Cumulative live birth rates after one or more complete cycles of IVF: a population-based study of linked cycle data from 178,898 women

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Running title: Cumulative live birth rates following IVF

Abstract

Study question: What is the chance of a live birth following one or more linked complete cycles of IVF (including ICSI)?

Summary answer: The chance of a live birth after three complete cycles of IVF was 42.3% for treatment commencing from 1999 to 2007.

What is known already: IVF success has generally been reported on the basis of live birth rates after a single episode of treatment resulting in the transfer of a fresh embryo. This fails to capture the real chance of having a baby after a number of complete cycles – each involving the replacement of fresh as well as frozen-thawed embryos.

Study design, size and duration:

Population based observational cohort study of 178,898 women between 1992 and 2007.

Participants/materials, setting, methods:

Participants included all women who commenced IVF treatment at a licenced clinic in the UK as recorded in the Human Fertilisation and Embryology Authority national database. Exclusion criteria included women whose treatment involved donor insemination, egg donation, surrogacy, and the transfer of more than three embryos. Cumulative rates of live birth, term (>37 weeks) singleton live birth, and multiple pregnancy were estimated for two time-periods, 1992-1998 and 1999-2007. Conservative estimates assumed that women who did not return for IVF would not have the outcome of interest while optimal estimates assumed that these women would have similar outcome rates to those who continued IVF.

Main results and the role of chance:

A total of 71,551 women commenced IVF treatment during 1992–1998 and an additional 107,347 during 1999–2007. After the third complete IVF cycle (defined as three fresh IVF treatments - including replacement of any surplus frozen-thawed embryos), the conservative CLBR in women who

commenced IVF during 1992-1998 was 30.8% increasing to 42.3% during 1999-2007. The optimal CLBRs were 44.6% and 57.1% respectively. After eight complete cycles the optimal CLBR was 82.4% in the latter time period. The conservative rate for multiple pregnancy per pregnant woman fell from 31.9% during the earlier time period to 26.2% during the latter.

Limitations and reason for caution:

Linkage of all IVF treatments to individual women was conducted. However, it was not possible to identify with certainty in all cases the episode of ovarian stimulation which generated some of the frozen embryos. Cumulative live birth rates could not be calculated for women who started treatment beyond 2007 as follow up data were incomplete in some of them. Following a change in legislation in 2008, linked data were only made available for research in women who gave formal consent for this purpose.

Wider implications of the findings:

Our results demonstrate, at a national level, the chances of livebirth in couples undergoing a number of complete (fresh and frozen) IVF cycles. They reflect improvements in reproductive technology and a more conservative embryo transfer policy. Although most couples in the UK still do not receive three complete IVF cycles; assuming no barriers to continuation of IVF treatment, around 83% of women receiving IVF would achieve a live birth by the eighth complete cycle, similar to the natural live birth rate in a non-contraception practising population. Our results support the call from NICE to develop consistent IVF policies based on three complete cycles.

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Key words: Cumulative live birth rate, IVF, live birth, multiple pregnancy, time.

Introduction

Globally, the estimated prevalence of infertility is around 9% (Boivin et al. 2007), whilst in the UK, around one in six couples experience problems conceiving (Oakley et al. 2008). Most couples with prolonged unresolved infertility eventually proceed to in vitro fertilisation (defined here as IVF or ICSI) and the number of women treated in the United Kingdom (UK) has increased annually from 6184 in 1991 to 49636 in 2013 (Human Fertilisation and Embryology Authority 2008a, Human Fertilisation and Embryology Authority 2012, Human Fertilisation and Embryology Authority 2013a). Worldwide, by the end of 2013 over five million people were estimated to have been born as a result of IVF (Adamson et al. 2012), with the UK accounting for over 4% of this total (Human Fertilisation and Embryology Authority 2014).

IVF success has generally been calculated and reported on the basis of live birth rates per treatment attempt involving either an intended fresh or frozen-thawed embryo replacement (Vrtacnik et al. 2014, Elizur et al. 2006, Ke et al. 2013, Sharma et al. 2002, Abuzeid et al. 2014).

The continued improvement in reproductive technology has seen an increase in the number of frozen-thawed embryo transfers (De Mouzon et al. 2010) and their associated pregnancy rates (Roque et al. 2013). This, combined with an emphasis on reducing multiple pregnancies and increasing single embryo transfers (National Collaborating Centre for Women's and Children's Health 2013), means that outcomes per fresh embryo transfer are no longer meaningful to patients and clinicians who want to know their chance of a live birth over an entire IVF programme (Maheshwari et al. 2015). The most appropriate way of reporting this is to estimate the cumulative chances of success per woman after a number of complete cycles, - defined as all fresh and frozen-thawed embryo transfer attempts resulting from one episode of ovarian stimulation (Moragianni and Penzias 2010). The complete cycle definition allows realisation of the total reproductive potential of each single fresh cycle including the contribution of all subsequent frozen-thawed embryo transfers derived from it (Jones et al. 1997, Stern et al. 2012). Cumulative live birth rates (CLBRs) following IVF

have been reported mainly at a sub-national level (Vrtacnik et al. 2014, Ke et al. 2013, Malizia et al. 2009, Elizur et al. 2006). Although they have been reported at the national level in the United States (Stern et al. 2013, Luke et al, 2012) and Australia and New Zealand (Macaldowie et al. 2013) not all the reports have been able to generate figures for cumulative live birth after several complete IVF cycles. Until now, no studies have reported such rates for the UK (Johnson and Franklin 2013). Given the national shift towards elective single embryo transfer and freezing of surplus embryos (National Collaborating Centre for Women's and Children's Health 2013, The Multiple Births Foundation, 2015), CLBRs are increasingly proving to be the currency of IVF. As such, it is important to determine what their values are for couples embarking on IVF, and how they have changed over time with increasing uptake of embryo freezing. Additionally, since multiple pregnancy is associated with increased maternal and perinatal morbidity and mortality (Mansour et al. 2014, Sunderam et al. 2014), it is useful to explore whether changes in practice have resulted in reducing cumulative multiple pregnancy rates and increasing the numbers of healthy babies – i.e. rates of term singleton live births (Min et al. 2004).

The Human Fertilisation and Embryology Authority (HFEA) has collected data on all licensed fertility treatments in the UK since 1992. An anonymised HFEA database is freely available for research purposes and has been utilised in several studies (Human Fertilisation and Embryology Authority 2013b, Sunkara et al. 2011, Nelson and Lawlor 2011, Bhattacharya et al. 2013,). However, as it only contains data at the individual (fresh or frozen) IVF treatment level there is no way of linking one or more complete IVF cycles to an individual woman in order to estimate CLBRs. However, a more detailed version of the HFEA database is available for research purposes under strict conditions which links all IVF treatments to complete cycles and to individual women (Williams et al 2013) and allows estimation of cumulative live birth rates. A population-based cohort study was conducted to investigate the cumulative live birth rate per woman following one or more linked complete cycles of IVF. This was repeated for outcomes of term singleton live birth per woman and multiple pregnancy per pregnant woman following IVF. We also aimed to explore whether the cumulative

live birth rate increased over time and the characteristics of women accessing IVF as well as their patterns of treatment over time.

Methods

Database access

Access to the detailed HFEA database was subject to approval from the North of Scotland Research Ethics Committee, the Confidentiality Advisory Group, and the HFEA Register Research Panel. Consent for IVF patient data to be used in research changed from 'presumed' to 'required' in October 2009. Therefore, from October 2009, only details relating to those patients who provided explicit consent for their data to be used in research were available.

Anonymised "per woman" data were transferred to the University of Aberdeen where they were stored and analysed using the dedicated secure Data Safe Haven (DaSH) University of Aberdeen server with access restricted to approved researchers.

Study population

Records of all fresh and frozen-thawed IVF (including ICSI) treatments in women who embarked on IVF in the UK between January 1992 and December 2011 were extracted. Since the treatment information were linked to the individual we were able to identify and code complete cycles of IVF for each woman by combining her fresh treatment with its associated frozen-thawed treatments (so that the total reproductive potential could be determined). For clarity, our definition of a complete cycle is all fresh and frozen-thawed embryo transfer attempts resulting from one episode of ovarian stimulation (National Collaborating Centre for Women's and Children's Health 2013). The following exclusion criteria were applied:

1. Women having any element of treatment involving donor insemination, egg donation, and surrogacy.
2. Women who had treatment where the express purpose was storage of eggs or embryos.
3. Women aged less than 18 or over 50 in their first treatment.
4. Women with more than three embryos transferred in any treatment since this was a very rare occurrence in the UK (20 over the whole study period).
5. Women whose first treatment in the database was a thawed embryo transfer since this indicated previous unrecorded treatment.
6. Women who received their first treatment in 2008 and 2009 were excluded so that a minimum of two years exposure time could be achieved for women commencing treatment in 2007. Two years was chosen since this captured over 90% of women's total exposure to treatment in the database. The years where the opt-in policy was in action (2010 to 2011) were excluded since their inclusion would have led to falsely higher discontinuation rates due to women opting not to disclose their treatment information in later treatments.

Baseline characteristics

Baseline characteristics of women at the beginning of their first complete cycle included age (<31, 31-35, 36-40, and >40 years), type of infertility (categorised as single diagnosis of tubal, endometriosis, anovulation, male factor, or unexplained, or as any multiple diagnosis), and year.

Outcomes

Since the complete cycle information was linked to individual women, this enabled us to identify the first live birth and first multiple pregnancy occurrences per woman over multiple complete cycles. Once a woman achieved her first live born baby from IVF they did not contribute any further to the cumulative rates. Outcomes were cumulative live birth rate per woman (CLBR), cumulative term singleton live birth rate per woman, and cumulative multiple pregnancy rate per pregnant woman.

Multiple pregnancy was defined as an occurrence of: more than one foetal sac each with foetal pulsation on scan; or one foetal sac but more than one birth outcome.

Statistical analysis

Descriptive statistics were calculated for patient and treatment characteristics at the first fresh IVF treatment. The median (interquartile range (IQR)) number of treatments per patient, median follow-up time and the most frequent fresh and frozen-thawed treatment patterns per patient were calculated. The live birth rate at the first fresh IVF treatment was calculated by year. These results were used to inform the development of separate time periods over which the CLBRs were calculated. This would enable investigation of the improvement in cumulative rates over time. Three different live birth rates were estimated:

Live birth rate and multiple pregnancy rate (per complete cycle)

The live birth rate per complete cycle was calculated by dividing the number of women in each complete cycle who had their first live birth by the total number of women who attempted that complete cycle. The multiple pregnancy rate per complete cycle was calculated by dividing the number of women in each complete cycle who had their first multiple pregnancy event by the number of women who had a pregnancy in that complete cycle.

Conservative CLBR

This assumes that none of the women who discontinued treatment would have had a live birth. At each successive complete cycle the total number of women who had their first treatment dependent live birth up to and including it were divided by the total number of women who ever attempted IVF. Any further live births occurring in subsequent cycles were not included in this analysis. The 95% confidence intervals were calculated using standard errors from the binomial distribution.

Optimal CLBR

This assumes that women who discontinued treatment would have had the same chance of a live birth or a multiple pregnancy as those who continued. The Kaplan-Meier estimate was used to calculate these rates and pointwise estimates of the 95% confidence intervals were obtained.

Cumulative rates were calculated by different age group and type of infertility values. This utilised the linked data by using the values of these characteristics of the woman at the start of her first complete cycle. For CLBR, all complete cycles were included up to either the end of follow-up or the first live birth occurrence, whichever came first.

The CLBR was only calculated for complete cycles where the number of women attempting that complete cycle was greater than 100. The above analyses were repeated for the outcome of term singleton live birth. The log-rank test was used to compare the optimal CLBRs between the two time periods and between age and type of infertility within each time period. The conservative cumulative multiple pregnancy rate per pregnant woman was calculated by dividing the number of women in each complete cycle who had their first multiple pregnancy event by the number of women who got pregnant up until that complete cycle.

Ethical approval

Ethical approval was obtained by the North of Scotland Research Ethics Committee (12/NS/0119).

Results

A total of 253,417 women underwent 464,333 autologous complete cycles of IVF in the UK from 1992 to 2011. After exclusions these figures reduced to 218,591 women (438,454 complete cycles) (see Figure 1). The live birth rate resulting from the first complete cycle of IVF increased from 16.1% in 1992 to 31.2% in 2007 (see Figure S1). From 1992 to 1998 the rates slowly increased to 23.1% before rising to 26.1% in 1999 where they remained steady until 2006 (29.7%). Based on the

stability of annual success rates for the first complete cycle, the CLBR was calculated for women who commenced IVF from 1999 to 2007. This was to minimize heterogeneity caused by changes in clinical practice over time. To assess whether the CLBR improved over time, the CLBR was also calculated for the earlier time period of 1992 to 1998 (period 1) and compared to the CLBR for 1999 to 2007 (period 2).A total of 71,551 women commenced IVF during period 1 and 107,347 during period 2 (see Figure 1). Table 1 shows couple and treatment characteristics at the start of the first complete cycle by time period. The proportion of women over the age of 35 who received IVF increased over time from 31.7% during period 1 to 39.6% during period 2. Unexplained infertility, the most frequent diagnosis during period 1 (43.8%) slipped to second place during the second period (27.2%) behind male factor (31.1%). In the first fresh treatment, the proportion of triple embryo transfers decreased from 38.8% in period 1 to 8.4% in period 2 (Table 2). However, the proportion of single embryo transfers remained the same (~8%) meaning that there were more double embryo transfers in period 2 (69.4%) than in period 1 (32.9%). The median (IQR) number of complete cycles was 1 (1, 2) in both time periods. The median (IQR) time from the start of the first complete cycle to the last fresh or frozen-thawed treatment in the last complete cycle (excluding women who only had one complete cycle with no frozen-thawed embryo transfer attempts) was lower in period 2 compared to period 1 (365 (185, 701) versus 314 (165, 609) days; $p<0.001$).

Treatment patterns

The most frequent treatment patterns were the same in both periods: one fresh treatment (period 1 48.4% versus period 2 51.4%), two consecutive fresh treatments (21.8% versus 21.9%), three consecutive fresh treatments (9.4% versus 8.5%), and one fresh treatment followed by one frozen-thawed treatment (4.2% versus 4.3%).

Cumulative live birth rates

The conservative (Figure 2A) and optimal (Figure 2B) CLBRs per woman after the third complete cycle for patients who commenced IVF from 1992 to 1998 were 30.8% and 44.6% respectively, increasing to 42.3% and 57.1% from 1999 to 2007 (see Table 3). The respective rates for term singleton live birth were 17.4% and 27.6% for 1992 to 1998 and 25.6% and 38.5% for 1999 to 2007 (Table S1). There was a highly significant difference between optimal cumulative live birth rates across the two time periods ($p<0.001$). After eight complete cycles the optimal CLBR was 82.4% in the latter time period. The conditional live birth rates per complete cycle tended to show a minimal decline with each successive complete cycle.

For those patients who did not achieve a live birth following their fresh embryo transfer attempt in their first complete cycle but who went on to have at least one frozen embryo transfer attempt, the conditional cumulative live birth rate after three frozen embryo transfer attempts was 33.7% in period 1 and 41.0% in period 2.

Age group

By age group, the CLBRs per women were higher in period 2 than period 1. After the third complete cycle, for those aged <31 at their first complete cycle the conservative CLBRs were 38.6% versus 52.4% in periods 1 and 2 respectively; ages 31-35 (34.6% versus 50.3%), ages 36-40 (22.1% versus 33.9%), ages >40 (5.9% versus 9.8%). The corresponding optimal CLBRs were 54.1% versus 67.9%, 47.7% versus 64.2%, 33.3% versus 47.0% and 11.4% versus 17.3% respectively. In each time period the optimal CLBRs were significantly different across the age groups ($p<0.001$).

Type of infertility

The CLBRs for type of infertility were not calculated for Period 1 as the number of events in some groups were too small. In Period 2, couples with a single diagnosis of male factor infertility at their first complete cycle had the highest CLBR of all types at 45.8% for the conservative estimate and 59.8% for the optimal estimate after the third complete cycle. This was followed closely by

endometriosis (44.8% conservative, 57.5% optimal), unexplained infertility (42.2% conservative, 56.2% optimal), tubal infertility (39.5% conservative, 54.6% optimal), and anovulation (39.4% conservative, 57.6% optimal). The CLBR for couples with more than one type of infertility was similar to that for couples with single types of infertility (40.1% conservative, 55.5% optimal). There was a significant difference between the optimal CLBRs across the types of infertility in the second period ($p<0.001$).

Multiple pregnancy rates by time period

By time period, 7495 (30.9%) of 24296 pregnancies during 1992 to 1997 were multiple pregnancies of which 6368 (85.0%) resulted in a multiple live birth. For IVF commencing during 1998 to 2007, 13702 (24.8%) of 55270 pregnancies were multiple pregnancies of which 11767 (85.9%) led to a multiple live birth. The multiple pregnancy rate per pregnant woman after the first complete cycle was 31.9% for those that commenced during period 1 and decreased to 26.2% during period 2. Cumulatively, the multiple pregnancy rates did not increase i.e. they remained the same as the rate in the first complete cycle for each period.

Discontinuation

The discontinuation rates after each complete cycle were very similar for the two time periods. Of those women whose first complete cycle did not result in a live birth 42.7% did not return for a second complete cycle over the following two years in period 1 versus 39.5% in period 2 (Figure S2). The withdrawal rate per complete cycle increased until complete cycle four and then remained reasonably steady.

Discussion

Statement of principal findings

In this study, national UK cumulative birth outcomes following one or more IVF complete cycles were calculated over two separate time periods – 1992 to 1998 and 1999 to 2007. The conservative estimates of the CLBR after three complete cycles increased by almost 40% from the earlier to the later period (from 30.8% to 42.3%) whilst optimal estimates increased by 30% (from 44.6% to 57.1%). The conservative cumulative multiple pregnancy rate decreased from around 32% in period 1 to 26% in period 2 across all complete cycles. By age group, the CLBR per woman declined from the age of 31 to 35 years. There was little difference between the CLBRs across the different types of infertility with conservative estimates ranging from 39% to 46% from 1999 to 2007. The log-rank test was statistically significant for this difference, however, this is almost certainly due to the large population size.

Strengths and weaknesses of the study

This is the first study to report CLBRs per woman following autologous IVF treatment for the whole of the UK using national population-based data from 1992 to 2009. Per woman rates were estimable because all IVF treatments were linked to the woman, a unique strength for a national IVF database with a long history of complete treatment capture. CLBRs were calculated over complete IVF cycles including fresh and frozen-thawed embryo transfers. This makes the results much more relevant for clinicians and patients.

Although we were able to link all treatments within women, it was not possible to identify with certainty from which complete cycle (i.e. episode of ovarian stimulation) each replaced frozen-thawed embryo came. However, our assumption that any frozen-thawed embryos were most likely to have been derived from the most recent egg retrieval episode is likely to be correct for all but a minority of women who may have undergone multiple consecutive fresh transfer attempts and reserved all frozen embryos for transfer at a later date. In reality, only 14% of all women in our dataset had a frozen-thawed embryo transfer attempt; thus, CLBRs tended to be dominated by the outcome of the first fresh treatment. CLBRs could not be calculated for women who started

311 treatment in 2008-2009 since the minimum two-year treatment exposure time would have
312 overlapped the phase, which began in October 2009, when patients had to give formal consent for
313 their data to be disclosed for research purposes (Human Fertilisation and Embryology Authority
314 2008b).

315 ***Strengths and weaknesses in relation to other studies***

316 The conservative estimate of the CLBR is a pessimistic one since it assumes that women who do not
317 achieve a live birth do not have any continued chance of getting pregnant – it reflects the observed
318 treatment specific CLBR. The optimal estimate is seen as optimistic since it assumes that women
319 who discontinue without having a live birth still have the same chance of a live birth as those who
320 continue. This future chance of live birth can be interpreted as either a hypothetical ideal world
321 scenario where there is no barrier to future treatment (which is only true for some women) or as
322 one arising from a natural conception (assuming that such chances are similar to those who continue
323 with IVF). A 'realistic' estimate of the CLBR can be calculated which assumes that women who
324 discontinue because of a medical indication had no continued chance of achieving a live birth, while
325 those who stopped treatment for other reasons had the same probability of achieving a live birth
326 after IVF as those who continued (Stolwijk et al. 2000). Unfortunately the HFEA database did not
327 hold the reasons for discontinuation of IVF treatment meaning calculation of the realistic estimate
328 was not possible. However, a previous study found that 22.5% of women who failed 2-4 IVF
329 attempts went on to have a treatment dependent live birth (Troude et al. 2012). Assuming a similar
330 rate in our study gives a realistic estimate of approximately 55.3% after three complete cycles which
331 is just lower than the optimal estimate of 57.1%. Without knowing the reason for withdrawal it is
332 possible that the realistic estimate may show lower rates for the later time period compared to the
333 earlier time period. For this to happen it would mean that the discontinuation rate due specifically
334 to medical indication had increased sufficiently enough over time to have the effect of lowering the

CLBR. With the lowering of the threshold for IVF treatment this is unlikely to be the case (Kamphuis et al. 2014).

It is not possible to directly compare the finding from the current study with that from the US since the latter did not assess the CLBRs over complete cycles of IVF but did so over cumulative fresh or frozen-thawed treatments (Luke et al. 2012). Also, the US study period was 2004 to 2008 whilst the present study's latter time period was from 1999 to 2007.

In Australia and New Zealand, the overall conservative CLBR after three successive fresh or frozen-thawed embryo transfers was 36.0% which is slightly lower than the UK rate of 39.8% after three complete cycles (Macaldowie et al. 2013). However, as for the US, that study examined CLBRs over cumulative fresh or frozen-thawed treatments rather than complete cycles as in our study. The study period was 2009 to 2011 meaning that only those women who began treatment in 2009 contributed at least two years' worth of treatment to the cumulative rates.

Meaning of the study

Our results provide an estimate of the chances of a couple taking a baby home after one or more complete cycles of IVF. They also confirm the fact that, despite rising female age, the CLBR in the U.K. has increased over time while the multiple pregnancy rate has declined. This reflects improvements in reproductive technology and the evolution towards a more conservative embryo transfer policy (McLernon et al. 2010).The multiple pregnancy rate per pregnant woman reduced from 31.9% in women who commenced IVF during period 1 to 26.2% during period 2 reflecting the reduction in triple embryo transfers. The latter rate is slightly lower than that reported in Canada in 2004 of 30% (Health Quality Ontario, 2006) and is actually lower than many countries' multiple birth rate including Guatemala (71.5%), Brazil (55.9%), Argentina (43.1%), Taiwan (40.5%) and USA (31.5%) (Sullivan et al. 2013). Since the end of our study period the HFEA have reported that the multiple pregnancy rate has reduced further to 16.4% in 2013 (Human Fertilisation and Embryology

Authority 2015) reflecting the strong drive by the HFEA to reduce the multiple pregnancy rate (Human Fertilisation and Embryology Authority 2013c).

Elective single embryo transfer (SET) with cryopreservation of surplus embryos can optimise the safety and success of IVF (National Collaborating Centre for Women's and Children's Health 2013). The traditional focus on presenting outcomes per fresh IVF treatment has tended to discourage use of elective SET which, inevitably, is associated with slightly lower live birth rates per fresh treatment but comparable cumulative outcomes. In addition, given the relatively modest success rates of IVF per fresh/frozen-thawed embryo transfer, commissioners and health planners, as well as patients who pay for IVF appreciate being able to base their decisions regarding treatment on a realistic expectation of CLBRs after one or more complete cycles of IVF i.e. a package of fresh (and their accompanying frozen-thawed) treatments.

Despite NICE recommendations in 2004, most couples in the UK still do not receive three complete IVF cycles. The majority of patients discontinue IVF after receiving one complete cycle which may be due to various reasons including the National Health Service's rationing of IVF in different regions (National Institute for Health and Clinical Excellence 2014), a lack of personal funds, psychological burden of treatment, relationship problems/divorce, physical burden (Lande et al. 2014, Verberg et al. 2008, Olivius et al. 2004). This was reflected in the conservative CLBRs which stabilised after three successive complete cycles. For those women with no barrier to continued treatment, our results show that the CLBR after eight complete cycles would be 82% (optimal estimate) which is similar to the live birth rate within two years in 30 to 35 year old women from a simulated natural population (Leridon 2004). The per complete cycle live birth rates declined slowly with each successive complete cycle e.g. a woman starting her second complete cycle of treatment has almost as high a chance of success as when she started her first. Our findings offer important reassurance to women contemplating whether to persist with treatment. They also add further support to a recent call

from NICE to end the postcode lottery of IVF treatment and to develop consistent IVF policies on access to treatment across all clinical commissioning groups (Everywomen 2013). Our findings for the optimal CLBR should be reassuring for countries, such as Belgium (Berg Brigham et al. 2013) and Israel (Lande et al. 2011), who conduct more than the UK's maximum of three complete cycles and where lack of patient funds is not such a potential barrier to treatment.

Unanswered questions and future research

CLBRs per woman over time are useful to inform clinicians, patients and policy makers about the national improvement in success rates and the overall chances of live birth. However, there is a need to provide patients with a more individualised estimate of their chances of live birth over multiple complete cycles. Clinical prediction models would allow clinicians to make more informed treatment decisions tailored to the characteristics of the woman and her treatment. The recently released IVFPredict clinical prediction tool can estimate the probability of a live birth for a specific treatment attempt number (Nelson and Lawlor 2011). However, it cannot estimate the cumulative chances of a live birth over multiple complete cycles of IVF.

Conclusions

The last two decades have witnessed a rise in CLBRs accompanied by a decline in multiples. Yet most UK couples who do not conceive after their first complete cycle do not receive a further two complete NHS funded IVF cycles as recommended by NICE. If there were no barriers to continuation of IVF treatment, around 83% of women receiving IVF would achieve a live birth by the eighth complete cycle, similar to the natural live birth rate in a non-contraception practising population. These data should be used to inform policy and counsel patients commencing IVF treatment.

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Author's Roles

DJM, SB, AM and AJL designed the study. DJM conducted the statistical analysis, literature search, and wrote the article. All authors contributed intellectually to the writing or revising of the manuscript, and approved the final version. DJM is the guarantor.

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Table 1. Characteristics of the couple at the start of their first complete cycle

Characteristics	Period, N(%), unless otherwise stated	
	1992 to 1998 N=71551	1999 to 2007 N=107347
Female Age (y), mean (SD)	33.4 (4.5)	34.1 (4.6)
<31	19646 (27.5)	23391 (21.8)
31 to 35	29260 (40.9)	41459 (38.6)
36 to 40	18343 (25.6)	33866 (31.5)
>40	4302 (6.0)	8631 (8.0)
Duration (y), median (IQR)	2 (2 to 4)	4 (3 to 6)
Type of infertility		
Unexplained only	31353 (43.8)	29181 (27.2)
Tubal only	10716 (15.0)	17634 (16.4)
Anovulation only	1115 (1.6)	7425 (6.9)
Endometriosis only	965 (1.3)	3591 (3.3)
Cervical only	83 (0.1)	47 (0.0)
Male factor only	440 (0.6)	33427 (31.1)
>1 type of infertility	26879 (37.6)	16042 (14.9)

581 **Table 2**. Treatment information for women commencing IVF during two time periods
582

Treatment information	Period, N(%), unless otherwise stated	
	1992 to 1998 N=71551	1999 to 2007 N=107347
First fresh treatment characteristics		
IVF	59322 (82.9)	64587 (60.2)
ICSI	12229 (17.1)	42760 (39.8)
Number of oocytes, median (IQR)	8 (4, 12)	8 (5, 13)
Number of embryos created, median (IQR)	4 (1, 7)	5 (2, 8)
Number of embryos transferred		
0	14349 (20.1)	14831 (13.8)
1	5886 (8.2)	9038 (8.4)
2	23555 (32.9)	74496 (69.4)
3	27761 (38.8)	8982 (8.4)
Cryopreservation of embryos	15184 (21.2)	27711 (25.8)
Overall treatment information (per woman)		
Number of fresh/frozen treatment attempts until end of follow-up[1], median (IQR)	2 (1, 3)	1 (1, 2)
Number of complete cycles until end of follow-up[1], median (IQR)	1 (1, 2)	1 (1, 2)
Number of couples with at least one frozen embryo transfer attempt	10609 (14.8%)	14979 (14.0%)
Number of complete cycles until first live birth[2], median (IQR)	1 (1, 2)	1 (1, 2)
Time (days) from first fresh treatment attempt to last fresh/frozen treatment attempt, median (IQR)[3]	365 (185, 701)	314 (165, 609)
Time (days) from first fresh treatment attempt to last fresh/frozen treatment attempt leading to live birth[2], median (IQR)	0 (0, 282)	0 (0, 196)

583

584 [1] Follow-up defined as first live birth or end of study (whichever came first)

585 [2] Only includes women who had a live birth

586 [3] Excludes women who only had one fresh treatment attempt i.e. no frozen embryo transfer
587 attempts or further ovarian stimulations.

588 **Table 3.** Live birth rates per complete cycle and cumulative live birth rates per woman by period
589

Period	Complete cycle	No. Women	No. women with at least one live birth	Conditional live birth rate	Conservative cumulative live birth rate	Optimal cumulative live birth rate
1992-1998	1	71551	13697	19.1 (18.85, 19.43)	19.1 (18.85, 19.43)	19.1 (18.86, 19.43)
	2	33155	5960	18.0 (17.56, 18.39)	27.5 (27.15, 27.80)	33.7 (33.27, 34.09)
	3	14288	2356	16.5 (15.88, 17.10)	30.8 (30.43, 31.10)	44.6 (44.09, 45.145)
	4	5649	905	16.0 (15.06, 16.98)	32.0 (31.69, 32.37)	53.5 (52.80, 54.18)
	5	2135	333	15.6 (14.06, 17.14)	32.5 (32.15, 32.84)	60.7 (59.82, 61.67)
	6	878	117	13.3 (11.08, 15.57)	32.7 (32.32, 33.00)	66.0 (64.78, 67.16)
	7	372	51	13.7 (10.21, 17.20)	32.7 (32.39, 33.07)	70.6 (69.06, 72.20)
	8	147	14	9.5 (4.78, 14.27)	32.8 (32.41, 33.09)	73.4 (71.43, 75.41)
1999-2007	1	107347	30546	28.5 (28.19, 28.73)	28.5 (28.19, 28.73)	28.5 (28.19, 28.73)
	2	46439	11116	23.9 (23.55, 24.32)	38.8 (38.52, 39.10)	45.6 (45.24, 45.93)
	3	17913	3791	21.2 (20.57, 21.76)	42.3 (42.05, 42.64)	57.1 (56.67, 57.52)
	4	6253	1189	19.0 (18.04, 19.99)	43.5 (43.15, 43.75)	65.3 (64.71, 65.80)
	5	2175	365	16.8 (15.21, 18.35)	43.8 (43.49, 44.09)	71.1 (70.38, 71.79)
	6	793	121	15.3 (12.76, 17.76)	43.9 (43.61, 44.20)	75.5 (74.55, 76.43)
	7	292	44	15.1 (10.97, 19.17)	43.9 (43.65, 44.24)	79.2 (77.89, 80.46)
	8	110	17	15.5 (8.70, 22.21)	44.0 (43.66, 44.26)	82.4 (80.59, 84.14)

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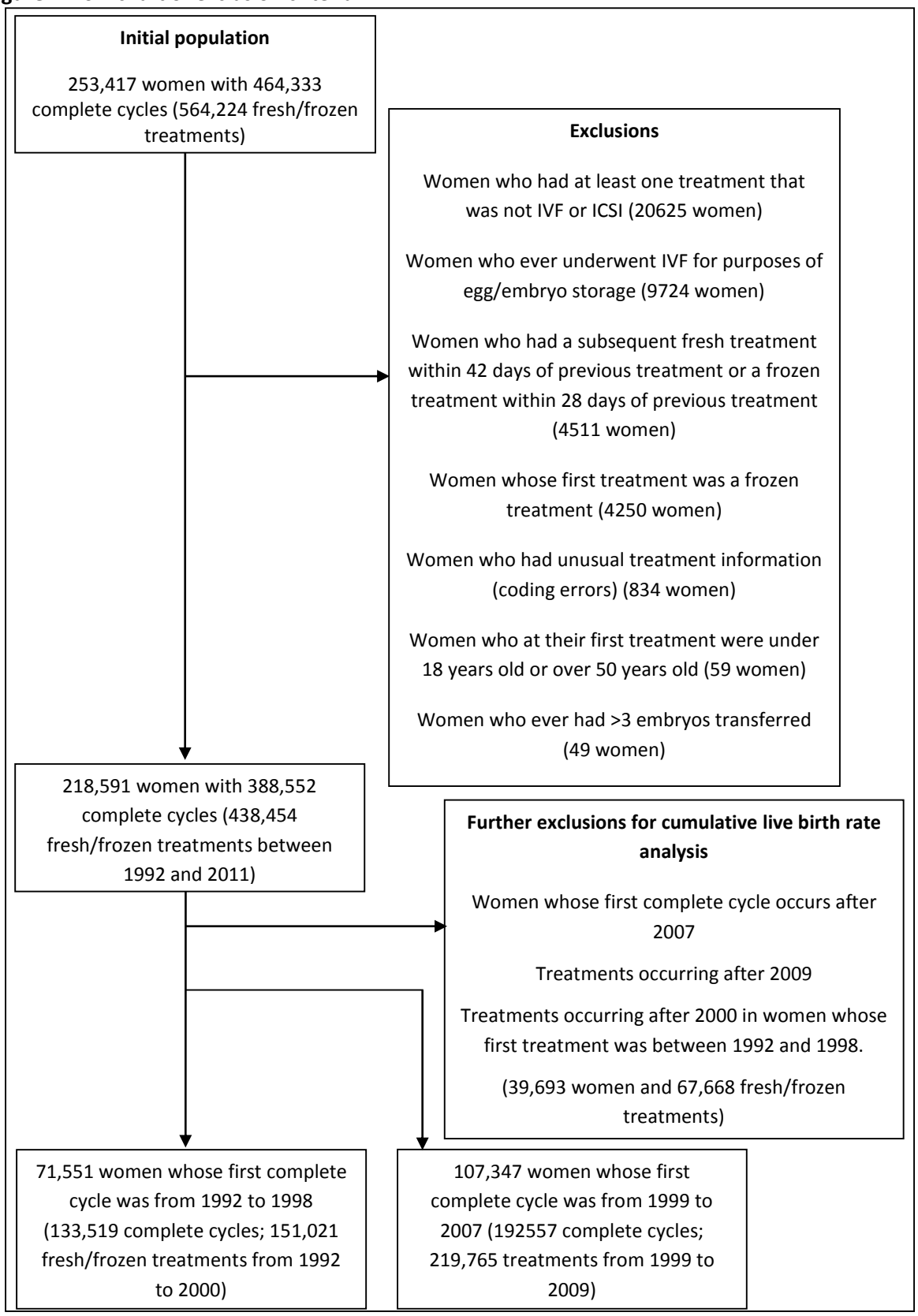
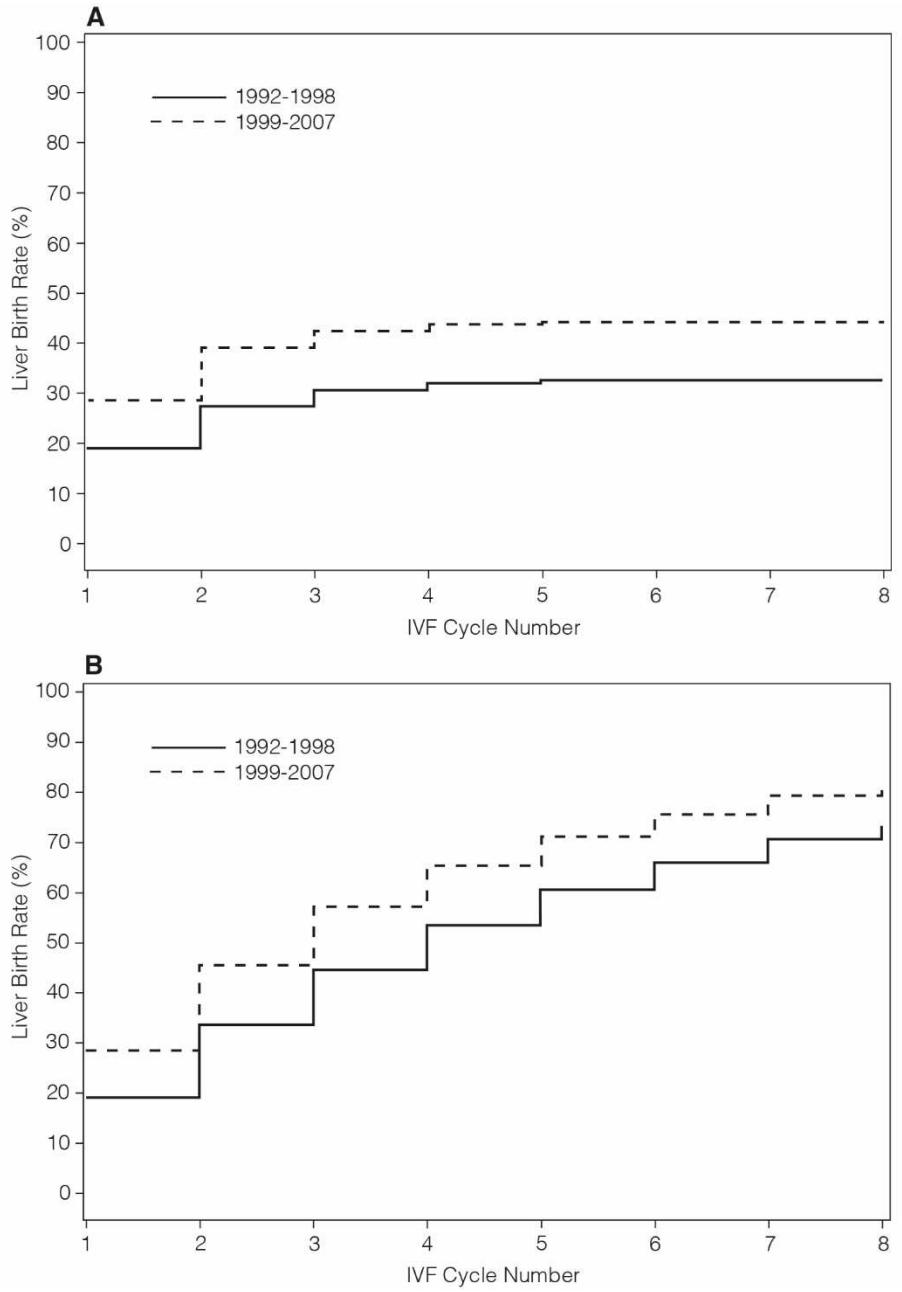
Figure legends

Figure 1 Flow chart of exclusion criteria



595 **Figure 2:** (A) Conservative cumulative live birth rates per woman and (B) optimal cumulative live
596 birth rates per woman over multiple complete cycles of IVF (including ICSI) for women commencing
597 treatment in 1992 to 1998 or 1999 to 2007



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Web extra material

Cumulative live birth rates per woman following in vitro fertilisation: a population-based study of data from 178,898 women

Contents

Table S1 Term singleton live birth rates per complete cycle and cumulative term singleton live birth rates per woman by period

Period	Complete cycle	No. Women	No. women with at least one term singleton live birth	Conditional term singleton live birth rate	Conservative cumulative term singleton live birth rate	Optimal cumulative term singleton live birth rate
1992-1998	1	71551	7596	10.6 (10.39, 10.84)	10.6 (10.39, 10.84)	10.6 (10.39, 10.84)
	2	33675	3451	10.2 (9.92, 10.57)	15.4 (15.17, 15.70)	19.8 (19.43, 20.13)
	3	14642	1430	9.8 (9.29, 10.25)	17.4 (17.16, 17.72)	27.6 (27.11, 28.12)
	4	5833	553	9.5 (8.73, 10.23)	18.2 (17.93, 18.49)	34.5 (33.77, 35.19)
	5	2218	217	9.8 (8.55, 11.02)	18.5 (18.23, 18.80)	40.9 (39.86, 41.92)
	6	923	75	8.1 (6.36, 9.89)	18.6 (18.33, 18.90)	45.7 (44.29, 47.11)
	7	397	29	7.3 (4.75, 9.86)	18.7 (18.37, 18.94)	49.7 (47.77, 51.58)
	8	159	12	7.5 (3.44, 11.65)	18.7 (18.39, 18.96)	53.5 (50.76, 56.19)
1999-2007	1	107347	18058	16.8 (16.60, 17.05)	16.8 (16.60, 17.05)	16.8 (16.60, 17.05)
	2	47505	6973	14.7 (14.36, 15.00)	23.3 (23.06, 23.57)	29.0 (28.71, 29.36)
	3	18600	2491	13.4 (12.90, 13.88)	25.6 (25.38, 25.90)	38.5 (38.09, 38.99)
	4	6583	778	11.8 (11.04, 12.60)	26.4 (26.10, 26.63)	45.8 (45.18, 46.42)
	5	2337	243	10.4 (9.16, 11.64)	26.6 (26.33, 26.85)	51.4 (50.57, 52.31)
	6	870	89	10.2 (8.22, 12.24)	26.7 (26.41, 26.94)	56.4 (55.16, 57.66)
	7	318	36	11.3 (7.84, 14.80)	26.7 (26.44, 26.97)	61.3 (59.46, 63.22)
	8	121	12	9.9 (4.59, 15.24)	26.7 (26.45, 26.98)	65.2 (62.50, 67.83)

Figure S1 Conditional live birth rate after the first complete cycle of IVF (including ICSI) by year

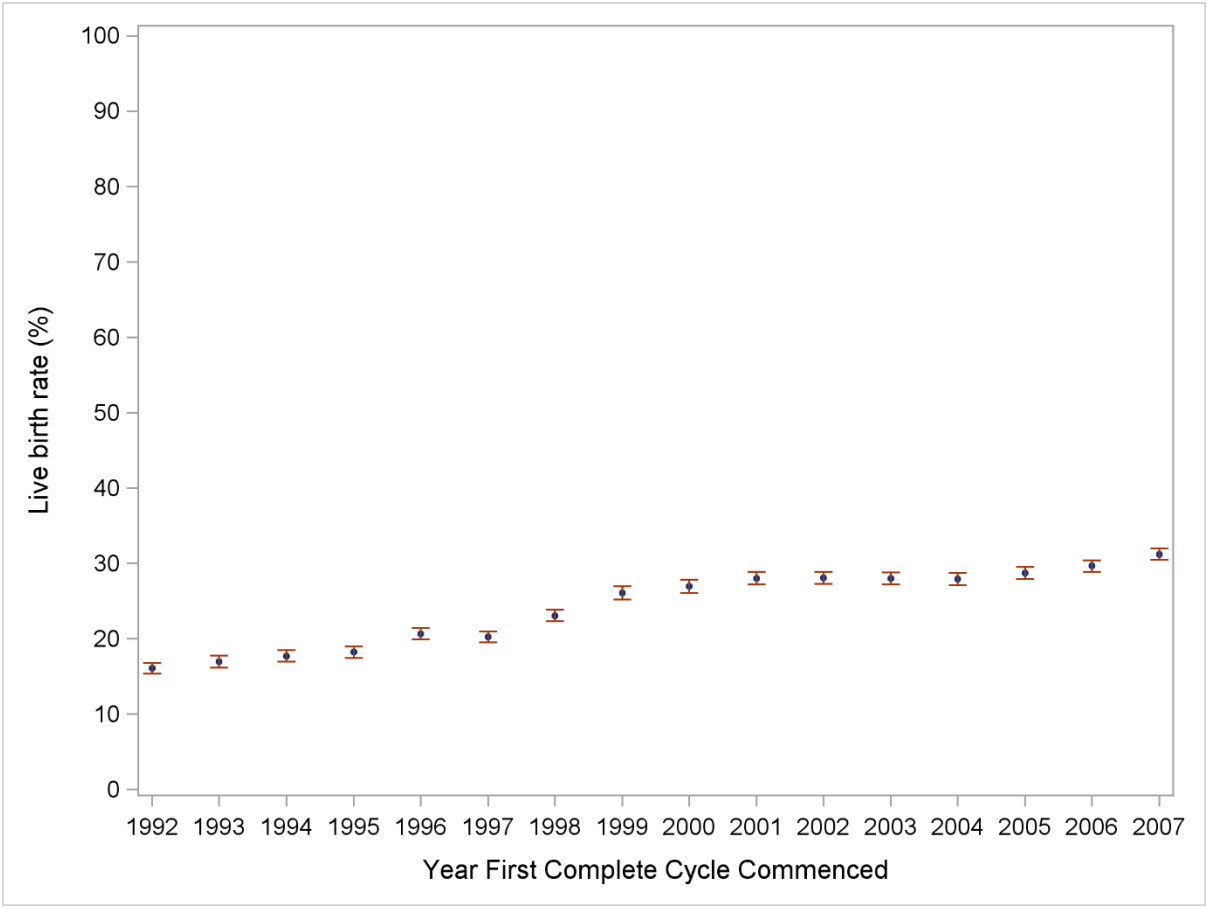

Figure S2 Discontinuation rate by complete cycle number by time period of first IVF treatment (including ICSI)