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ARTICLE

Evolution of cumulative live birth and dropout rates over six complete IVF/ICSI cycles: a large prospective cohort study

BIOGRAPHY

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KEY MESSAGE

Cumulative live birth rates over six complete IVF and intracytoplasmic sperm injection cycles increased, and cumulative multiple live birth rates decreased, when the period 2014–2017 was compared with 2009–2012. Dropout rates, however, remained high and increased after cycle one and two; this warrants further attention.

ABSTRACT

Research question: How do cumulative live birth rates (CLBR), cumulative multiple live birth rates (CMLBR) and dropout rates over six IVF and intracytoplasmic sperm injection (ICSI) cycles change over time?

Design: Prospective longitudinal cohort (n = 16,073 patients; 48,946 cycles) starting a first fresh assisted reproductive technology cycle between 1 January 2014 and 31 December 2016, with follow-up until 31 December 2017. Outcomes between the periods 2014–2017 and 2009–2012 were compared.

Results: Conservative estimates of CLBR after six complete cycles were significantly higher in women younger than 35 years after every cycle: one to three, adjusted P-value [p adj] < 0.0001; four, p = 0.01; five, p adj = 0.03; six, p adj = 0.04) and after the first cycle in women aged 35–37 years (p adj = 0.04) in 2014–2017 versus 2009–2012. For an optimal estimate, the CLBR was significantly higher after the first three cycles in women younger than 35 years (all p adj < 0.0001) and after the first cycle in women aged 35–37 years (p adj = 0.04). The CMLBR rate decreased from 5.1% ± 0.19 (SE) to 4.1% ± 0.16 for the conservative estimate and from 8.6% ±0.37 (SE) to 6.7% ± 0.30 for the optimal estimate after six complete cycles for the whole cohort. Dropout rates of complete cycles were 26.5% 29.4%, 33.4%, 38.9% and 47.3% after the first to fifth cycle, respectively. Compared with 2009–2012, the dropout rate in the current period was significantly higher for the first (P < 0.0001) and second (P = 0.0124) cycle.

Conclusion: Over six complete IVF/ICSI cycles, CLBR and dropout rates increased and multiple live birth rates decreased when 2014–2017 was compared with 2009–2012.

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KEYWORDS

Cumulative live birth rate
Cumulative multiple live birth rate
Discontinuation
Drop-out rate
IVF/ICSI

INTRODUCTION

The best parameter for comparing outcome and safety of pregnancies with multiple gestation after assisted reproductive technology (ART) is yet to be determined. Many investigators, however, agree that effectiveness and safety should be reported separately (*Braakhekke et al., 2015*; *Wilkinson et al., 2017*) rather than reporting the cumulative live birth of a healthy singleton (*Barnhart, 2014*). For a full appraisal of a patient's chance of success of an ART treatment, calculations need to be made at the patient rather than cycle level. The cumulative live birth rate (CLBR) accurately reflects the effectiveness of ART and considers patients who discontinue treatment (*De Neubourg et al., 2016*), recent advances in cryopreservation technology and an increase in the number of freeze-all cycles for different reasons (*Blockeel et al., 2019*). Safety issues associated with ART are reflected in cumulative multiple live birth rate.

The calculation of CLBRs remains challenging compared with presenting data as live birth rate per cycle; the latter is an easy way of presenting outcome provided that the denominator is clearly defined (*Wilkinson et al., 2016*). In a previous study (*De Neubourg et al., 2016*), we analysed CLBRs between 2009 and 2012 to investigate whether the reduction in the number of multiple pregnancies was at the expense of success for the patients. When CLBRs were compared with other registries and studies that showed similar low multiple gestation and live births, it seems that this was not the case. Some additional factors that could challenge comparisons of CLBRs were, however, highlighted. High dropout rates of 23.7% after the first complete cycle increasing to 27.3%, 33%, 40.8% and 46.9% % after the second to fifth complete cycles for all women younger than 43 years of age were reported (*De Neubourg et al., 2016*). This is an important finding in a healthcare system in which 90% of costs related to the IVF and intracytoplasmic sperm injection (ICSI) cycle are covered, and in which dropout rates could be calculated because the national registry enables patients to be tracked even if they transfer to other ART centres.

In the present study, the same methodology as *De Neubourg et al. (2016)* was used to compare CLBRs and dropout rates between 2014 and 2017 and 2009 and 2012, including some parameters that may influence outcomes, such as the woman's age and the number of cycles.

MATERIALS AND METHODS

Study population and data collection system

All patients aged younger than 43 years with a Belgian national insurance number who started a first fresh ART cycle between 1 January 2014 and 31 December 2016, with follow-up until 31 December 2017, were included in the analysis. First fresh ART cycle refers to cycles in which first oocytes were retrieved, irrespective of whether an embryo transfer took place; freeze-all cycles were, therefore, also included. Registration of all ART cycles, i.e. every individual cycle (oocyte retrieval or with frozen–thawed embryo transfer) by ART centres is mandatory in Belgium (*De Neubourg et al., 2013*), and consent for transmitting non-identifying data is provided by patients in the respective fertility centres. The data are transmitted to, and stored in, the National register. A unique identification number is generated by the system at the start of the IVF/ICSI or frozen–thawed cycle; this allows data to be collected prospectively for each specific cycle. The addition of a hashed version of the patients' Belgian national insurance number to a cycle makes it possible to collect data pertaining to every treatment cycle that a patient undergoes. Before data analysis, data are first quality checked and inconsistencies resolved. The registration system allows follow-up of all subsequent cycles from a patient even if they transfer to another centre. Only autologous cycles were studied. Patients were assigned to the appropriate age category at the time of their first cycle. The CLBRs were calculated per fresh non-cancelled cycle, with all frozen–thawed embryo transfer cycles attached to the fresh cycle of origin, constituting a complete cycle. The CLBR is calculated by dividing the number of live births over complete cycles by the number of patients that started a first fresh ART cycle and is expressed as a percentage. A consecutive use of cryopreserved embryos is obligatory before new embryos may be created in Belgium (*De Neubourg et al., 2013*). Up to six fresh cycles for a maximum duration of 48 months since the start of the first oocyte retrieval were analysed. Patients were excluded from the analysis if they had no Belgian insurance number, if they had undergone previous IVF/ICSI cycles (both fresh and frozen–thawed embryo transfer cycle) or had undergone pre-implantation genetic testing or in-vitro maturation. Cycles that followed a first live birth conceived through ART, and cycles that used donor oocytes or fresh cycles with a higher rank than six, were also excluded.

Outcome parameters

Live birth was defined as the birth of a baby weighing 500 g or more, or 22 weeks or more of gestation if birth weight was unknown (*Zegers-Hochchild et al., 2017*). Deliveries of a pregnancy with multiple gestation are counted as one live birth. Cycles for which the live birth status was unknown because the patient was lost-to-follow up were inputted as follows: cycles in which fetuses were still observed on a 20–25-week ultrasound scan were assumed to have developed full term, resulting in a live birth; other cycles were assumed not to have led to a live birth. For the calculation of CLBR, multiple-gestation pregnancies that led to live births were counted as one birth; cumulative multiple live births were analysed separately.

Statistical methods

Conservative estimates of CLBR assume that women who did not return for treatment would not achieve a live birth and, therefore, underestimates CLBR; optimal estimates of CLBR assume that these women would have live birth rates similar to those for women continuing treatment and, therefore, overestimate CLBR. The conservative estimate of CLBR was calculated as the number of live births up to, and including, a specific cycle, divided by the number of women who started their first ART cycle during the study period. The optimal estimate of CLBR was based on the Kaplan–Meier estimate when all cycles were included in the analysis. The standard errors for both these live birth rates were computed with the use of binomial distribution. Log-rank test was used to assess differences in CLBR between age groups. The analysis for cumulative multiple live births is conducted in the same way as a multiple live birth.

The conditional live birth rate at a specific cycle was the probability of a live birth at that cycle and was equal

to the number of live births per course of treatment divided by the number of women who received ART treatment in that cycle.

The dropout rate of a complete cycle was calculated as the number of patients who did not achieve a live birth and did not proceed to a subsequent fresh cycle divided by the number of women who did not achieve a live birth. Chi-squared test was used to compare dropout rates between periods or age categories. For all pair-wise comparisons between age categories, a Bonferroni correction for multiple testing was applied. SAS software, version 9.4 was used for all analyses. No ethical approval was required for this research question (EC/PM/NVD/2020.077).

RESULTS

Characteristics of the study population and treatment cycles

The final data set for analysis included 16,073 patients and 48,946 cycles (both fresh and frozen–thawed embryo transfer cycles) between 2014 and 2017 (FIGURE 1). Age distribution was as follows: younger than 35 years (n = 10,055 patients); between 35 years and younger than 38 years (n = 2620); between 38 years and younger than 41 years (n = 2186) and between 41 years and younger than 43 years (n = 1212). The mean age of the patients was 32.8 ± 5.07 (SD) in 2014–2017 compared with 32.2 ± 5.12 (SD) years ($P < 0.0001$) in the previous period examined.

The mean number of fresh cycles per patient until live birth was 1.67 ±1.03 (SD) and significantly lower ($P < 0.0001$) compared with 1.79 ± 1.09 (SD) for the period 2009–2012. The number of frozen–thawed embryo transfer cycles per patient until live birth was 0.71 and significantly higher ($P < 0.0001$) compared with 0.55 for the period 2009–2012. Among all patients observed during the treatment period, 90.5% underwent their ART treatments in the same fertility centre, whereas 9.2% consulted two centres and 0.4% three or four centres. Selective embryo reduction was carried out in 57 cycles (0.2% of the fresh cycles). Before the censoring of cycles after live birth, pregnancy outcome per cycle was missing in 2.8% of the 52,694 cycles. All except four of those cycles did not have data on pregnancy evolution at 20–25 weeks' gestation. They were presumed not to have achieved a live birth in the calculation of live birth estimates. The four cycles that had data available on pregnancy evolution at 20–25 weeks of gestation were inputted as having achieved a live birth.

Cumulative live birth rates

An overview of the calculation of the conditional live birth rate, the conservative and optimal estimate of CLBR for the whole cohort up to six complete cycles is presented in TABLE 1. The conservative estimate of CLBR for all ages after three and six cycles is 51.6 ± 0.39 (SE) and 55.4 ± 0.39 (SE) respectively, whereas this is 61.2 ± 0.46 (SE) and 76.8 ± 0.64 (SE) for the optimistic estimate of CLBR. The conditional live birth rate declines from 33.2% to 14.1% over six cycles.

The conservative (FIGURE 2) and optimal (FIGURE 3) estimates of CLBR after six complete cycles per age category show a decrease with increasing age for both conservative and optimal estimates. The conservative estimates of CLBR after six complete cycles are significantly higher in women aged younger than 35 years of age after every cycle: cycles one to three (Bonferroni-adjusted P-value [p adj] < 0.0001; cycle four, p = 0.01; cycle five, p adj = 0.03; cycle six, p adj = 0.04) in the period 2014–2017 compared with the period 2009–2012 and after the first cycle in women aged 35–37 years (p adj = 0.04). In the optimal estimate, the CLBR was significantly higher after the first three cycles in women aged younger than 35 years (p adj < 0.0001 for all) and after the first cycle in women aged 35–37 years (p adj = 0.04) when 2014–2017 was compared with 2009–2012.

Cumulative multiple live birth rates

Overall, the cumulative multiple live birth rate declined from 5.1% ± 0.19 (SE) to 4.1% ± 0.16 for the conservative estimate and from 8.6% ± 0.37 (SE) to 6.7% ± 0.30 for the optimal estimate after six complete cycles for the whole cohort. In patients aged younger than 35 years, a further decline in the cumulative multiple birth rate from 6.0–4.6% after six cycles was observed in the conservative estimate (FIGURE 4) and from 10.3–7.8% in the optimal estimate (FIGURE 5). In the latter approach, the decrease is statistically significant from the third cycle onwards (cycle four, p adj = 0.001; cycle five, p adj = 0.002; and cycle six, p adj = 0.006).

Dropout rates

Dropout rates of complete cycles were as high as 26.5% for patients who did not achieve a live birth after the first complete fresh cycle and increased to 29.4%, 33.4 %, 38.9% and 47.3% after the second to fifth cycle, respectively. Dropout rates calculated in a cumulative way showed that 52.6% of patients who did not achieve a live birth ceased further ART treatment after the second cycle and this was 72.3% after the third, 85.2% after the fourth and 93.3% after the fifth cycle. Compared with the period 2009–2012, the dropout rate in the current period was significantly higher for cycle one ($P < 0.0001$) and cycle two ($P = 0.0124$) but not for cycle three ($P = 0.6850$).

The dropout rate for the group aged 41–42 years was significantly higher after the first and second cycle compared with all age groups: 38–40 years ($P = 0.0005$); 35–37 years ($P = 0.0394$); and younger than 35 years ($P = 0.0063$) after the first cycle and 38–40 years ($P < 0.0001$); 36–37 years ($P < 0.0001$); and younger than 35 years ($P < 0.0001$) after the second cycle. After the third cycle, the dropout rate for the group aged 41–42 years was significantly higher than for the groups aged 38–40 years ($P = 0.0004$) and 35–37 years ($P = 0.0384$). After the fourth cycle, no significant difference between the age categories was found. The group aged younger than 35 years had significantly more dropouts than the group aged 38–40 years ($P = 0.0049$) after the fifth cycle.

DISCUSSION

Between 2014 and 2017, an increase in the mean age of patients starting their first IVF/ICSI cycle by 6 months was observed, from 32.2 years to 32.8 years compared with the period 2009–2012. A significant decrease in the mean number of IVF/ICSI cycles until live birth was observed, from 1.79 to 1.67 cycles. This is probably a result of the significant increase in the mean number of frozen–thawed embryo transfer cycles per patient until live birth from 0.55 for the period 2009–2012 to 0.71 for the period 2014–2017. When CLBR is calculated over complete cycles, however, the information on the actual number of frozen–thawed embryo transfer cycles is not always clear.

In addition, our analysis shows that the CLBR after six complete cycles

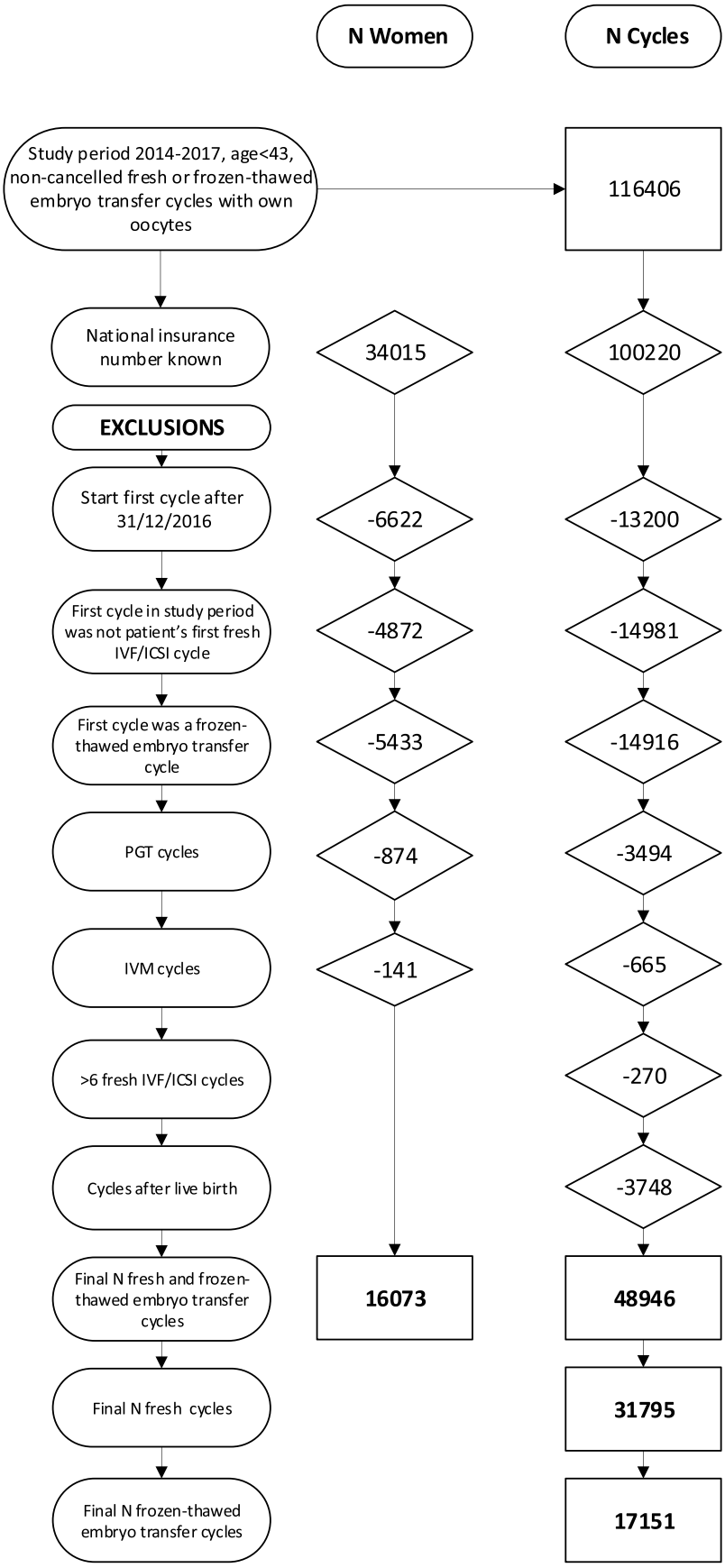

FIGURE 1 IVF and intracytoplasmic sperm injection cycles available for study before and after exclusions.

TABLE 1 CALCULATION OF CONDITIONAL LIVE BIRTH RATE, CONSERVATIVE AND OPTIMAL ESTIMATE OF CUMULATIVE LIVE BIRTH RATE FOR THE WHOLE COHORT UP TO SIX COMPLETE CYCLES (2014–2017)

Rank	Number of women	Number of live births	Conditional live birth rate, %	Conservative cumulative live birth rate, %	Standard error conservative cumulative live birth rate, %	Optimal cumulative live birth rate, %	Standard error optimal cumulative live birth rate %	Withdrawal, %
1	16073	5336	33.2	33.2	0.37	33.2	0.37	–
2	7891	2092	26.5	46.2	0.39	50.9	0.43	26.5
3	4096	862	21.0	51.6	0.39	61.2	0.46	29.4
4	2155	359	16.7	53.8	0.39	67.7	0.49	33.4
5	1097	180	16.4	54.9	0.39	73.0	0.55	38.9
6	483	68	14.1	55.4	0.39	76.8	0.64	47.3

(–) there is no withdrawal at the start of the first cycle

was significantly higher in women aged younger than 35 years after every cycle in 2014–2017 compared with 2009–2012 and after the first cycle in women aged 35–37 years as a conservative estimate, whereas, as a more optimal estimate, the CLBR was significantly higher after the first three cycles in women aged younger than 35 years and after the first cycle in women aged 35–37 years.

It is important to detect a significant increase in CLBR in younger patients, but the descriptive analysis of CLBR does not provide exploratory information. Reasons for a possible increase include changes in treatment strategies, i.e. an increase in freeze-all cycles or blastocyst transfers, or improved laboratory techniques. These may vary per cycle and per centre, making analysis difficult. The wider use of vitrification, however, is likely to have influenced this tendency (*Rienzi et al., 2017*).

Over one-quarter of patients (26.5%) who do not achieve a live birth do not embark on a second cycle and this is 29.4% and 33.4% after the second and third cycle, respectively. This is significantly higher after the first and second cycle compared with 2009–2012. Women aged 40–42 years are more affected than younger patients after the first and second cycle, as described by *Troude et al. (2014)*. These patients may have opted for oocyte donation. Although it is assumed that patients who choose not to continue treatment transfer to other fertility centres, this was only the case for 9.5% of our patients. This is much lower than the 34.8% reported by *Domar et al. (2018)*, who conducted a cross-sectional study in a private infertility centre in which only one-third of patients who discontinued treatment completed the survey. The expense of IVF treatment is an important reason for discontinuation (*Bedrick et al., 2019*); however, we can assume that, for most patients in the present analysis, this was not the case. Indeed, for all patients, 90% of the IVF/ICSI costs were covered. Cost, is not, however, the only factor influencing discontinuation. In Sweden,

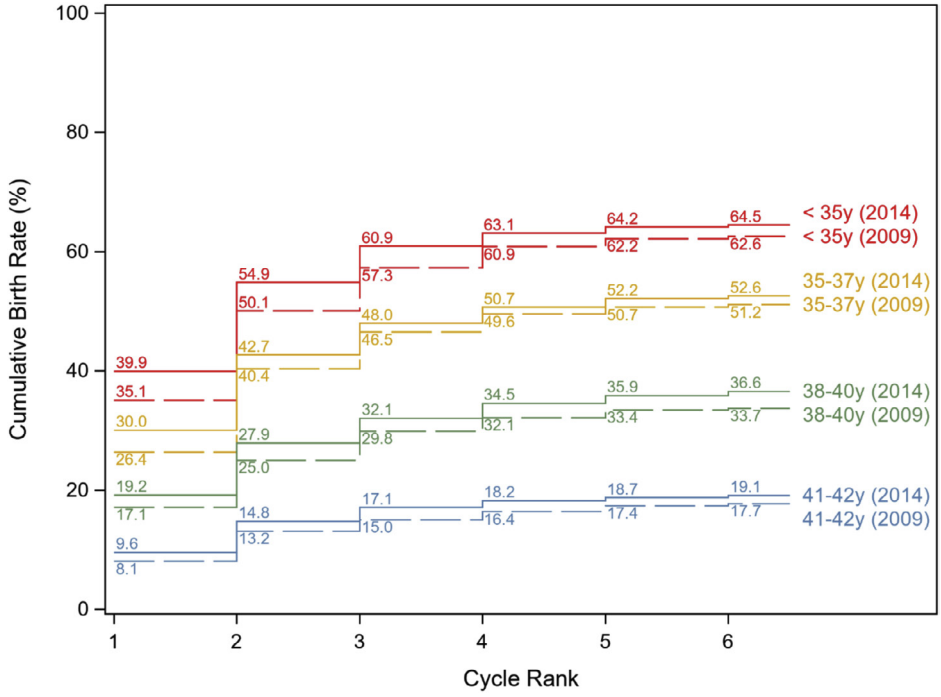

FIGURE 2 Conservative estimate of cumulative live birth rate in 2009–2012 (*De Neubourg et al., 2016*) and 2014–2017. Significant differences were found in women aged younger than 35 years of age (p adj < 0.0001 for cycles one to three; p = 0.01 for cycle four; p adj = 0.03 for cycle five; p adj = 0.04 for cycle six) and in women aged 35–37 years of age (p adj = 0.04 for cycle one).

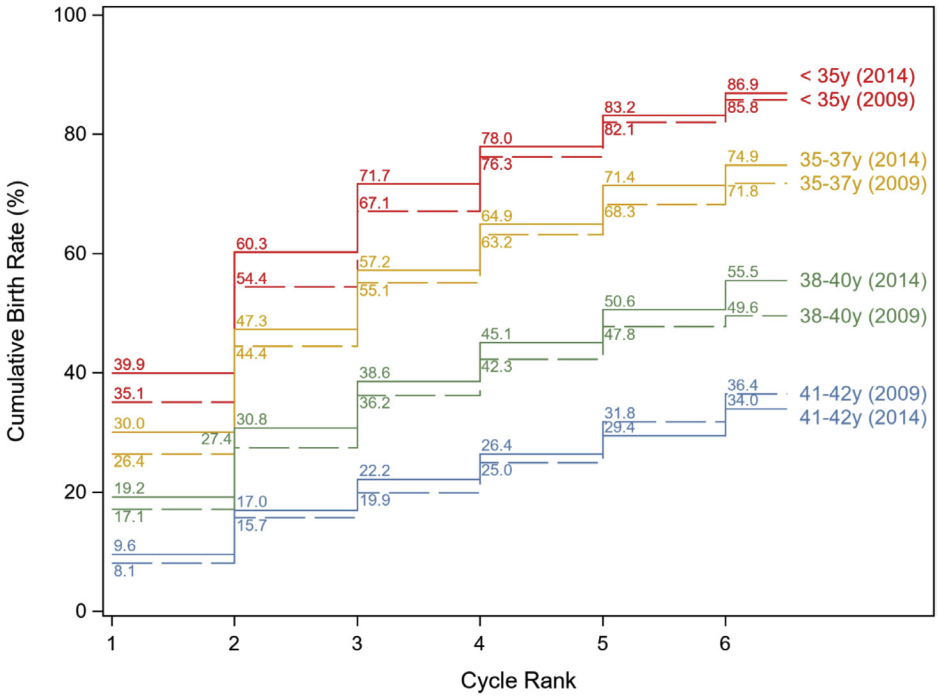

FIGURE 3 Optimal estimate of cumulative live birth rate in 2009–2012 (*De Neubourg et al., 2016*) and 2014–2017. Significant differences were found in women aged younger than 35 years of age (p adj < 0.0001 for cycles one, two and three) and in women aged 35–37 years of age (p adj = 0.04 for cycle one).

65% of couples who do not achieve a live birth do not complete the full treatment programme of three cycles (*Olivius et al., 2002*).

When calculating CLBR, no exact method is available to determine the dropout rate of patients who do not achieve a live birth, because the reasons are largely unknown. Patients can refrain from further treatment on the advice of their doctor because of poor prognosis, the psychological burden of pursuing treatment, or both. They may also experience serious relationship problems with their partner or may conceive naturally. Therefore, investigators have suggested different ways of presenting discontinuation in ART. *Gameiro et al. (2013)* has suggested that doctors should discuss treatment compliance,

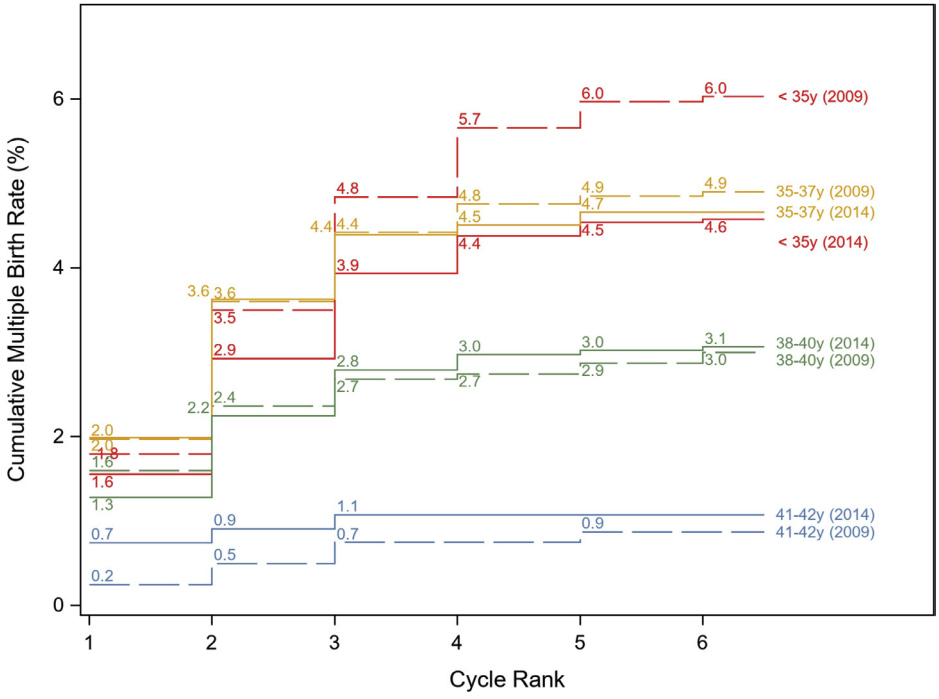

FIGURE 4 Conservative estimate of cumulative multiple live birth rate in 2009–2012 (*De Neubourg et al., 2016*) and 2014–2017.

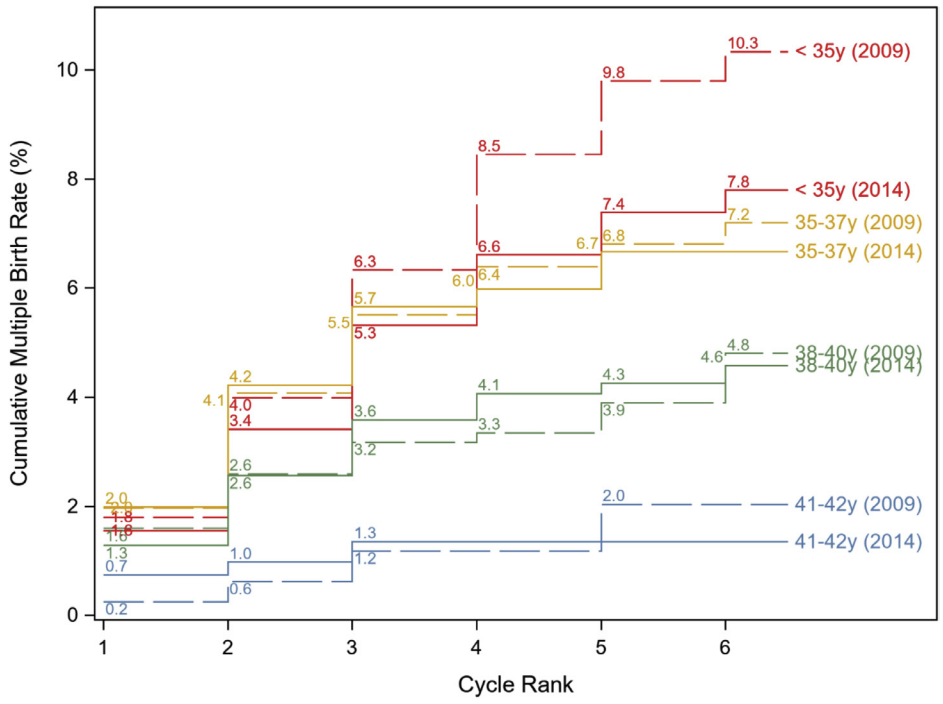

FIGURE 5 Optimal estimate of cumulative multiple live birth rate in 2009–2012 (*De Neubourg et al., 2016*) and 2014–2017. Significant differences were found in women younger than 35 years of age (cycle four, p adj = 0.001; cycle five, p adj = 0.002; and cycle six, p adj = 0.006).

treatment, discontinuation and doctor censoring with their patients. When CLBR is calculated conservatively, it will be underestimated in the younger patient population by giving them a zero chance of achieving a live birth in the next cycle and it will be overestimated in the optimal approach for older patients because their chance of having a successful next cycle will be lower than that of the population still in treatment. This was confirmed by *Modest et al. (2018)* who calculated CLBR using 'inverse probability weighting' by creating subpopulations of dropouts that had similar characteristics to patients still in treatment.

Another interesting observation is the further decline in the cumulative multiple birth rate in patients aged younger than 35 years, with a statistically significant decrease from the third cycle onwards in the optimal estimate. This is an important finding because, in this age category, mandatory single embryo transfer exists in the first two cycles only, but it is clear that single embryo transfer is increasingly being undertaken on a voluntary basis.

The strength of the present study lies in the consistency and reliability of the data in a mandatory online registration system, allowing comparisons to be made over time and patients to be followed even when transferring fertility centres. The study covers the entire Belgian population, as the social security system covers 99% of inhabitants and women can access fertility diagnosis and treatment easily. When indicated, women are permitted to undergo six complete IVF/ICSI cycles in their lifetime, with 90% of costs covered until the age of 43 years. In addition, the number of embryos transferred in relation to the age of the patient, rank of the cycle and embryo quality is restricted, with the aim of reducing the number of pregnancies of multiple gestation. Also, IVF/ICSI can only be carried out in fertility clinics licensed by the government as banks for human reproductive tissues and cells. The results of the present study will certainly apply for states or countries with a similarly organized healthcare system.

The lack of information on the occurrence of natural conceptions is a limitation of the present study. Natural conceptions have been reported to account for 17% treatment (independent live births after previous failed IVF/ICSI) in a follow-up period of 5 years (*ElMokhallalati, 2019*). *Domar et al. (2018)* reported 24.1% natural conceptions as a reason for discontinuation for at least 1 year among women completing a survey. Both studies included small cohorts, and the study by *Domar et al. (2018)* may represent an overestimation of natural conceptions.

The most important complication of IVF/ICSI, i.e. the high proportion of pregnancies with multiple gestation, first needs to be tackled; a future challenge is to reduce dropout rates among patients who choose to discontinue IVF/ICSI treatment despite a good prognosis. *Gameiro (2012)* cites reasons for patients discontinuing treatment, including patient characteristics, different aspects of the treatment and cycle, as well as characteristics of the IVF clinic. More patient-centred care is urged (*Gameiro, 2012*). Because of the burden of treatment, all initiatives to support patients throughout the IVF journey are warmly welcomed and are likely to make a bigger difference than discussing the smaller benefits of add-ons (*Harper et al., 2017*). It will be a challenge for healthcare providers in fertility centres, as well as society at large, to support these young patients and facilitate them through their treatment journey.

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