Human Reproduction, Vol.31, No.3 pp. 572–581, 2016
Advanced Access publication on January 18, 2016 doi:10.1093/humrep/dev336

human reproduction

ORIGINAL ARTICLE *Infertility*

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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Submitted on July 20, 2015; resubmitted on November 5, 2015; accepted on December 9, 2015

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 (HFEA) 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. BMI and ethnicity could not be reported: these demographics are not recorded in the HFEA database.

WIDER IMPLICATIONS OF THE FINDINGS: Our results demonstrate, at a national level, the chances of live birth 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.

STUDY FUNDING/COMPETING INTEREST(S): This work was funded by a Chief Scientist Office Postdoctoral Training Fellowship in Health Services Research and Health of the Public Research (Ref PDF/12/06). The views expressed here are those of the authors and not necessarily those of the Chief Scientist Office. S.B. reports grants from Chief Scientist Office Scotland during the conduct of the study. His institution has received support from Pharmaceutical companies (for educational seminars), which is not related to the submitted work. D.J.M., A.M. and A.J.L. have no conflicts of interest to declare.

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* fertilization (defined here as IVF or ICSI) and the number of women treated in the UK has increased annually from 6184 in 1991 to 49 636 in 2013 (Human Fertilisation and Embryology Authority, 2008a, 2012, 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 (Sharma *et al.*, 2002; Elizur *et al.*, 2006; Ke *et al.*, 2013; Abuzeid *et al.*, 2014; Vrtacnik *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 (SETs) (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 realization 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 (Elizur *et al.*, 2006; Malizia *et al.*, 2009; Ke *et al.*, 2013; Vrtacnik *et al.*, 2014). Although they have been reported at the national level in the USA (Luke *et al.*, 2012; Stern *et al.*, 2013) 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 SET 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 anonymized HFEA database is freely available for research purposes and has been utilized in several studies (Sunkara *et al.*, 2011; Nelson and Lawlor, 2011; Human Fertilisation and Embryology Authority, 2013b; 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 CLBRs. A population-based cohort study was conducted to investigate the CLBR 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 CLBR 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.

Anonymized '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:

(i) Women having any element of treatment involving donor insemination, egg donation and surrogacy.
(ii) Women who had treatment where the express purpose was storage of eggs or embryos.
(iii) Women aged less than 18 or over 50 in their first treatment.
(iv) 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).
(v) Women whose first treatment in the database was a thawed embryo transfer since this indicated previous unrecorded treatment.
(vi) Women who received their first treatment in 2008 and 2009 were excluded so that a minimum of 2 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 (2010–2011) 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 (categorized 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 CLBR per woman, 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 fetal sac each with fetal pulsation on scan; or one fetal 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 utilized 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 Fig. 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 Supplementary data, Fig. 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 1992–1998 (period 1) and compared with the CLBR for 1999–2007 (period 2). A total of 71 551 women commenced IVF during period 1 and 107 347 during Period 2 (see Fig. 1). Table I 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 years 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 II). However, the proportion of SETs 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

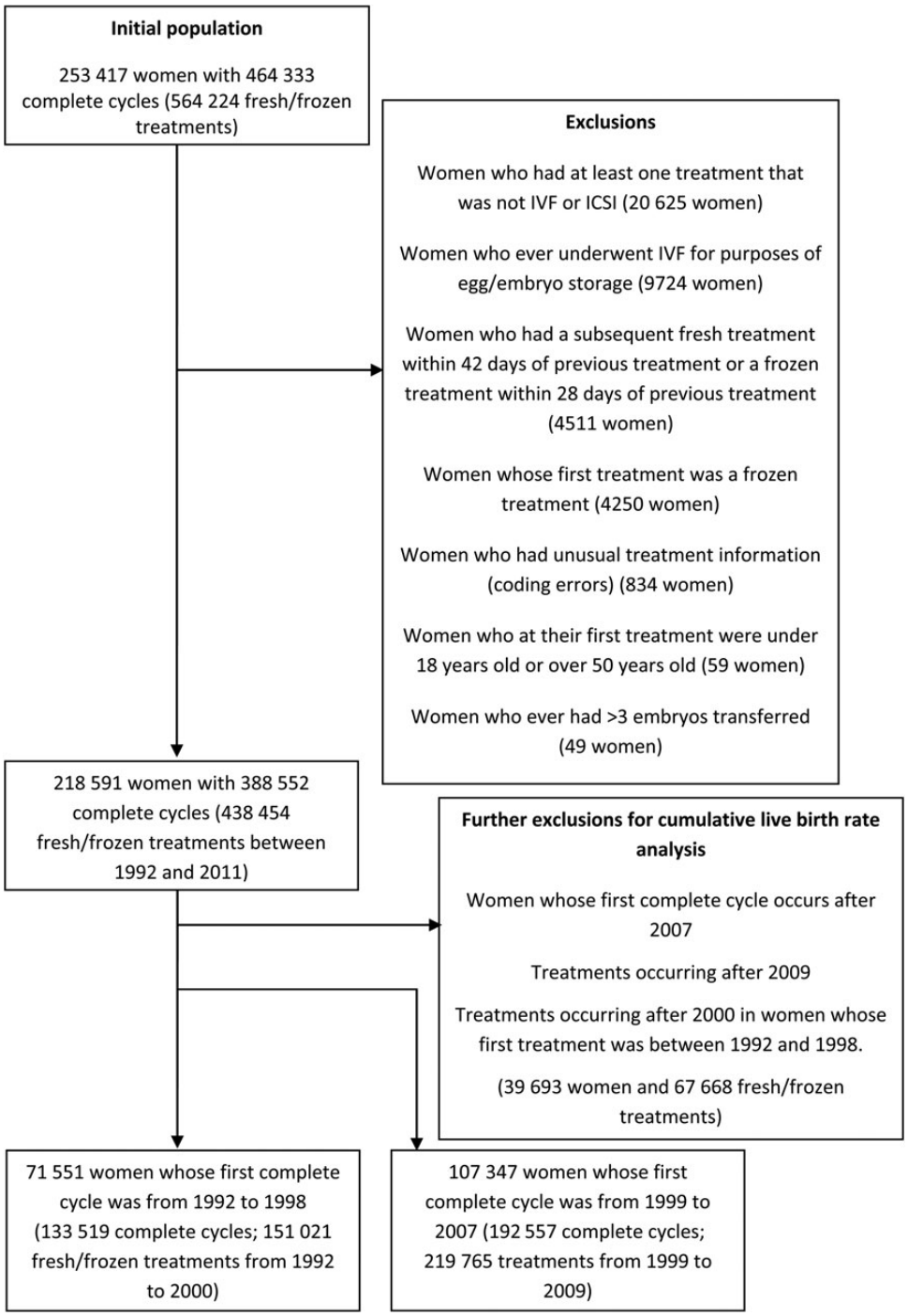

Figure 1 Flow chart of exclusion criteria.

cycle (excluding women who only had one complete cycle with no frozen-thawed embryo transfer attempts) was lower in period 2 compared with 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 (Fig. 2A) and optimal (Fig. 2B) CLBRs per woman after the third complete cycle for patients who commenced IVF from 1992 to

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

Characteristics	Period, *n* (%), unless otherwise stated	
	1992–1998 *n* = 71 551	1999–2007 *n* = 107 347
Female age (year), mean (SD)	33.4 (4.5)	34.1 (4.6)
<31	19 646 (27.5)	23 391 (21.8)
31–35	29 260 (40.9)	41 459 (38.6)
36–40	18 343 (25.6)	33 866 (31.5)
>40	4302 (6.0)	8631 (8.0)
Duration (year), median (IQR)	2 (2–4)	4 (3–6)
Type of infertility		
Unexplained only	31 353 (43.8)	29 181 (27.2)
Tubal only	10 716 (15.0)	17 634 (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)	33 427 (31.1)
>1 type of infertility	26 879 (37.6)	16 042 (14.9)

1998 were 30.8 and 44.6%, respectively, increasing to 42.3 and 57.1% from 1999 to 2007 (see Table III). 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 (Supplementary data, Table SI). There was a highly significant difference between optimal CLBRs 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 CLBR 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 years 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 ($P < 0.001$).

Table II Treatment information for women commencing IVF during two time periods.

Treatment information	Period, *n* (%), unless otherwise stated	
	1992–1998 *n* = 71 551	1999–2007 *n* = 107347
First fresh treatment characteristics		
IVF	59 322 (82.9)	64 587 (60.2)
ICSI	12 229 (17.1)	42 760 (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	14 349 (20.1)	14 831 (13.8)
1	5886 (8.2)	9038 (8.4)
2	23 555 (32.9)	74 496 (69.4)
3	27 761 (38.8)	8982 (8.4)
Cryopreservation of embryos	15 184 (21.2)	27 711 (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	10 609 (14.8%)	14 979 (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)

[1]Follow-up defined as first live birth or end of study (whichever came first).
[2]Excludes women without a live birth but includes women with a live birth who conceived in their first fresh attempt (coded as 0 days) since their first treatment is also their last.
[3]Excludes women who only had one fresh treatment attempt, i.e. no frozen embryo transfer attempts or further ovarian stimulations.

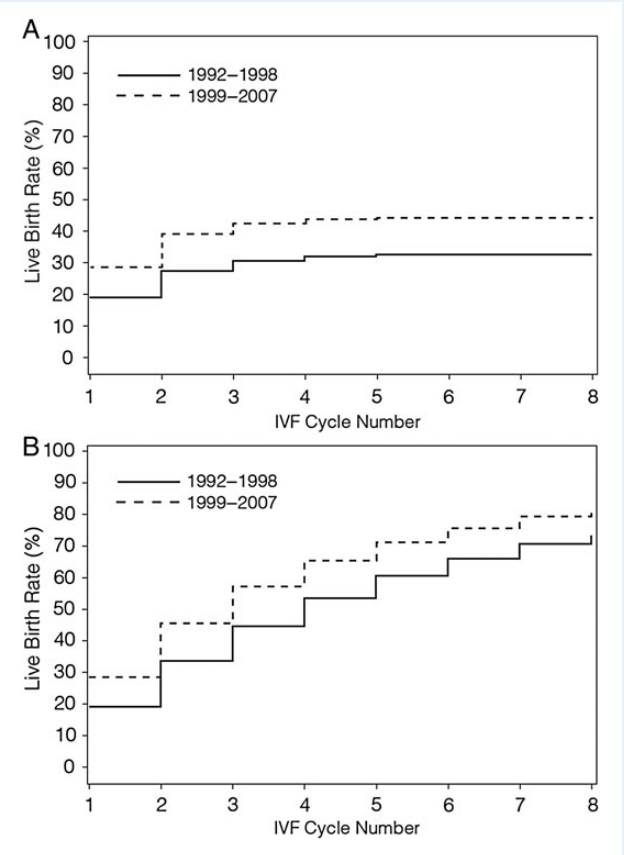

Figure 2 (**A**) Conservative cumulative live birth rates per woman and (**B**) optimal cumulative live birth rates per woman over multiple complete cycles of IVF (including ICSI) for women commencing treatment in 1992 to 1998 or 1999 to 2007.

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

During 1992–1997, 7495 (30.9%) of 24 296 pregnancies were multiple pregnancies of which 6368 (85.0%) resulted in a multiple live birth. For IVF commencing during 1998–2007, 13 702 (24.8%) of 55 270 pregnancies were multiple pregnancies of which 11 767 (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 2 years in Period 1 versus 39.5% in Period 2 (Supplementary data, Fig. S2). The withdrawal rate per complete cycle

Table III Live birth rates per complete cycle and cumulative live birth rates per woman by period.

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	71 551	13 697	19.1 (18.85, 19.43)	19.1 (18.85, 19.43)	19.1 (18.86, 19.43)
	2	33 155	5960	18.0 (17.56, 18.39)	27.5 (27.15, 27.80)	33.7 (33.27, 34.09)
	3	14 288	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	107 347	30 546	28.5 (28.19, 28.73)	28.5 (28.19, 28.73)	28.5 (28.19, 28.73)
	2	46 439	11 116	23.9 (23.55, 24.32)	38.8 (38.52, 39.10)	45.6 (45.24, 45.93)
	3	17 913	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)

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—1992–1998 and 1999–2007. 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 31–35 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 treatment in 2008–2009 since the minimum 2-year treatment exposure time would have overlapped the phase, which began in October 2009, when patients had to give formal consent for their data to be disclosed for research purposes (Human Fertilisation and Embryology Authority, 2008b).

Strengths and weaknesses in relation to other studies

The conservative estimate of the CLBR is a pessimistic one since it assumes that women who do not achieve a live birth do not have any continued chance of getting pregnant—it reflects the observed treatment specific CLBR. The optimal estimate is seen as optimistic since it assumes that women who discontinue without having a live birth still have the same chance of a live birth as those who continue. This future chance of live birth can be interpreted as either a hypothetical ideal world scenario where there is no barrier to future treatment (which is only true for some women) or as one arising from a natural conception (assuming that such chances are similar to those who continue with IVF). A 'realistic' estimate of the CLBR can be calculated which assumes that women who discontinue because of a medical indication had no continued chance of achieving a live birth, while those who stopped treatment for other reasons had the same probability of achieving a live birth after IVF as those who continued (Stolwijk et al., 2000). Unfortunately, the HFEA database did not hold the reasons for discontinuation of IVF treatment meaning calculation of the realistic estimate was not possible. However, a previous study found that 22.5% of women who failed two to four IVF attempts went on to have a treatment independent live birth (Troude et al., 2012). Assuming a similar rate in our study gives a realistic estimate of ~55.3% after three complete cycles which is just lower than the optimal estimate of 57.1%. Without knowing the reason for withdrawal it is possible that the realistic estimate may show lower rates for the later time period compared with the earlier time period. For this to happen it would mean that the discontinuation rate due specifically 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 2009–2011 meaning that only those women who began treatment in 2009 contributed at least 2 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 UK 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 SET with cryopreservation of surplus embryos can optimize 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, and physical burden (Olivius *et al.*, 2004; Verberg *et al.*, 2008; Lande *et al.*, 2014). This was reflected in the conservative CLBRs which stabilized 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 2 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 individualized 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 first 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 practicing population. These data should be used to inform policy and counsel patients commencing IVF treatment.

Supplementary data

Supplementary data are available at http://humrep.oxfordjournals.org/.

Acknowledgements

We thank the Human Fertilisation and Embryological Authority (HFEA) for granting us permission to analyse their database, for extracting the requested information and for assisting with our queries in an efficient manner. We acknowledge the data management support of the Grampian Data Safe Haven (DaSH) and the associated financial support of NHS Research Scotland, through NHS Grampian investment in the Grampian DaSH. For more information, visit the DaSH website http://www.abdn.ac.uk/iahs/facilities/grampian-data-safe-haven.php.

Authors' roles

D.J.M., S.B., A.M. and A.J.L. designed the study. D.J.M. 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. D.J.M. is the guarantor.

Funding

This work was supported by a Chief Scientist Office Postdoctoral Training Fellowship in Health Services Research and Health of the Public Research (Ref PDF/12/06). The views expressed here are those of the authors and not necessarily those of the Chief Scientist Office. The funder did not have any role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; nor in the decision to submit the paper for publication. D.M. had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflict of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). S.B. reports grants from Chief Scientist Office Scotland during the conduct of the study. His institution has received support from Pharmaceutical companies (for educational seminars) which is not related to the submitted work. D.J.M., A.M. and A.J.L. have no conflicts of interest to declare.

References

Abuzeid MI, Bolonduro O, La Chance J, Abozaid T, Urich M, Ullah K, Ali T, Ashraf M, Khan I. Cumulative live birth rate and assisted reproduction:

impact of female age and transfer day. *Facts Views Vis Obgyn* 2014; **6**:145–149.

Adamson GD, Zegers-Hochschild F, Ishihara O, Sullivan E, Mansour R, Nygren KG, Banker M, Dyer S, de Mouzon J. ICMART world report: preliminary 2008 data. *Hum Reprod* 2012;**27**(Suppl 2):ii38–ii39.

Berg Brigham K, Cadier B, Chevreul K. The diversity of regulation and public financing of IVF in Europe and its impact on utilization. *Hum Reprod* 2013; **28**:666–675.

Bhattacharya S, Maheshwari A, Mollison J. Factors associated with failed treatment: an analysis of 121,744 women embarking on their first IVF cycles. *PLOS One* 2013;**8**:e82249.

Boivin J, Bunting L, Collins JA, Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. *Hum Reprod* 2007;**22**:1506–1512.

De Mouzon J, Goossens V, Bhattacharya S, Castilla JA, Ferraretti AP, Korsak V, Kupka M, Nygren KG, Nyboe Andersen A, European IVF-monitoring (EIM) Consortium, for the European Society of Human Reproduction and Embryology (ESHRE). Assisted reproductive technology in Europe, 2006: results generated from European registers by ESHRE. *Hum Reprod* 2010;**25**:1851–1862.

Elizur SE, Lerner-Geva L, Levron J, Shulman A, Bider D, Dor J. Cumulative live birth rate following in vitro fertilization: study of 5310 cycles. *Gynecol Endocrinol* 2006;**22**:25–30.

Everywomen J. Cassandra's prophecy: why we need to tell the women of the future about age-related fertility decline and 'delayed' childbearing. *Reprod BioMed Online* 2013;**27**:4–10.

Health Quality Ontario. In vitro fertilization and multiple pregnancies: an evidence-based analysis. *Ont Health Technol Assess Ser.* 2006;**6**:1–63.

Human Fertilisation and Embryology Authority. A long term analysis of the HFEA register data (1991–2006). 2008a. http://www.hfea.gov.uk/docs/Latest_long_term_data_analysis_report_91-06.pdf.pdf (5 January 2016, date last accessed).

HFEA's Human Fertilisation and Embryology Act. 2008b http://www.legislation.gov.uk/ukpga/2008/22/contents#pt1-pb8-l1g25 (5 January 2016, date last accessed).

Human Fertilisation and Embryology Authority. Fertility treatment in 2012: trends and figures. 2012. http://www.hfea.gov.uk/docs/FertilityTreatment2012TrendsFigures.PDF (5 January 2016, date last accessed).

Human Fertilisation and Embryology Authority. Fertility treatment in 2013: trends and figures. 2013a. http://www.hfea.gov.uk/docs/HFEA_Fertility_Trends_and_Figures_2013.pdf (5 January 2016, date last accessed).

Human Fertilisation and Embryology Authority. Access anonymised HFEA data. 2013b. http://www.hfea.gov.uk/5874.html (5 January 2016, date last accessed).

Human Fertilisation and Embryology Authority. Multiple births and single embryo transfer review. 2013c. http://www.hfea.gov.uk/Multiple-births-after-IVF.html (5 January 2016, date last accessed).

Human Fertilisation and Embryology Authority. Facts & figures for researchers and the media. 2014. http://www.hfea.gov.uk/99.html (5 January 2016, date last accessed).

Human Fertilisation and Embryology Authority. Improving outcomes for fertility patients: multiple births. 2015. http://www.hfea.gov.uk/docs/Multiple_Births_Report_2015.pdf (5 January 2016, date last accessed).

Johnson MH, Franklin S. Editorial: A patient perspective. *Reprod BioMed Online* 2013;**27**:1–3.

Jones HW Jr, Jones D, Kolm P. Cryopreservation: a simplified method of evaluation. *Hum Reprod* 1997;**12**:548–553.

Kamphuis EI, Bhattacharya S, van der Veen F, Mol BWJ, Templeton A. Are we overusing IVF? *Br Med J* 2014;**348**:g252.

Ke H, Chen X, Liu Y, Ye D, He Y, Chen A. Cumulative live birth rate after three ovarian stimulation IVF cycles for poor ovarian responders according to the Bologna criteria. *J Huazhong Univ Sci Technol* 2013; **33**:418–422.

Lande Y, Seidman DS, Maman E, Baum M, Dor J, Hourvitz A. Couples offered free assisted reproduction treatment have a very high chance of achieving a live birth within 4 years. *Fertil Steril* 2011;**95**:568–572.

Lande Y, Seidman DS, Maman E, Baum M, Hourvitz A. Why do couples discontinue unlimited free IVF treatments? *Gynecol Endocrinol* 2015; **31**:233–236.

Leridon H. Can assisted reproduction technology compensate for the natural decline in fertility with age? A model assessment. *Hum Reprod* 2004; **19**:1548–1553.

Luke B, Brown MB, Wantman E, Lederman A, Gibbons W, Schattman GL, Lobo RA, Leach RE, Stern JE. Cumulative birth rates with linked assisted reproductive technology cycles. *N Engl J Med* 2012;**366**:2483–2491.

Macaldowie A, Wang YA, Chambers GM, Sullivan EA. *Assisted Reproduction Technology in Australia and New Zealand 2011*. National Perinatal Epidemiology and Statistics Unit, the University of New South Wales, Sydney. 2013. https://npesu.unsw.edu.au/surveillance/assisted-reproductive-technology-australia-new-zealand-2011 (5 January 2016, date last accessed).

Maheshwari A, McLernon D, Bhattacharya S. Cumulative live birth rate: time for a consensus? *Hum Reprod* 2015;**30**:2703–2707.

Malizia BA, Hacker MR, Penzias AS. Cumulative live-birth rates after in vitro fertilization. *N Engl J Med* 2009;**360**:236–243.

Mansour R, Ishihara O, Adamson GD, Dyer S, de Mouzon J, Nygren KG, Sullivan E, Zegers-Hochschild F. International Committee for Monitoring Assisted Reproductive Technologies world report: Assisted Reproductive Technology 2006. *Hum Reprod* 2014;**29**:1536–1551.

McLernon DJ, Harrild K, Bergh C, Davies MJ, de Neubourg D, Dumoulin JCM, Gerris J, Kremer JAM, Martikainen H, Mol BW *et al*. Clinical effectiveness of elective single versus double embryo transfer: meta-analysis of individual patient data from randomised trials. *Br Med J* 2010;**341**:c6945.

Min JK, Breheny SA, MacLachlan V, Healy DL. What is the most relevant standard of success in assisted reproduction? The singleton, term gestation, liver birth rate per cycle initiated: the BESST endpoint for assisted reproduction. *Hum Reprod* 2004;**19**:3–7.

Moragianni VA, Penzias AS. Cumulative live-birth rates after assisted reproductive technology. *Curr Opin Obstet Gynecol* 2010;**22**:189–192.

National Collaborating Centre for Women's and Children's Health. *Fertility: Assessment and Treatment for People with Fertility Problems*. National Institute for Health and Clinical Excellence clinical guideline. 2013. http://www.nice.org.uk/guidance/cg156/evidence (5 January 2016, date last accessed).

National Institute for Health and Clinical Excellence. *NICE Calls for an end to Postcode Lottery of IVF Treatment*. 2014. https://www.nice.org.uk/news/article/nice-calls-for-an-end-to-postcode-lottery-of-ivf-treatment (5 January 2016, date last accessed).

Nelson SM, Lawlor DA. Predicting live birth, preterm delivery, and low birth weight in infants born from in vitro fertilisation: a prospective study of 144,018 treatment cycles. *PLOS Med* 2011;**8**:e1000386.

Oakley L, Doyle P, Maconochie N. Lifetime prevalence of infertility and infertility treatment in the UK: results from a population-based survey of reproduction. *Hum Reprod* 2008;**23**:447–450.

Olivius C, Friden B, Borg G, Bergh C. Why do couples discontinue in vitro fertilization treatment? A cohort study. *Fertil Steril* 2004;**81**:258–261.

Roque M, Lattes K, Serra S, Solà I, Geber S, Carreras R, Checa MA. Fresh embryo transfer versus frozen embryo transfer in in vitro fertilization cycles: a systematic review and meta-analysis. *Fertil Steril* 2013;**99**:156–162.

Sharma V, Allgar V, Rajkhowa M. Factors influencing the cumulative conception rate and discontinuation of in vitro fertilization treatment for infertility. *Fertil Steril* 2002;**78**:40–46.

Stern JE, Hickman TN, Kinzer D, Penzias AS, Ball GD, Gibbons WE. Can the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) be used to accurately report clinic total reproductive potential (TRP)? *Fertil Steril* 2012;**97**:886–889.

Stern JE, Brown MB, Wantman E, Kalra SK, Luke B. Live birth rates and birth outcomes by diagnosis using linked cycles from the SART CORS database. *J Assist Reprod Genet* 2013;**30**:1445–1450.

Stolwijk AM, Wetzels AMM, Braat DDM. Cumulative probability of achieving an ongoing pregnancy after in-vitro fertilization and intracytoplasmic sperm injection according to a woman's age, subfertility diagnosis and primary or secondary subfertility. *Hum Reprod* 2000; **15**:203–209.

Sullivan EA, Zegers-Hochschild F, Mansour R, Ishihara O, de Mouzon J, Nygren KG, Adamson GD. International Committee for Monitoring Assisted Reproductive Technologies (ICMART) world report: assisted reproductive technology 2004. *Hum Reprod* 2013;**28**:1375–1390.

Sunderam SKD, Kissin DM, Crawford SB, Folger SG, Jamieson DJ, Barfield WD. Assisted Reproductive Technology Surveillance – United States, 2011. *MMWR Surveill Summ* 2014;**63**:1–28.

Sunkara SK, Rittenberg V, Raine-fenning N, Bhattacharya S, Zamora J, Coomarasamy A. Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles. *Hum Reprod* 2011;**26**:1768–1774.

The Multiple Births Foundation. 2015 One at A time. http://www.oneatatime.org.uk (5 January 2016, date last accessed).

Troude P, Bailly E, Guibert J, Bouyer J, de la Rochebrochard E, for the DAIFI Group. Spontaneous pregnancies among couples previously treated by in vitro fertilization. *Fertil Steril* 2012;**98**:63–68.

Verberg MFG, Eijkemans MJC, Heijnen EMEW, Broekmans FJ, de Klerk C, Fauser BCJM, Macklon NS. Why do couples drop-out from IVF treatment? A prospective cohort study. *Hum Reprod* 2008; **23**:2050–2055.

Vrtacnik U, Bokal EV, Davjak R. Cumulative delivery rate after providing full reimbursement in vitro fertilization programme: a 6-years survey. *BioMed Res Int* 2014. http://dx.doi.org/10.1155/2014/850478.

Williams CL, Bunch KJ, Stiller CA, Murphy MFG, Botting BJ, Wallace WH, Davies M, Sutcliffe AG. Cancer risk among children born after assisted conception. *New Engl J Med* 2013;**369**:1819–1827.