarking reports.

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