Title: Cumulative live birth rates following miscarriage in an initial complete cycle of IVF: a retrospective cohort study of 112,549 women.

Running title: Cumulative live birth rates after IVF miscarriage

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Abstract

Study Question: In women undergoing IVF/ICSI who miscarry in their first complete cycle, what is the chance of a live birth in subsequent complete cycles, and how does this compare with those whose first complete cycle ends with live birth or without a pregnancy?

Summary Answer: After two further complete cycles of IVF/ICSI, women who had miscarried or had a live birth in their first complete cycle had a higher chance of live birth (40.9% and 49.0% respectively) than those who had no pregnancies (30.1%).

What is known already: Cumulative live birth rates after one or more complete cycles of IVF have been reported previously, as have some of the risk factors associated with miscarriage, both in general populations and in those undergoing IVF. Chances of cumulative live birth after a number of complete IVF cycles involving replacement of fresh followed by frozen embryos after an initial miscarriage in a population undergoing IVF treatment have not been reported previously.

Study design, size and duration: National population-based cohort study of 112549 women who started their first IVF treatment between 1999 and 2008.

Participants/materials, setting, methods: Data from the United Kingdom Human Fertilisation and Embryology Authority (HFEA) register on IVF/ICSI treatments, using autologous gametes were analysed. Cumulative live birth rates (CLBRs) were estimated in women who a) had miscarriage (and no live birth), b) at least one live birth or c) no pregnancy in their first complete cycle of IVF/ICSI (including fresh and frozen embryo transfers following a single oocyte retrieval episode). A multivariable analysis was performed to assess the effect of first complete cycle outcome on subsequent CLBRs after adjusting for confounding factors such as female age, duration of infertility and cause of infertility.

Main results and the role of chance: In their first complete cycle, 9,321 (8.3%) women had at least one miscarriage (and no live birth); 33,152 (29.5%) had at least one live birth and 70,076 (62.3%) had

no pregnancies. After two further complete cycles, conservative CLBRs (which assume that women who discontinued treatment subsequently never had a live birth) were 40.9%, 49.0% and 30.1% , while optimal CLBRs (which assume that women who discontinue have the same chance of live birth as those treated) were 49.5%, 57.9% and 38.4% in the miscarriage, live birth and no pregnancy groups respectively. Odds of cumulative live birth for women who miscarried in their first complete cycle were 42% higher than those who had no pregnancy [odds ratio (95% confidence interval) = 1.42 (1.34, 1.50)], and twice as high for live birth versus no pregnancy [2.04 (1.89, 2.20)]. Negative predictors for live birth in all women included tubal infertility [0.88 (0.82, 0.94)] and increasing age [18-40 years=0.94 (0.94, 0.95); >40 years=0.63 (0.59, 0.66)].

Limitations and reason for caution: CLBRs could not be estimated for treatments occurring after September 2008 due to potentially incomplete data following regulatory changes regarding consent for data use in research. Additionally, covariates not included in the HFEA database (including body mass index, smoking, previous history of miscarriage and gestational age at miscarriage) could not be adjusted for in our analysis.

Wider implications of the findings: Miscarriage following IVF can be devastating for couples who are uncertain about their ultimate prognosis. Our findings will provide reassurance to these couples as they consider their options for continuing treatment.

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Key words:

Cumulative live birth rate, IVF, miscarriage, live birth, pregnancy, assisted reproductive technology.

Introduction

IVF is the treatment of choice for couples with prolonged unresolved infertility (National Collaborating Centre for Women's and Children's Health 2013). A total of 52,288 women underwent 67,708 cycles of IVF or ICSI in the UK in 2014 and 1.5% of all babies born in the UK each year are conceived using IVF or ICSI (Human Fertilisation and Embryology Authority 2012). Although 26.5% of IVF treatments in the UK result in a live birth (Human Fertilisation and Embryology Authority 2016) 22.3% of IVF pregnancies end in miscarriage (Sunkara et al. 2014).

A miscarriage can be a devastating experience for any individual (Toffol et al. 2013) but especially so for women who conceive through ART (Cheung et al. 2013, Toffol et al. 2013). This prompts some patients to discontinue further treatment due to fears about the emotional burden associated with repeated failed cycles of IVF (Harris and Daniluk 2010). Patients who continue with treatment following a previous miscarriage have described high levels of anxiety affecting their decision to invest in future treatments and pregnancies due to the uncertainty of the process and the fear of another pregnancy loss (Freda et al. 2003, Harris and Daniluk 2010).

Previous work has identified some of the risk factors associated with miscarriage including increasing maternal age (Baker et al. 2010, Croucher et al. 1998, Hipp et al. 2016), previous miscarriages and polycystic ovary syndrome (Joham et al. 2014, Knudsen et al. 1991, Kupka et al. 2004, Rai and Regan 2006). IVF-specific risk factors include the transfer of cryopreserved embryos, cleavage-stage embryo transfer, decreased response to ovarian stimulation (linked to maternal age), previous miscarriages in IVF conceptions and certain causes of infertility such as uterine factor and endometriosis (Croucher et al. 1998, Hipp et al. 2016, Kupka et al. 2004, Yang et al. 2015).

Of the existing studies on miscarriage following IVF, only a handful have reported on the effect of a previous miscarriage on subsequent success rates (Croucher et al. 1998, Kalu et al. 2011, Kupka et al.

2004, Yang et al. 2015). Both Kupka et al., (2004) and Yang et al., (2015) reported overall IVF related clinical pregnancy rates and miscarriage rates following miscarriage. Kupka et al., (2004) reported these following any history of previous miscarriage, while Yang et al., (2015) studied success rates after miscarriage in the first embryo transfer. However, they did not compare cumulative live birth rates of those who had a miscarriage with those who had a live birth or those who did not get pregnant over multiple cycles, therefore not reflecting the ongoing, cyclical nature of IVF treatment. Although cumulative live birth rates have been acknowledged as the optimum way of expressing outcomes after a course of IVF treatment, this is the first to examine the effect of previous miscarriage on cumulative live birth rates (CLBRs), while adjusting for confounders in terms of patient and treatment characteristics.

The Human Fertilisation and Embryology Authority collects IVF treatment data from all licenced UK treatment centres. An anonymised version of this database can be freely used in research (Human Fertilisation and Embryology Authority 2013). However, these individual fresh or frozen treatments are not linked to complete cycles (defined as all fresh and frozen-thawed embryo transfer attempts resulting from one episode of ovarian stimulation) (Moragianni and Penzias 2010) or to individual women, and so do not allow for calculation of CLBRs. Where strict ethical requirements are met, the HFEA allows access to a more detailed version of this database which does link treatments to women, providing the opportunity to estimate CLBRs per woman and, thus, the total reproductive potential of each cycle (McLernon et al. 2016, McLernon et al. 2016).

In women who had i) a miscarriage (and no live birth); ii) no pregnancy; or iii) a live birth, by the end of their first complete IVF cycle (i.e. fresh followed by frozen replacement cycles after an initial episode of oocyte retrieval) we estimated the cumulative live birth rates following subsequent complete cycles of IVF. We estimated the chance of a live birth over subsequent complete cycles in each of the three groups of women after adjusting for other patient and treatment characteristics.

Materials and methods

Database access

Access to the more detailed version of the HFEA database was granted following approval from the HFEA Register Research Panel, the North of Scotland Research Ethics Committee and the Confidentiality Advisory Group. The data were anonymised and transferred to the University of Aberdeen where they were stored on the Data Safe Haven (DaSH) server for analysis. Access to this dedicated secure server was limited to the authors.

Ethical approval

The North of Scotland Research Ethics Committee granted ethical approval (12/NS/0119).

Study population

Records on all women who initiated their first complete IVF cycle in the UK at a licenced clinic from January 1999 to September 2008 with frozen embryo transfers continuing until September 2009 were extracted. Complete cycles were combined on a per-woman basis and were defined as all fresh and frozen-thawed embryo transfers associated with one episode of ovarian stimulation (Moragianni and Penzias 2010). This allowed estimation of the total reproductive potential of each complete cycle, as well as the calculation of CLBRs.

The following exclusion criteria were applied (see Figure 1):

(i) Women older than 50 years, or less than 18 years, at the time of their first treatment.

(ii) Women whose treatment involved surrogacy or use of donor eggs or sperm.

(iii) Women whose treatment was for the purpose of egg/embryo storage only.

(iv) Women who appeared to have previous unrecorded treatments (i.e. frozen-thawed embryo transfer listed as their first treatment).

(v) Women whose first fresh embryo transfer attempt occurred after 30th September 2008.

(vi) Women whose treatments, as recorded in the database, lacked important data such as outcome of first cycle, diagnosis type, etc.

(vii) Women with a diagnosis of cervical infertility.

(viii) Women who were lost to follow up during their first cycle and so had no recorded outcome.

(ix) Women with first complete cycle outcomes other than miscarriage, live birth or no pregnancy (i.e. termination, ectopic pregnancy, molar pregnancy, stillbirth, embryo reduction).

(x) Treatments occurring after 30th September 2009 were excluded because after this date the policy for giving consent for identifying IVF patient data to be used in research changed from assumed (opt-out) to required (opt-in). This meant that including treatments from further years would have led to inaccurate discontinuation rates in analysis if women chose not to give consent for the use of their treatment information after this point.

Baseline characteristics

We considered the following characteristics for women at the start of their first treatment: year; duration of infertility (years); type of infertility (unexplained, endometriosis, tubal, anovulatory, or multiple diagnoses); and age. Treatment characteristics were also assessed, including: type of treatment used (IVF/ICSI); number of oocytes collected; number of embryos transferred; number of complete cycles undertaken; number of complete cycles until live birth and time (days) from first

155 treatment to the treatment that led to live birth. Descriptive numbers of other causes of pregnancy
156 loss were also recorded but for the purposes of the research question, we focussed on miscarriage
157 (including biochemical pregnancy).

158 Exposure groups

159 Participants were stratified into three cohorts depending on the best outcome of first complete cycle
160 of treatment: any live birth, miscarriage (and no live birth), and no pregnancy. Women whose outcome
161 did not fall into these categories (e.g. ectopic pregnancy, termination, stillbirth, embryo reduction)
162 were not included in analysis due to relatively small numbers.

163 Outcomes

164 The main outcomes were cumulative live birth rate per woman from the second complete cycle
165 onwards.

166 In women who had a live birth resulting from IVF treatment in their first complete cycle, and continued
167 with treatment, the cumulative live birth rate was calculated for the occurrence of their second live
168 birth. All complete cycles contributed to the CLBR up until the complete cycle in which a second live
169 birth occurred or until their last unsuccessful complete cycle.

170 For women who did not have a live birth in their first complete cycle (i.e. experienced a miscarriage
171 or did not get pregnant), and continued with treatment, the cumulative live birth rate for the
172 occurrence of their first live birth was calculated. Women who achieved a first live birth from IVF no
173 longer contributed to the cumulative live birth rate.

174 Statistical Analysis

175 Descriptive statistics of the first and second complete cycle patient and treatment characteristics were
176 generated both for each cohort. Patient-level characteristics studied were the mean (SD) of age;

median (interquartile range (IQR)) of duration of infertility; the frequency and percentage of primary versus secondary infertility and of each type of infertility (more than one cause, tubal, anovulatory, male factor, endometriosis, and unexplained). Treatment-level characteristics collected for both first and second complete cycles included frequency and percentage of IVF and ICSI treatments; the median (IQR) number of eggs retrieved; frequency and percentage of the number of embryos transferred and the stage at which they were transferred (no transfer, single cleavage, single blastocyst, double cleavage, double blastocyst, triple cleavage, triple blastocyst). For the first complete cycle alone the following additional characteristics were studied: frequency and percentage of live births; median (IQR) number of complete cycles until live birth and median (IQR) time (days) from first treatment until last treatment before live birth. The descriptive statistics of patients at the first complete cycle are shown in Supplementary Table I, and treatment information in Supplementary Table II.

Additionally, the outcomes of the second complete cycle were analysed for each cohort and broken down into the following categories: no pregnancy, live birth (and no pregnancy loss), miscarriage (and no live birth), miscarriage (and live birth), other pregnancy loss, discontinued treatment after first complete cycle, and lost to follow up.

As well as cumulative live birth rates, conditional live birth rates were estimated from the second complete cycle onwards for each of the three cohorts (i.e. miscarriage, no pregnancy, live birth). Three different live birth rates were calculated for each of the three cohorts:

Live birth rate per complete cycle (conditional live birth rate)

This was calculated by dividing the number of women who had their first live birth (with exception of women from the live birth cohort for whom it was second live birth) in each complete cycle by the number of women who attempted that complete cycle. 95% confidence intervals were calculated using the standard errors from the binomial distribution.

Conservative cumulative live birth rate

This method assumes that women who discontinued treatment would never have a live birth. At each complete cycle the number of women who had a live birth from complete cycle two until that complete cycle inclusive was divided by the number of women who continued treatment into complete cycle two.

Complete cycles occurring after the complete cycle which resulted in a first live birth were excluded from the CLBRs. For women who had a live birth in their first complete cycle, complete cycles occurring after that which resulted in their second live birth were excluded. Women who did not return for treatment were also not included in further analyses. The 95% confidence intervals were calculated as for the conditional live birth rates.

Optimal cumulative live birth rate

Optimal estimates of the CLBR are based on the assumption that women who did not return to treatment would have the same chance of a live birth as those who did. As for the conservative rates, women were excluded from further assessment after live birth or discontinuation occurred (Figure S1). The optimal CLBRs were calculated using Kaplan-Meier estimates, with Greenwood's formula used to calculate the standard error for each of these, and 95% confidence intervals estimated from the standard errors. The log-rank test was used to compare the differences in optimal CLBRs between each cohort group.

For both conservative and optimal CLBR estimates, if less than 100 women from the cohort being assessed attempted a complete cycle, it was excluded.

Multivariable analysis

A multivariable logistic regression model was used to assess the effect of each cohort on the cumulative chances of a live birth from the second complete cycle onwards whilst adjusting for

confounding factors. Complete cycle number was included in the model as a categorical covariate (i.e. each row of data represented a complete cycle per patient) along with the cohort i.e. outcome of first complete cycle (live birth versus no pregnancy, miscarriage versus no pregnancy). The following factors as measured at the start of the second complete cycle were included: female age; duration of infertility; primary versus secondary infertility; time (months) since the last embryo transfer attempt of complete cycle one; cause of infertility; treatment type (IVF/ICSI); number of oocytes collected and number and stage of embryos transferred (no transfer, single cleavage, single blastocyst, double cleavage, double blastocyst, triple cleavage, triple blastocyst). Female age at second complete cycle was found to have a non-linear relationship with the probability of live birth and was fitted as two linear effects.

The data was analysed using IBM SPSS v23.

Results

After exclusion criteria were applied, 113518 women who entered their first complete cycle between January 1999 and September 2008 were included. Of these, 112549 were then grouped into 3 cohorts according to the outcome of their first complete cycle i.e. no pregnancy (n=70076 (62.3%)), live birth (n=33152 (29.5%)) and miscarriage (n=9321 (8.3%)). The other outcomes were other forms of pregnancy loss, including ectopic pregnancy, stillbirth, termination and embryo reduction. Table I shows causes of pregnancy loss in women who had a pregnancy loss (and no live birth) in their first complete cycle. Miscarriage and biochemical pregnancy were the two most frequent pregnancy losses in the first complete cycle (4.2 and 3.9% of the whole population respectively). All other pregnancy losses were excluded and miscarriage and biochemical pregnancy were grouped into one miscarriage cohort. The proportion of pregnant women who had a miscarriage anywhere in the first complete cycle, regardless of live birth, in our population was 25.7%.

Characteristics of participants

The mean age (SD) of women at the start of their second complete cycle was similar across all three cohorts at 35 years (Table II). The median duration of infertility was four years for the miscarriage cohort, slightly lower than for the no pregnancy and live birth cohorts at 5 and 6 years respectively. The distribution of infertility diagnoses was similar across all cohorts, with male factor the most frequent diagnosis, followed closely by unexplained infertility.

Table III presents treatment characteristics of the first fresh transfer of couples' second complete cycle by outcome of first complete cycle. Women who had no pregnancies in their first complete cycle had a lower median (IQR) number of oocytes collected (8 (5-12)) than those who had miscarriage (9 (5-13)) or live birth (10 (6-14)). Of those women who had no pregnancy in their first complete cycle, 11.7% had no embryos transferred in their first fresh cycle – a 4.9% increase compared to the other two cohorts in both of which 6.8% had no transfer.

There was missing data for the following characteristics at the start of the second complete cycle: duration of infertility (5147; 10.6%); cause of infertility (214; 0.4%) and stage and number of embryos transferred (721; 1.4%). Over all woman assessed, 5953 (12.1%) had missing data in any of the second complete cycle characteristics.

We assumed that this information was missing at random and used a complete case analysis.

Of women who had a miscarriage in their first complete cycle, 12.1% went on to have another miscarriage and no live birth in the second complete cycle, and 2.2% had another miscarriage but also a live birth – both of these were an increase compared to the other two cohorts (Table IV). The proportion of women who had a live birth and no pregnancy loss in the second complete cycle was highest in the live birth cohort at 36.6%, compared to 29.3 and 21.5% in the miscarriage and no pregnancy cohorts respectively.

Live birth rates

The cumulative live birth rate was calculated for each of the three cohorts over a maximum of six complete cycles. Miscarriage (and no live birth) in the first complete cycle was associated with an optimal cumulative live birth rate of 72.4% after a further five complete cycles. All live birth rates calculated showed a difference between the cohorts.

In subsequent complete cycles, by first complete cycle outcome

The conditional and cumulative live birth rates varied across the three cohorts (Table V).

The conditional live birth rate at the second complete cycle differed between the three cohorts at 22.8% for those who had no pregnancies, 31.7% for miscarriage and 38.8% for those who had a live birth in their first complete cycle. In each cohort, the conditional live birth rate decreased with each successive complete cycle.

An outcome of miscarriage in the first complete cycle was associated with a higher conservative (44.0%) and optimal (67.1%) CLBR at complete cycle five compared to no pregnancy (33.1 and 57.8% respectively) (see Figure 2). However, an outcome of live birth in the first complete cycle was associated with the highest cumulative live birth rates: at complete cycle five, the conservative and optimal estimates were 52.6 and 75.5%. The difference in optimal CLBRs between the three cohorts was highly significant (p <0.001).

Age group

Figure 3 illustrates optimal cumulative live birth rates in each cohort group stratified by age group at first complete cycle. Across all cohort groups, optimal cumulative live birth rates decreased in older age groups.

Multivariable analysis

The results of the final model are represented in Table VI.

Women who had either a miscarriage or a live birth over the first complete cycle of IVF had a higher chance of live birth over subsequent complete cycles compared to women who never had a pregnancy in their first complete cycle. Women who miscarried in their first complete cycle had 42% increased odds of live birth compared to women who had no pregnancy [adjusted odds ratio (95% confidence interval) =1.42 (1.34, 1.50)]. Those who had a live birth in their first complete cycle also had improved chances of live birth: their odds were twice those of women who had no pregnancy [2.04 (1.89, 2.20)].

When compared to the second complete cycle, chances of live birth decreased with each successive cycle. Increasing female age at the second complete cycle was associated with decreased odds of live birth, especially over the age of 40 years [18-40 years = 0.94 (0.94, 0.95); >40 years=0.63 (0.59, 0.66)]. Over 40 years the odds of a live birth decreased by 37% with every increasing year of age. Increasing duration of infertility was associated with lower chances of a live birth [0.99 (0.98, 0.99)]. A diagnosis of tubal infertility at the second complete cycle was the only diagnostic group which significantly reduced the chances of live birth [0.88 (0.82, 0.94)].

Not having a previous live birth (primary infertility) and time between first and second complete cycles were not significantly associated with cumulative live birth and were excluded from the model.

Year of second complete cycle, which accounted for changes in practice and treatment with time, was positively associated with live birth [1.03 (1.02, 1.04)]. Additionally, the chances of a live birth increased by 11% when IVF was used rather than ICSI [1.11 (1.05, 1.16)]. The chance of live birth increased with increasing numbers of eggs collected at the second complete cycle [1.04 (1.04, 1.04) per egg].

Compared with double cleavage stage embryo transfers, single, double and triple blastocyst transfers were all associated with an increased chance of live birth. The transfer of a single cleavage stage

embryo had half the chances of a live birth compared to the transfer of two cleavage stage embryos [0.49 (0.45, 0.54)].

Discussion

Principal findings

We have reported the chances of cumulative live birth following miscarriage in the first complete IVF cycle, and compared the odds of future live birth to women whose first complete cycle outcome was either no pregnancy or live birth.

The chances of subsequent live birth increased in a dose dependent manner from no pregnancy to miscarriage to live birth in the first complete cycle. Although both pregnancy loss and non-pregnancy are viewed as a 'failure', our results show that the two have very different prognoses.

Strengths & weaknesses

This study estimated the cumulative chance of live birth following miscarriage in an IVF population, and successfully adjusted for known individual patient and treatment predictors of success in IVF using a multivariable model. Previous studies have reported chance of live birth in IVF after miscarriage, but did not report CLBRs. Some reported the results of one subsequent cycle rather than CLBRs over multiple subsequent cycles (Croucher et al. 1998, Kalu et al. 2011, Yang et al. 2015), while others reported live birth rate per oocyte retrieval, but could not report cumulative rates as there was no connection between woman and cycle (Kupka et al. 2004). CLBRs report success over complete cycles of continued treatment more accurately than single cycle live birth rates, and are seen as a better measure for counselling couples on chances of success in future cycles (Stern et al. 2010).

One previous study did report cumulative success rates after initial miscarriage, however the authors chose to use clinical pregnancy rates rather than live birth rates (Bates Jr and Ginsburg 2002). For women who have experienced miscarriage and are concerned about future pregnancy loss, a CLBR is

a more clinically relevant measure than a pregnancy rate alone. Additionally, this study did not adjust for confounding factors using a multivariable model (Bates Jr and Ginsburg 2002).

One limitation of our study is that women who started their first IVF treatment after September 2008 were not included in the analysis. This was due to the risk of incomplete data after changes to regulations regarding consent for data use in research. If women chose not to disclose their information for complete cycles occurring after this date our analysis would have returned a higher discontinuation rate not representative of the population resulting in underestimated cumulative live birth rates. The lack of the most recent data means that our data may not reflect current practice, for example: higher frequency of single blastocyst transfers and frozen embryo transfers.

The estimates for CLBRs contain certain assumptions: the optimal estimate assumes that women who discontinue treatment have a similar chance of live birth as those who continue, while the conservative estimate assumes the opposite: that those who discontinue have no chance of live birth. Neither option presents a perfect estimate, as the reasons women leave treatment are likely to be highly variable and not reported in the HFEA database. By taking into account the available potential confounders (e.g. type of infertility and age) with the multivariable model, we have adjusted for treatment continuation based on the available covariates (such as female age).

Due to the retrospective nature of this study, our analysis was limited to predictors included in the HFEA database. For example, the HFEA database does not contain information on body mass index, smoking, alcohol intake, ovarian reserve or embryo quality. We were unable to assess the contribution of diminished ovarian reserve (which is strongly associated with increasing age) separately from polycystic ovary syndrome (PCOS), as they were not differentiated into different variables in the HFEA database and no separate measures such as antral follicle count were included in the database. One important variable that was not available in the HFEA database was previous miscarriage status. However, we were able to select only women with primary infertility and repeat our analysis. There was no significant difference in either the CLBRs or results of the multivariable analysis.

Comparison with existing literature

Our findings are consistent with previous work on IVF outcomes after miscarriage (Bates Jr and Ginsburg 2002, Croucher et al. 1998, Kalu et al. 2011), and support the verdict that women who have achieved pregnancy (whether that pregnancy resulted in live birth or miscarriage) in a previous cycle have a better chance of subsequent live birth than those who did not become pregnant.

However, while Kalu et al. found that any difference between the outcome cohorts lost significance in women >40 years (Kalu et al. 2011), in our sample it remained significant in all age groups. This could be due to the much larger sample size in our dataset: Kalu et al. had 348 women in their >40 age group, while our dataset had 9,019. Additionally, only the second cycle and no frozen transfers were included, meaning that reproductive potential was not assessed as fully as with the cumulative live birth rates used in this study.

Early pregnancy loss is often due to chromosomal anomalies in the embryo, which become more common with increasing maternal age (van den Berg et al. 2012). Pregnancy loss due to chromosomal anomalies associated with increased maternal age is unrelated to the efficacy of fertility treatment, as pregnancy has been achieved. However, for women who have no pregnancies, treatment has 'failed', perhaps due to unfavourable uterine environment or other causes of infertility, or lesser response to ovulation induction. This could contribute to the increased live birth rate in women who experience miscarriage in their initial complete cycle compared to those who have no pregnancies.

Of the causes of infertility assessed, only tubal infertility was a significant, negative, indicator for live birth. One previous study using the HFEA database found a similar effect (McLernon et al. 2016a), and suggested it may be due to the effects of treatment variables dominating the impact of the different diagnoses, particularly for anovulatory, male factor only or unexplained infertility where mild infertility may be more prevalent. It could be that infertility diagnosis has a smaller effect on chance of live birth in those who have previously been able to achieve pregnancy with treatment than those who have not. Compared to women who have previously achieved pregnancy, women who have not

become pregnant could have a more fundamental barrier to pregnancy related to implantation of the embryo or a lower number of eggs available, perhaps making diagnosis a more influential negative predictor for these women and lowering their chance of live birth.

Interactions between immunogenetic mechanisms and human reproduction have been documented in normal pregnancy. It has been suggested that expression, regulation and interactions of factors such as HLA expression, cytokine activity, and natural killer cells all contribute to early pregnancy loss and reproductive failure (Choudhury and Knapp 2000a, Choudhury and Knapp 2000b). Additionally, Wang et al. have previously demonstrated a positive association between early pregnancy loss and subsequent clinical pregnancy (Wang et al 2003). Although the exact reason for the dose-response relationship between miscarriage and subsequent clinical pregnancy is unknown, it can be theorised that there is some immunogenetic mechanism causing the uterus to be better prepared after an initial miscarriage so it can carry a subsequent pregnancy to term. Similar factors are likely to be important in the IVF population analysed in our study, both in terms of the pathophysiology of pregnancy loss and in the increase in live birth rate compared to those who do not achieve pregnancy.

Meaning of the results/Clinical implications

Our results are useful both for clinicians and for couples who have suffered a miscarriage in an initial cycle of IVF/ICSI, especially when facing the already emotionally and financially burdened decision of whether to continue treatment. Additionally, the use of the HFEA Register database, which contains information on all fertility treatments in the UK makes the results of our analysis particularly relevant for use in the UK. When communicating with couples, cumulative live birth rates are a better representation of success rates over a complete journey of IVF than traditional live birth rates and so our analysis of success rates over multiple complete cycles will aid informed decision-making and help tailor expectations for these couples.

Research Implications

We propose future studies assessing the effect of timing of miscarriage on subsequent cycle outcomes, as the differing aetiologies for early and late pregnancy losses may affect future chances of live birth. There is a need for studies that are able to adjust for other confounders that we have been unable to address, such as history of previous miscarriage, BMI, smoking and ovarian reserve. Additionally, in a larger dataset the effects of other types of pregnancy loss e.g. ectopic or molar pregnancies could be assessed.

Conclusion

Women who have a live birth or miscarriage in their first complete cycle of IVF have a higher chance of having an IVF baby than women who do not become pregnant. This information is reassuring for couples considering their options for continuing treatment after an initial pregnancy loss.

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Author's Roles

DJM and SiB and SoB designed the study. NJC conducted the literature search and statistical analysis and wrote the article. All authors contributed intellectually to the writing or revising of the manuscript, and approved the final version.

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Competing interests

None of the authors has any conflicts of interest to declare. All have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author).

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Table I: Cause of pregnancy loss in first complete cycle, as a proportion of the whole population.

PREGNANCY LOSS (*n* = 10290)	***n* (%)**
BIOCHEMICAL PREGNANCY	4826 (4.2)
MISCARRIAGE	4495 (3.9)
ECTOPIC PREGNANCY	514 (0.5)
>1 LOSS OF ANY KIND	176 (0.2)
TERMINATION	170 (0.1)
STILLBIRTH	100 (0.1)
MOLAR PREGNANCY	9 (0.01)

Table II: Age and other characteristics of women entering their second cycle, by outcome of first cycle.

CHARACTERISTIC	**OUTCOME OF FIRST CYCLE,** *n* (%) unless otherwise stated		
	NO PREGNANCY	**MISCARRIAGE**	**LIVE BIRTH**
n (%)	39413 (79.9)	5369 (10.9)	3931 (8.0)
Age (year), mean (SD)	35 (4.4)	35 (4.2)	35 (3.9)
<31	6258 (15.9)	802 (14.9)	427 (15.4)
31-35	14555 (36.9)	1987 (37.0)	1499 (38.1)
36-40	14588 (37.0)	2097 (39.1)	1636 (41.6)
>40	4012 (10.2)	483 (9.0)	369 (9.4)
Duration of infertility, median(IQR)	5 (3-7)	4 (3-7)	6 (4-8)

CHARACTERISTIC	OUTCOME OF FIRST CYCLE, *n* (%) unless otherwise stated		
	NO PREGNANCY	**MISCARRIAGE**	**LIVE BIRTH**
Missing	4277 (10.9)	515 (9.6)	355 (9.0)
Type of infertility			
Primary	28965 (73.5)	3665 (74.0)	2737 (78.7)
Secondary	10448 (26.5)	1704 (26.0)	1194 (21.3)
Cause of infertility			
>1 cause	5845 (14.8)	791 (14.7)	605 (15.4)
Tubal	6544 (16.6)	874 (16.3)	564 (14.3)
Anovulatory	2547 (6.5)	355 (6.6)	224 (5.7)
Male factor	13175 (33.4)	1858 (34.6)	1627 (41.4)
Endometriosis	1393 (3.5)	154 (2.9)	108 (2.7)
Unexplained	9737 (24.7)	1316 (24.5)	782 (19.9)
Missing	172 (0.4)	21 (0.4)	21 (0.5)

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529 **Table III:** Treatment information for second cycle, by outcome of first cycle.

TREATMENT INFORMATION	OUTCOME OF FIRST CYCLE, *n* (%) unless otherwise stated		
	NO PREGNANCY	**MISCARRIAGE**	**LIVE BIRTH**
IVF	19768 (50.2)	2764 (51.5)	1829 (46.5)
ICSI	19645 (49.8)	2605 (48.5)	2102 (53.5)
Oocytes collected, median (IQR)	8 (5-12)	9 (5-13)	10 (6-14)
Stage and number of embryos transferred			
No transfer	4597 (11.7)	366 (6.8)	268 (6.8)
Single cleavage	3346 (8.5)	376 (7.0)	341 (8.7)
Single blastocyst	133 (0.3)	34 (0.6)	93 (2.4)
Double cleavage	25095 (63.7)	3757 (70.0)	2726 (69.3)
Double blastocyst	1067 (2.7)	244 (4.5)	222 (5.6)
Triple cleavage	4462 (11.3)	507 (9.4)	209 (5.3)
Triple blastocyst	114 (0.3)	18 (0.3)	17 (0.4)
Missing	599 (1.5)	67 (1.2)	55 (1.4)

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532 **Table IV:** Outcomes of second complete cycle, by outcomes of first complete cycle.

OUTCOME OF SECOND COMPLETE CYCLE	**OUTCOME OF FIRST COMPLETE CYCLE,** *n* (%) *n*= 48713[1]		
	NO PREGNANCY	**MISCARRIAGE**	**LIVE BIRTH**
NO PREGNANCY	26835 (68.1)	2953 (55.0)	1942 (49.4)
LIVE BIRTH, NO LOSS	8488 (21.5)	1571 (29.3)	1440 (36.6)
MISCARRIAGE, NO LIVE BIRTH	3260 (8.3)	650 (12.1)	404 (10.3)
MISCARRIAGE AND LIVE BIRTH	437 (1.1)	118 (2.2)	72 (1.8)
OTHER LOSS	331 (0.8)	66 (1.2)	51 (1.3)
LOST TO FOLLOW UP	62 (0.2)	11 (0.2)	22 (0.6)

[1]Total study population (*n*=112549) minus women who discontinued treatment after the first complete cycle (*n*= 63836: no pregnancy = 30663, miscarriage = 3952, live birth = 29221).

539 **Table V:** Live birth rates by first cycle outcome

COHORT (FIRST CYCLE OUTCOME)	Cycle	Live births	N. From cohort	Conditional live birth rate / cycle	Conservative cumulative live birth rate	Optimal cumulative live birth rate
NO PREGNANCY	2	8993	39413	22.8 (22.40, 23.23)	22.8 (22.40, 23.23)	22.8 (22.39, 23.21)
	3	2888	15503	18.6 (18.02, 19.24)	30.1 (29.69, 30.60)	38.4 (37.83, 38.97)
	4	892	5701	15.7 (14.70, 16.59)	32.4 (31.95, 32.87)	49.7 (48.97, 50.43)
	5	265	2073	12.8 (11.35, 14.22)	33.1 (32.62, 33.54)	57.8 (56.87, 58.73)
	6	88	797	11.0 (8.87, 13.22)	33.3 (32.84, 33.77)	64.1 (62.92, 65.28)
	7	30	317	9.5 (6.24, 12.69)	33.4 (32.91, 33.85)	69.0 (67.50, 70.50)
MISCARRIAGE	2	1704	5369	31.7 (30.49, 32.98)	31.7 (30.49, 32.98)	31.7 (30.45, 32.95)
	3	494	2123	23.3 (21.47, 25.07)	40.9 (39.62, 42.25)	49.5 (48.00, 51.00)
	4	123	739	16.6 (13.96, 19.33)	43.2 (41.90, 44.55)	59.8 (58.04, 61.56)
	5	40	286	14.0 (9.97, 18.01)	44.0 (42.65, 45.30)	67.1 (64.99, 69.21)
	6	13	109	11.9 (5.84, 18.01)	44.2 (42.89, 45.55)	72.4 (69.80. 75.00)
LIVE BIRTH	2	1524	3931	38.8 (37.25, 40.29)	38.8 (37.25, 40.29)	38.8 (37.28, 40.32)
	3	403	1341	30.1 (27.60, 32.51)	49.0 (47.46, 50.58)	57.9 (56.09, 59.71)
	4	107	454	23.6 (19.66, 27.47)	51.7 (50.18, 53.30)	68.5 (66.40, 70.60)
	5	35	166	21.1 (14.88, 27.29)	52.6 (51.07, 54.19)	75.5 (72.97, 78.03)

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Table VI: Couple characteristics at the second complete cycle and their effect on the chance of live birth over multiple subsequent complete cycles (adjusted odds ratios from final model).

COUPLE CHARACTERISTICS	ADJUSTED ODDS RATIO (95% CI)
OUTCOME OF FIRST COMPLETE CYCLE	
MISCARRIAGE (VERSUS NO PREGNANCY)	**1.42 (1.34, 1.50)**
LIVE BIRTH (VERSUS NO PREGNANCY)	**2.04 (1.89, 2.20)**
FEMALE AGE (YEARS)[1]	
18-40	**0.94 (0.94, 0.95)**
>40	**0.63 (0.59, 0.66)**
DURATION OF INFERTILITY (YEARS)	**0.99 (0.98, 0.99)**
YEAR OF SECOND CYCLE	**1.03 (1.02, 1.04)**
TYPE OF INFERTILITY	
TUBAL (YES VERSUS NO)	**0.88 (0.82, 0.94)**
MALE FACTOR (YES VERSUS NO)	1.07 (1.00, 1.14)
UNEXPLAINED (YES VERSUS NO)	1.04 (0.97, 1.11)
ANOVULATORY (YES VERSUS NO)	1.02 (0.96, 1.09)
ENDOMETRIOSIS (YES VERSUS NO)	0.97 (0.90, 1.06)
COMPLETE CYCLE NUMBER (VERSUS CYCLE 2)	
3	**0.86 (0.82, 0.90)**
4	**0.72 (0.67, 0.78)**
5	**0.63 (0.55, 0.71)**
6	**0.54 (0.43, 0.67)**
TREATMENT CHARACTERISTICS	
TREATMENT USED (IVF VERSUS ICSI)	**1.11 (1.05, 1.16)**
NUMBER OF EGGS COLLECTED	**1.04 (1.04, 1.04)**
STAGE OF EMBRYOS TRANSFERRED (VERSUS DOUBLE CLEAVAGE)	
NONE TRANSFERRED	**0.28 (0.25, 0.31)**
SINGLE CLEAVAGE	**0.49 (0.45, 0.54)**
SINGLE BLASTOCYST	**1.59 (1.24, 2.05)**
DOUBLE BLASTOCYST	**1.75 (1.59, 1.94)**
TRIPLE CLEAVAGE	0.98 (0.92, 1.05)
TRIPLE BLASTOCYST	**1.45 (1.04, 2.01)**
Nagelkerke R^2= 0.123	

[1] Female age at second complete cycle was found to have a non-linear relationship with the probability of live birth and was fitted as two linear effects.

Figure Legends

Figure 1: Flow chart of exclusion criteria

Figure 2: Optimal (A) and conservative (B) cumulative live birth rates per woman by outcome of first complete cycle.

Figure 3: Optimal cumulative live birth rates, by age group and outcome of first complete cycle (A) miscarriage (B) live birth (C) no pregnancy.

Supplementary figure 1: Continuation rates after Cycle 1, by outcome of first complete cycle. Women who had a live-birth in their first complete cycle had a much higher discontinuation rate after this first complete cycle than those who did not.