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ARTICLE

Cumulative live birth rates following insemination with donor spermatozoa in single women, same-sex couples and heterosexual patients

BIOGRAPHY

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KEY MESSAGE

Cumulative live birth rates up to 29% can be achieved in a large donor insemination programme involving same-sex couples and single women. No more than six treatment cycles seem reasonable in women <40 years of age and three attempts up to 42 years of age. IUI-D with mild ovarian stimulation performs better than treatment in a natural cycle.

ABSTRACT

Research question: What is the cumulative live birth rate (LBR) following donor intrauterine insemination (IUI-D) treatment in a large, retrospective, single-centre cohort of single women, same-sex couples and heterosexual patients?

Design: Outcomes from 8922 treatments performed in 3333 consecutive women (45% single, 43% from same-sex and 12% from heterosexual couples) were analysed in a 13-year retrospective study from a private, HFEA-regulated UK centre between January 2004 and December 2016.

Results: A total of 795 live births resulted in an overall delivery rate of 8.9% per cycle, including 24 (3%) twins. Age-specific crude and expected cumulative LBR calculated in four age groups (<35, 35–37, 38–39 and 40–42 years) were 29, 23, 21, 12% and 66, 49, 54, 28%, respectively. A plateau was reached after six cycles, beyond which there were few additional live births. There was no significant difference in cumulative LBR between single women and same-sex couples. In a multivariate analysis, female age (adjusted odds ratio [aOR] 0.92; 95% confidence interval [CI] 0.90–0.93; $P < 0.0001$), previous live birth following IUI-D (aOR 2.15; 95% CI 1.69–2.73; $P < 0.0001$) and mild stimulation (aOR 1.27; 95% CI 1.09–1.48; $P = 0.02$) had a significant effect on outcome, but relationship status or cycle rank did not.

Conclusions: These results indicate there is little benefit performing more than six cycles of IUI-D in all women up to 40 years old, including those from same-sex relationships, while only three attempts seem reasonable in those aged 40–42 years. These results do not reflect current clinical guidelines in the UK. The authors found that consecutive IUI cycles, especially with mild stimulation, were an efficient treatment in all indications.

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KEYWORDS
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Donor spermatozoa
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Same-sex couples
Single women

INTRODUCTION

An increasing number of same-sex couples and single women have sought fertility treatment in the past two decades, as social attitudes have changed and clinics have become increasingly accessible to them (Bodri et al., 2018; Priddle, 2015). Because many of these patients are not infertile but 'only' require the use of donor spermatozoa, they often opt for a clinic's least invasive and simplest treatment; for a growing majority this means that the favoured option is donor intrauterine insemination (IUI-D) with no or minimal medication and monitoring.

The uptake of IUI-D was interrupted in 2005 by new requirements from the UK regulator giving donor-conceived children, at the age of 18, the right to identifying information about their donor. This was reported to have led to a sharp decline in the availability of donor spermatozoa and a consequent reduction in IUI-D cycles (Shukla et al., 2013). However, any such trend was reversed when, in 2012, fixed expenses to sperm donors were introduced and the Human Fertilisation and Embryology Authority (HFEA, 2020) agreed to the importation of sperm samples from overseas donor banks. Thereafter, greater attention to donor recruitment and customer care by the UK's own sperm banks increased domestic donor choices for UK women, who then increasingly sought treatment at home rather than in overseas centres (Ahuja, 2015). A recent report from the HFEA confirmed that the number of UK sperm donors almost quadrupled between 2004 and 2016, and IUI-D treatments almost trebled from 2008 (HFEA, 2018), consistent with a worldwide trend (Sawyer et al., 2013; Soares et al., 2019).

Few studies have evaluated cumulative LBR following IUI-D treatments. The optimum number of IUI-D attempts prior to IVF treatment remains unclear and ill defined (Custers et al., 2008; De Brucker et al., 2009). Current UK guidance in selected patient groups (including women in same-sex relationships) recommends up to 12 cycles: six initial attempts followed by fertility testing, and then another series of six attempts (NICE, 2017). However, in the same NICE guidance, insemination with partner spermatozoa in patients with unexplained infertility, mild male factor or mild endometriosis is not advised; instead, after 2 years of expectant management, only IVF is recommended. This national policy, based on weak evidence, has drawn fierce criticism, not least because a potentially efficient, less invasive and, compared with IVF, cheaper treatment has been denied (Bahadur et al., 2016, 2017). In fact, the choice of treatment is far from clear and should be based on proven effectiveness and safety rather than focusing only on the perceived higher success of IVF treatment (Kandavel and Cheong, 2018; Mol et al., 2018).

The aim of this large, 13-year retrospective study was to calculate age-specific crude and expected cumulative LBR in a range of patients in a large, single-centre donor insemination programme, which over the past two decades has provided fertility care, especially to single women and same-sex couples in the UK.

MATERIALS AND METHODS

Study population

This retrospective analysis included 3333 consecutive patients from a single centre (London Women's Clinic, London, UK) who underwent a total of 8922 cycles of IUI-D between January 2004 and December 2016. The outcome of all treatment cycles was followed up until December 2017. For the analysis of cumulative delivery rates all cycles up until the first achieved live births were considered (n = 8293). The protocols employed complied with UK regulation (Human Fertilisation and Embryology Act, 1990, 2008) and were performed in a facility inspected and certified by the HFEA. This retrospective analysis did not require ethical committee or institutional review board approval, as it assessed clinical outcomes from previously validated and approved procedures, practised under licence from the HFEA. All participating patients provided informed written consent for the use of their clinical data in this analysis.

Natural cycle or stimulated IUI and laboratory procedures

Participating women had a normal basic fertility work-up, including general and gynaecological history, infectious screening, ovarian reserve markers, cervical smear and pelvic ultrasound. Tubal patency was evaluated with hystero contrast sonography (HyCoSy) or X-ray hysterosalpingography, even if it was not compulsory in all patients, especially in those who did not have any risk factors. However, after three failed inseminations and before proceeding with any new insemination attempts, verification of tubal patency was strongly encouraged. The indications for IUI-D were severe male infertility or request for treatment from same-sex couples and single women. Patients were treated in individual cycles or were offered a series of three successive treatments. All patients were eligible for a subsequent treatment. IUI-D was usually performed in a spontaneous natural cycle indicated by home urinary LH monitoring. Otherwise, patients received minimal-dose ovarian stimulation, either clomiphene citrate 50–100 mg/day between cycle days 3 and 7, or gonadotrophin 50–75 IU on alternate days or daily from cycle day 2–3 (based on physician preference). Stimulation was accompanied by transvaginal ultrasound scanning from cycle day 8–10 onwards. In natural cycles IUI-D was scheduled approximately 24 h after a spontaneous LH surge (detected by testing kits in the morning), and in stimulated cycles 36 h after human chorionic gonadotrophin administration (Ovitrelle; Merck Serono, Feltham, Middlesex, UK) and following confirmation of 1–3 leading follicles ≥17 mm. Cycles were cancelled if more than three follicles of ≥15 mm were present.

Before treatment an anonymous phenotypically matched sperm donor was selected, usually from the UK's largest private sperm bank (London Sperm Bank) or occasionally from foreign providers (Cryos or European Sperm Bank from Denmark, or Xytex or Seattle Sperm Bank from the USA). Foreign sperm banks had to comply with UK requirements for donor screening and anonymity and the samples were shipped to the study centre in advance. The frozen spermatozoa were thawed on the day of insemination. On average one ampoule or straw was thawed per patient. It was thawed for 10 min at 37°C and prepared with double density gradient (SpermGrad™ 40%, 80%, Vitrolife, Göteborg, Sweden) and centrifugation 0.6 RCF or relative centrifugal value is already the correct g value (previously it was 2000 rpm). A single insemination was performed with a minimum of 5×10^6 inseminated sperm count of progressively motile spermatozoa in a disposable catheter

(Wallace IUI Catheter, CooperSurgical, London, UK) by a nurse practitioner or consultant. In stimulated cycles (either with clomiphene or gonadotrophin), luteal support was also given in the form of vaginal progesterone 400 mg once daily suppositories (Cyclogest; Actavis Healthcare, Barnstaple, UK).

Cumulative outcome and multivariate analysis

The primary outcome of this retrospective cohort study was cumulative LBR. Live birth was defined as a child born after 22 weeks or weighing at least 500 g. Pregnancy outcomes were verified using patient questionnaires and telephone follow-up if no answers were obtained. Multiple live births were counted as one live birth. For the cumulative analysis patients were not re-enrolled after having a first delivery.

In line with previous reports, two approaches frequently employed to estimate the effectiveness of treatment according to the number of cycles are described here. The first method calculates outcome by dividing the number of women achieving live birth to a predetermined number of cycles (numerator) by the total number of women who had IUI-D (denominator). The outcome measure associated with this method is referred to as the 'crude live birth rate'. The other method estimates the cumulative LBR after a specified number of cycles using life table analysis (Kaplan–Meier method) and considering the effect of censoring (dropout) (*Daya, 2005*; *Maheshwari et al., 2015*). The outcome measure associated with this method is referred to as the 'expected live birth rate'. Dropout per cycle was defined as the percentage of those patients who did not achieve a live birth and discontinued further treatment without providing an explanation.

Expected cumulative LBR (curves) were compared by log-rank tests. A P-value of 0.01 or less is considered to be statistically significant. Cumulative LBR were compared for four subgroups according to patient age: under 35, 35–37, 38–39 and 40–42 at the time of the first IUI-D attempt. Cumulative LBR were not calculated for women ≥43 years because of the low numbers achieving live births.

The association between five patient- or cycle-related prognostic factors and live birth was examined in all treatment cycles (n = 8922) by a multivariate logistic regression analysis. Beside female age (years), this statistical model also included previous successful IUI-D treatment with live birth (yes/no), current cycle rank (1st to 2nd as reference, versus 3rd to 4th, 5th to 6th cycle, and 7th or higher), stimulation type (non-stimulated as reference, versus mild stimulation) and relationship status (same-sex as reference, versus single or heterosexual). Relationship status was self-reported on patient history questionnaires and restated at the initial consultation. Computational procedures were performed using SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics

A total of 3333 consecutive women underwent 8922 treatment cycles during 2004–2016. Patients were single women (45%), from same-sex couples (43%) or in a heterosexual relationship (12%). Same-sex couples and heterosexual patients were significantly younger than single women (P < 0.0001; TABLE 1). Most treatments were performed in a natural cycle (58%), the rest with mild stimulation. The proportion of single women increased with advancing age (17 to 88%), while the proportion of same-sex and heterosexual patients decreased (64 to 8% and 19 to 4%, respectively) (FIGURE 1).

Overall LBR related to age, ovarian stimulation and relationship status

In total there were 795 live births resulting in an overall 8.9% per cycle LBR (TABLE 1). Altogether 600 patients continued treatment until having (only) one child, 90 having (only) two consecutive children, and five patients having up to three consecutive children. Overall twin delivery rate was 3% (24/795) and only one triplet birth occurred as a result of monozygotic twinning in one of the twin pairs. Overall LBR of natural versus stimulated cycles was 8.5 versus 9.4%. Single women had a significantly lower LBR than same-sex or heterosexual patients (6.7 versus 11.0 and 10.0%, P < 0.0001) (TABLE 1).

LBR according to the different age groups and stimulation protocols are shown in TABLE 2. Overall rates declined steadily with advancing female age and were found in the five groups (under 35, 35–37, 38–39, 40–42, 43 or above) to be 12.5, 9.7, 8.2, 5.4 and 0.4%, respectively. The oldest patient achieving a live birth was 44 years old. Stimulated cycles were significantly more successful in the

TABLE 1 BASELINE PATIENT AND CYCLE CHARACTERISTICS ACCORDING TO RELATIONSHIP STATUS AND OVARIAN STIMULATION

Groups	Patients (n)	Cycles (n)	Live births (n, %)	Age (mean ± SD), years
Relationship status				
Same-sex couples	1439	4238	447 (11.0%)	34.6 ± 4.2[b]
Heterosexual	408	1001	101 (10.0%)	33.8 ± 4.7[b]
Single women	1486	3683	247 (6.7%)[a]	38.9 ± 3.9[b]
Ovarian stimulation				
Natural	–	5172	442 (8.5%)	35.7 ± 4.6[c]
Stimulated	–	3750	353 (9.4%)	37 ± 4.6[c]
Total	3333	8922	795 (8.9%)	36.3 ± 4.7

[a] P < 0.0001 with chi-squared test,

[b] P < 0.0001 with one-way analysis of variance test,

[c] P < 0.0001 with Student's t-test.

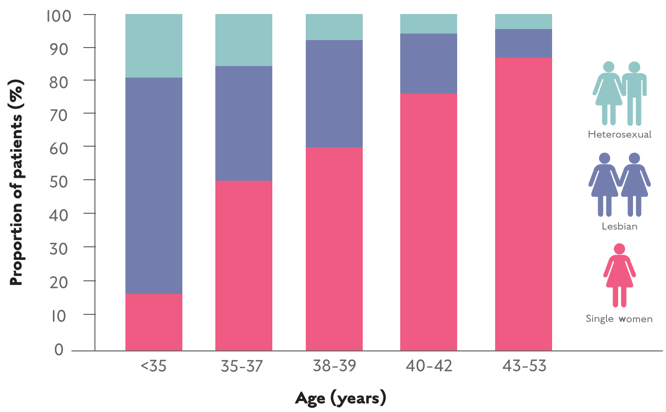

FIGURE 1 Relative proportion of single women or lesbian/heterosexual couples in different age groups (n = 3333).

TABLE 2 LIVE BIRTH RATES (%) ACCORDING TO PATIENT AGE AND OVARIAN STIMULATION

Age groups	Natural cycles	Mild stimulation	Total
Under 35	11.3% (216/1919)[a]	15.0% (151/1009)[a]	12.5% (367/2928)
35–37	9.2% (126/1367)	10.5% (86/816)	9.7% (212/2183)
38–39	8.3% (67/810)	8.2% (59/722)	8.2% (126/1532)
40–42	4.1% (32/777)[b]	6.7% (55/827)[b]	5.4% (87/1604)
43 and over	0.3% (1/299)	0.5% (2/376)	0.4% (3/675)

[a] P = 0.004 and

[b] P = 0.025 with chi-squared test.

under 35 and 40–42 years age groups (P = 0.004 and P = 0.025, respectively).

Cumulative LBR related to age and relationship status

Crude and expected cumulative LBR according to age are represented in FIGURES 2 AND 3 and Supplementary Table 1. LBR per cycle within the same age group were stable and did not decrease significantly with increasing cycle rank (Supplementary Table 1). Maximal crude cumulative LBR for all patients decreased with advancing female age: 29, 23, 21 and 12% in the under 35, 35–37, 38–39 and 40–42 years age groups, respectively (P = 0.002 between the <35 and 35–37 years, P = 0.40 between the 35–37 and 38–39 years, and P < 0.0001 between the 38–39 and 40–42 years groups). A plateau in success rates was reached after approximately six cycles. Expected cumulative LBR for all patients were 66, 49, 54, 28% in the under 35, 35–37, 38–39 and 40–42 years groups, respectively (P = 0.001 between the <35 and 35–37 years, P = 0.54 between the 35–37 and 38–39 years, and P = 0.001 between the 38–39 and 40–42 years groups). In the oldest age group (≥43 years) only one live birth occurred, in a 44-year-old patient.

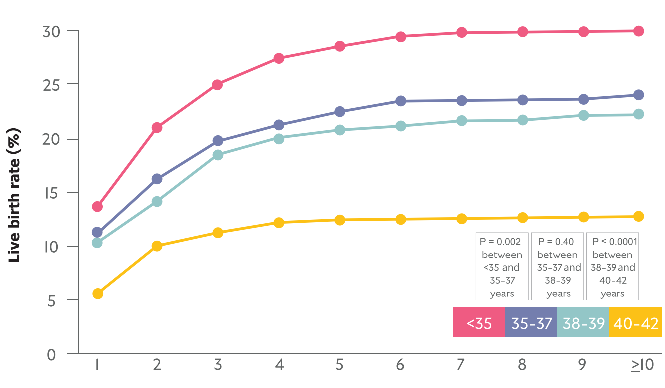

FIGURE 2 Crude cumulative live birth rates according to age (P = 0.002 between <35 and 35–37 years, P = 0.40 between the 35–37 and 38–39 years, and P < 0.0001 between 38–39 and 40–42 year groups, with chi-squared test).

Maximal crude cumulative LBR in same-sex couples versus single women were not significantly different: 31 versus 26 (P = 0.23), 24 versus 22 (P = 0.49), 21 versus 20 (P = 0.72) and 16 versus 10% (P = 0.051) in the under 35, 35–37, 38–39, 40–42 years age groups, respectively (FIGURE 4A). Similarly, maximal crude cumulative LBR in same-sex versus heterosexual couples were not significantly different: 31 versus 24 (P = 0.50), 24 versus 17 (P = 0.29), 21 versus 22 (P = 0.73) and 16 versus 15% (P = 0.34) in the under 35, 35–37, 38–39, 40–42 years age groups, respectively (FIGURE 4B).

Dropout rates

Overall dropout rates per cycle varied between 28% and 50%. Age-specific cumulative dropout rate curves were notably steeper with increasing patient age (FIGURE 5).

Multivariate analysis

In a multivariate analysis, female age (adjusted odds ratio [aOR] 0.92; 95% confidence interval [CI] 0.90–0.93; P < 0.0001), previous IUI-D live birth (aOR 2.15; 95% CI 1.69–2.73; P < 0.0001) and ovarian stimulation (aOR 1.27; 95% CI 1.09–1.48; P = 0.02) had a significant effect on outcome, but not relationship status (P = 0.160) or cycle rank (P = 0.465).

DISCUSSION

This 13-year cohort study, which is thought to be the largest published to date, shows first that acceptable cumulative LBR can be achieved in a series of IUI-D treatments in a broad range of single, same-sex or heterosexual women, especially if under 40 years old. However, in the 'real-life' setting of this study, where dropout rate was found to have a notable impact, a plateau in success rates was observed, with little additional benefit found from performing more than six treatments.

The current UK clinical guidelines do not recommend IUI as a first-line treatment for patients with unexplained infertility, mild endometriosis or mild male factor.

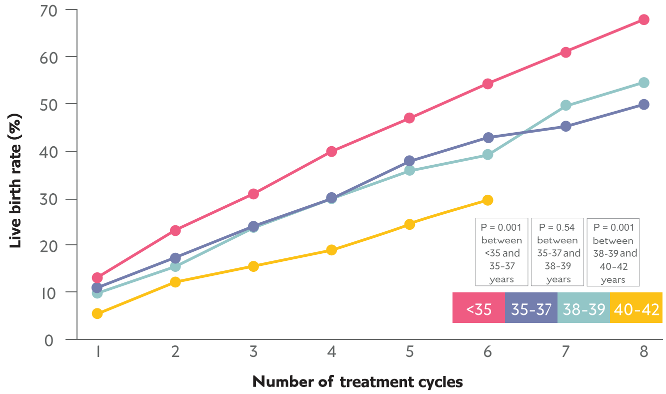

FIGURE 3 Expected cumulative live birth rates according to age (P = 0.001 between the <35 and 35–37 years, P = 0.54 between the 35–37 and 38–39 years, and P = 0.001 between the 38–39 and 40–42 years groups).

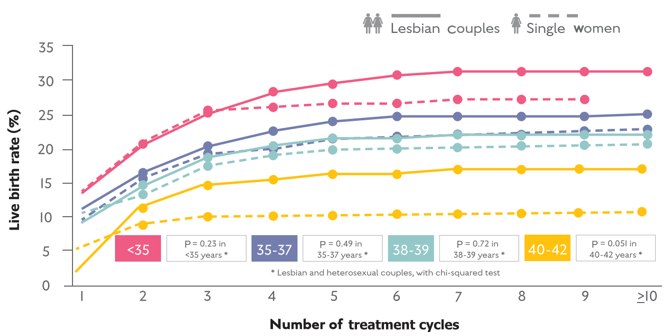

FIGURE 4A Age-specific crude cumulative live birth rates in lesbian couples and single women (P = 0.23 in the <35 years, P = 0.49 in the 35–37 years, P = 0.72 in the 38–39 years and P = 0.051 in the 40–42 years groups, with chi-squared test).

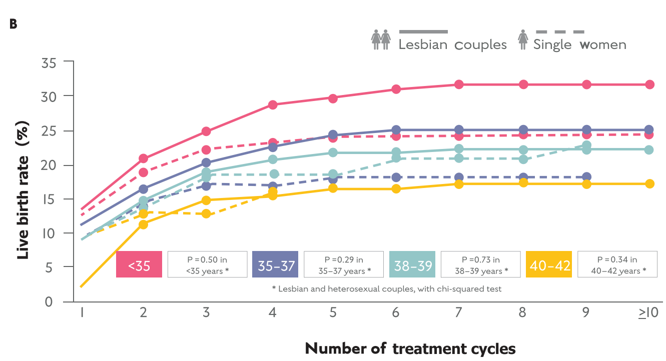

FIGURE 4B Age-specific crude cumulative live birth rates in lesbian couples and heterosexual couples (P = 0.50 in the <35 years, P = 0.29 in the 35–37 years, P = 0.73 in the 38–39 years and P = 0.34 in the 40–42 years groups, with chi-squared test).

Instead, expectant management for 2 years is advised before considering IVF (*NICE, 2017*). This has attracted considerable criticism – that the guidance is based on only a few studies of limited quality, it overestimates the risk of multiple pregnancies with stimulated IUI, and has encouraged IVF clinics to withdraw IUI in favour of IVF treatment (*Bahadur et al., 2016*).

However, more recent high-quality evidence suggests that a series of IUI treatments is actually superior to expectant management alone and provides acceptable success rates with low risk of multiple conceptions (*Bahadur and Homburg, 2019*). In addition, a trial from New Zealand, which randomized 201 women to three cycles of stimulated IUI or expectant management, achieved significantly higher cumulative LBR in the IUI arm (31 versus 9%) (*Farquhar et al., 2018*). A recent large multicentre Dutch trial comparing a maximum of four cycles of gonadotrophin versus clomiphene-stimulated IUI treatments in 738 couples with unexplained infertility found comparable ongoing LBR within 6 months (31 versus 26%) and uniformly low multiple rates (1.4 versus 2.2%) (*Danhof et al., 2018*, *2020*). The authors concluded that both treatments could be offered as an effective but less invasive, less burdensome and less costly treatment than IVF in this patient group. A more recent register-based national cohort study from Denmark reached similar conclusions (*Malchau et al., 2017*). By crosslinking the national ART and birth registries it was possible to determine the long-term likelihood of live birth in patients who started their fertility treatment either through partner IUI or immediate ART. Of the 12,488 patients who began their treatment with IUI (most having no more than three attempts), 34.2% conceived within 2 years, 38.0% switched to ART and 16.6% conceived naturally. The results support Danish national guidelines (*Malchau et al., 2017*), that IUI represents a valid first-line treatment for couples with idiopathic, mild male factor or anovulatory infertility.

While the UK's NICE guidelines do not recommend IUI as first-line treatment for unexplained, mild male and endometriosis-linked infertility, they do support IUI for same-sex couples (*NICE, 2017*). Their recommendation is 12 unstimulated cycles: six initial attempts (intracervical or intrauterine) followed by fertility testing and a further series of six treatments. The definition of this exact number of treatment cycles was not based on everyday clinical data derived from a large sample of patients in which age and relationship status were properly accounted for. Results of this study show that such factors clearly affect outcome, including rates of dropout.

According to an HFEA report on recent trends in UK ART, the number of IUI-D cycles has been steadily rising since 2006 (*HFEA, 2018*). However, this was largely explained by an increase in privately funded cycles; in 2016 NHS-funded treatments were still at a low level (only 16% of performed donor insemination cycles). Thus, by not distinguishing properly between different patients (according to age and relationship status)

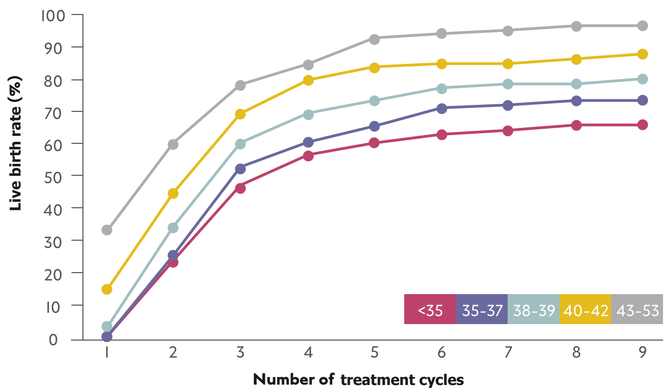

FIGURE 5 Cumulative dropout rates according to age.

and recommending a blanket number of treatment cycles, the NICE guidance has had an undeniably negative effect on IUI treatments (with donor and partner spermatozoa) within the NHS. Conversely, as this study also suggests, prospective patients who could afford funded treatment have largely ignored the NICE guidance (and the NHS) and they now constitute the majority of our donor insemination cycles.

This study strongly supports the utility of six (but not 12) IUI-D treatments, preferably stimulated in a mild protocol and in women <40 years of age regardless of their relationship status. After six failed insemination cycles, changing to IVF treatment would be warranted. IUI-D treatment in women aged 43 years or older is not encouraged, because above this age limit treatment is considered futile. However, women who have already conceived through IUI-D are encouraged to repeat treatment for further children.

To date several studies involving smaller or larger series of IUI-D treatments from single or multiple centres have been published, examining cumulative success rates and various prognostic factors (TABLE 3). However, only two (and one very recent) investigated (De Brucker et al., 2009, Soares et al., 2019) a mixed patient population which included single women and same-sex couples; the rest looked only at heterosexual patients being treated for severe male factor infertility (Botchan et al., 2001; Guan et al., 2016; Khalil et al., 2001; Na et al., 2018; Vitthala et al., 2008).

One of the more robust of these studies reported on age-specific LBR in an IUI-D treatment series involving 6630 cycles (De Brucker et al., 2009). As in this study, it also included different populations of same-sex couples, single and heterosexual patients covering a wide age range. Cumulative LBR were remarkably high, even in a real-life scenario with dropout, decreasing from 71 to 26% (from youngest to oldest) through the different age groups. The differences in LBR between this and the current study might be explained by a lower dropout rate than this study and a higher rate of stimulated cycles (82 versus 42%). The reasons for a higher dropout in the current study are probably multifactorial; partly related to switching to more efficient IVF treatment, to self-censoring, or to potentially changing to other clinics. It is remarkable that cumulative dropout rate curves were steeper in older patients, implying that patient age is an important contributor to dropout. The high cost of the treatment in a private setting is probably another decisive factor. In the multivariate analysis of De Brucker et al. (2009), only female age had a significant effect – but not ovarian stimulation (although most cycles were already stimulated) or indication (as a synonym for relationship status). In the oldest age group, the authors encouraged IUI-D treatment until 42 years, just as in this series. The effect of age was questioned by the same authors in a matched study of a smaller number of patients between 40 and 45 years of age (De Brucker et al., 2013). Although cumulative LBR from six IUI-D or three primary ICSI cycles were not significantly different (24 versus 26%), the authors did recommend immediate ICSI because of a much shorter time to pregnancy.

The most recent multicentre study came from a Spanish group (Soares et al., 2019) examining potential differences in outcomes between single women, heterosexual and same-sex couples requiring IUI-D (5318 cycles) against a control group having autologous partner insemination (1910 attempts). In contrast to the current study, their study protocol had ovarian stimulation in all attempts, a more vigorous approach which led to a higher per cycle success rate, but multiple conception rates as high as 13.5%. They were unable to detect any differences in per cycle

TABLE 3 MAIN CHARACTERISTICS OF RETROSPECTIVE STUDIES ON DONOR INSEMINATION

Author, year	Country	Population	Patients, *n*	Female age, mean ± SD	Cycles, *n*	LBR/cycle	Multiple LBR	Cumulative LBR
Botchan, 2001	Israel	Hetero	1.001	33.6 ± 6.1	6.139	9.9%	n/a	n/a
Khalil, 2001	Denmark	Hetero	305	n/a	1.131	26.5%	24.2%	61%
Vitthala, 2008	UK	Hetero	235	33	704	14.4%	0%	43.4%
de Brucker, 2009	Belgium	Single, lesbian, hetero	1.654	n/a	6.630	14%	8.7%	56%
Guan, 2016	China	Hetero	1.355	27.8	2.821	25.8%	n/a	53.7%
Na, 2018	China	Hetero	3.451	28.2	8.750	20.9%	2.3%	50.9%
Soares, 2019	Spain	Single, lesbian, hetero	2.515	n/a	5.318	12.4–17.7%	10.4–13.5%	n/a
Linara, 2020	UK	Single, lesbian, hetero	3.333	36.3 ± 4.7	8.922	8.9%	3%	20.9%

n/a = not available.

LBR among the three groups but, unsurprisingly, concluded that couples needing autologous insemination had a lower rate. From their multivariate analysis only female age and low ovarian reserve had any significant impact. In contrast to the current study, age-specific cumulative LBR was not a focus of their study, which included a maximum of only four attempts, just two age categories and applied an 'estimated' life table calculation, which considerably overestimated success.

In this series female age had a significant effect (both in the multivariate analysis and in comparing cumulative curves), although these differences were not significant between the 35–37 and 38–39 years groups. Success rates dropped sharply afterwards, reaching only 12% cumulatively for 40–42-year-old patients. Similarly, as in another relevant published study (*De Brucker et al., 2009*), LBR was extremely low for patients aged 43 or older, thereby defining a clear upper age limit for IUI-D treatment and futility of treatment above it.

Apart from female age and previous IUI-D success, only mild ovarian stimulation had an additionally significant effect on outcome. This higher success rate was probably related to more intensive monitoring and a potentially higher number of mature follicles. Thus, the per cycle LBR in this study is lower than found in many of these other studies, which overwhelmingly used ovarian stimulation; there was a high proportion of natural cycle IUI-D in the current study. If the outcomes of the stimulated cycles alone from this study are compared with the recent Spanish results (*Soares et al., 2019*), the LBR are much closer: 13, 8.2, 6.7% versus 17.4, 11.1, 6% in ≤37, 38–39, ≥40 years age groups, respectively. Moreover, the current study uses an ovarian stimulation protocol which could be considered as mild, using clomiphene only or low-dose gonadotrophins. Retrospective and prospective IUI-D studies have consistently demonstrated that gonadotrophin stimulation results in higher pregnancy rates than in unstimulated cycles, or even with clomiphene citrate alone (*Matorras et al., 2002*; *Thijssen et al., 2017*).

It should also be noted that most of the study subjects over this 13-year period were not 'typical' infertile patients, but same-sex couples or single women often requesting the simplest treatment (without hormonal medication) and the simplest monitoring (natural cycle IUI and LH testing at home). In a self-funding clinical setting such as in the current study, patient preference is a major determinant of the type of treatment chosen, the number of intended cycles and dropout rates. The results of this study clearly demonstrate that IUI-D in a natural cycle is associated with a lower LBR than in a mildly stimulated cycle, even though more frequently requested by patients. We are thus contemplating a change of established practice (through enhanced patient education) to a more vigorous stimulation approach which may yield higher LBR, albeit, if not monitored carefully, at a potential cost of more multiple conceptions (*Zolton et al., 2020*). Another potential reason for a lower LBR is that many patients (especially single women, but even lesbian patients) might have had some unknown infertility factors, such as undiagnosed tubal obstructions or reduced oocyte quality, that were left undetected by a relatively simple initial fertility work-up. Previous successful IUI treatment at the study centre appeared a strong positive prognostic factor, and a good reason why patients who previously conceived with IUI-D are encouraged to continue treatment if wanting more children. However, exact information on previous parity or gestational history was not completely available for all patients and this prognostic factor could not be evaluated precisely in the multivariate analysis.

The main limitation of this large retrospective study is that several patient- or cycle-related factors were not available or completely gathered (body mass index, parity, smoking, ovarian reserve markers, number of mature follicles, donor sperm parameters). This limited the multivariate part of the analysis. In addition, no data were available on reasons for patient dropout, which had the most notable effect on cumulative success rates. Future studies, therefore, to better evaluate the cumulative chances of success, might aim to gather all important prognostic factors prospectively, or assign different patient groups in an age-stratified and prospective manner to a predefined number of treatment cycles.

In conclusion, this 13-year series shows that consistently acceptable cumulative LBR can be achieved in a large donor insemination programme which includes same-sex couples and single women. In contrast to current UK clinical guidelines, these data indicate that no more than six treatment cycles seem reasonable in women <40 years of age, and three attempts seem to be reasonable up to 42 years of age, irrespective of whether donor or partner spermatozoa are used. Mild ovarian stimulation performed better than treatment in a natural cycle and patients who have achieved a previous IUI-D success are encouraged to continue for conceiving further offspring. Future prospective studies are needed to better distinguish between different patient groups, who might benefit more from tailored treatment approaches.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rbmo.2020.08.010.

REFERENCES

Ahuja, K.K. **Patient pressure: Is the tide of cross-border reproductive care beginning to turn?** Reproductive biomedicine online 2015; 30: 447–450

Bahadur, G., Homburg, R. **Growing body of evidence supports intrauterine insemination as first line treatment and rejects unfounded concerns about its efficacy, risks and cost effectiveness.** JBRA assisted reproduction 2019; 23: 62–67

Bahadur, G., Homburg, R., Muneer, A., Racich, P., Alangaden, T., Al-Habib, A., Okolo, S. **First line fertility treatment strategies regarding iui and ivf require clinical evidence.** Human reproduction 2016; 31: 1141–1146

Bahadur, G., Woodward, B., Homburg, R., Al-Habib, A., Muneer, A. **Pitfalls of nice recommendations on fertility treatment.** Bmj 2017; 356: j751

Bodri, D., Nair, S., Gill, A., Lamanna, G., Rahmati, M., Arian-Schad, M., Smith, V., Linara, E., Wang, J., Macklon, N., Ahuja, K.K. **Shared motherhood ivf: High delivery rates in a large study of treatments for lesbian couples using partner-donated eggs.** Reproductive biomedicine online 2018; 36: 130–136

Botchan, A., Hauser, R., Gamzu, R., Yogev, L., Paz, G., Yavetz, H. **Results of 6139 artificial insemination cycles with donor spermatozoa.** Human reproduction 2001; 16: 2298–2304

Custers, I.M., Steures, P., Hompes, P., Flierman, P., Van Kasteren, Y., Van Dop, P.A., Van Der Veen, F., Mol, B.W. **Intrauterine insemination: How many cycles should we perform?** Human reproduction 2008; 23: 885–888

Danhof, N.A., Van Wely, M., Repping, S., Koks, C., Verhoeve, H.R., De Bruin, J.P., Verberg, M.F.G., Van Hooff, M.H.A., Cohlen, B.J., Van Heteren, C.F., Fleischer, K., Gianotten, J., Van Disseldorp, J., Visser, J., Broekmans, F.J.M., Mol, B.W.J., Van Der Veen, F., Mochtar, M.H. **SUPER Study Group. Follicle stimulating hormone versus clomiphene citrate in intrauterine insemination for unexplained subfertility: A randomized controlled trial.** Human reproduction 2018; 33: 1866–1874

Danhof, N.A., Van Wely, M., Repping, S., Van Der Ham, D.P., Klijn, N., Janssen, I., Rijn-Van Weert, J.M., Twisk, M., Traas, M.a.F., Pelinck, M.J., Perquin, D.a.M., Boks, D.E.S., Sluijmer, A., Mol, B.W.J., Van Der Veen, F., Mochtar, M.H. **on behalf of the Amsterdam SUPER Study Group. Gonadotrophins or clomiphene citrate in couples with unexplained infertility undergoing intrauterine insemination: A cost-effectiveness analysis.** Reproductive biomedicine online 2020; 40: 99–104

Daya, S. **Life table (survival) analysis to generate cumulative pregnancy rates in assisted reproduction: Are we overestimating our success rates?** Human reproduction 2005; 20: 1135–1143

De Brucker, M., Camus, M., Haentjens, P., Verheyen, G., Collins, J., Tournaye, H. **Assisted reproduction using donor spermatozoa in women aged 40 and above: The high road or the low road?** Reproductive biomedicine online 2013; 26: 577–585

De Brucker, M., Haentjens, P., Evenepoel, J., Devroey, P., Collins, J., Tournaye, H. **Cumulative delivery rates in different age groups after artificial insemination with donor sperm.** Human reproduction 2009; 24: 1891–1899

Farquhar, C.M., Liu, E., Armstrong, S., Arroll, N., Lensen, S., Brown, J. **Intrauterine insemination with ovarian stimulation versus expectant management for unexplained infertility (tui): A pragmatic, open-label, randomized, controlled, two-centre trial.** Lancet 2018; 391: 441–450

Guan, H.T., Zheng, Y., Wang, J.J., Meng, T.Q., Xia, W., Hu, S.H., Xiong, C.L., Rao, M. **Relationship between donor sperm parameters and pregnancy outcome after intrauterine insemination: Analysis of 2821 cycles in 1355 couples.** Andrologia 2016; 48: 29–36

Human Fertilisation & Embryology Authority (HFEA), 2018. Fertility treatment 2014–2016: Trends and figures. https://www.hfea.gov.uk/media/3188/hfea-fertility-trends-and-figures-2014-2016.pdf

Human Fertilisation & Embryology Authority (HFEA), 2020. https://www.hfea.gov.uk/donation/donors/donating-your-sperm/

Kandavel, V., Cheong, Y. **Does intrauterine insemination have a place in modern art practice? Best practice and research.** Clinical obstetrics and gynaecology 2018; 53: 3–10

Khalil, M.R., Rasmussen, P.E., Erb, K., Laursen, S.B., Rex, S., Westergaard, L.G. **Intrauterine insemination with donor semen. An evaluation of prognostic factors based on a review of 1131 cycles.** Acta obstetricia et gynecologica Scandinavica 2001; 80: 342–348

Maheshwari, A., Mclernon, D., Bhattacharya, S. **Cumulative live birth rate: Time for a consensus?** Human reproduction 2015; 30: 2703–2707

Malchau, S.S., Henningsen, A.A., Loft, A., Rasmussen, S., Forman, J., Nyboe Andersen, A., Pinborg, A. **The long-term prognosis for live birth in couples initiating fertility treatments.** Human reproduction 2017; 32: 1439–1449

Matorras, R., Diaz, T., Corcostegui, B., Ramon, O., Pijoan, J.I., Rodriguez-Escudero, F.J. **Ovarian stimulation in intrauterine insemination with donor sperm: A randomized study comparing clomiphene citrate in fixed protocol versus highly purified urinary fsh.** Human reproduction 2002; 17: 2107–2111

Mol, B.W., Tjon-Kon-Fat, R., Kamphuis, E., Van Wely, M. **Unexplained infertility: Is it over-diagnosed and over-treated? Best practice and research.** Clinical obstetrics and gynaecology 2018; 53: 20–29

Na, L., Chen, Y., Zhai, H., Liao, A., Huang, D. **Effects of maternal body mass index on pregnancy outcome after 8570 artificial insemination cycles with donor's sperm.** Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology 2018; 34: 1068–1072

National Institute for Health and Care Excellence (NICE), 2017. Intrauterine insemination. https://www.nice.org.uk/guidance/cg156/chapter/Recommendations#intrauterine-insemination-2

Priddle, H. **How well are lesbians treated in uk fertility clinics?** Human fertility 2015; 18: 194–199

Sawyer, N., Blyth, E., Kramer, W., Frith, L. **A survey of 1700 women who formed their families using donor spermatozoa.** Reproductive biomedicine online 2013; 27: 436–447

Shukla, U., Deval, B., Jansa Perez, M., Hamoda, H., Savvas, M., Narvekar, N. **Sperm donor recruitment, attitudes and provider practices–5 years after the removal of donor anonymity.** Human reproduction 2013; 28: 676–682

Soares, S.R., Cruz, M., Vergara, V., Requena, A., Garcia-Velasco, J.A. **Donor iui is equally effective for heterosexual couples, single women and lesbians, but autologous iui does worse.** Human reproduction 2019; 34: 2184–2192

Thijssen, A., Creemers, A., Van Der Elst, W., Creemers, E., Vandormael, E., Dhont, N., Ombelet, W. **Predictive factors influencing pregnancy rates after intrauterine insemination with frozen donor semen: A prospective cohort study.** Reproductive biomedicine online 2017; 34: 590–597

Vitthala, S., Gelbaya, T.A., Hunter, H., Roberts, S.A., Nardo, L.G. **Stimulated intrauterine insemination (siui) and donor insemination (di) as first line management for a selected subfertile population: The manchester experience.** Journal of assisted reproduction and genetics 2008; 25: 431–436

Zolton, J.R., Lindner, P.G., Terry, N., Decherney, A.H., Hill, M.J. **Gonadotrophins versus oral ovarian stimulation agents for unexplained infertility: A systematic review and meta-analysis.** Fertility and sterility. 2020; 113

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