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Intrauterine insemination—No more Mr. N.I.C.E. guy?

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ABSTRACT

Objective: To determine the per cycle chance of a live birth and to identify factors that may support a more individualised application of IUI in view of National Institute for Health and Care Excellence (NICE) updated guideline on fertility 2013.

Study design: A retrospective, cohort study of 851 couples (1688 cycles) with unexplained, mild endometriosis, one patent Fallopian tube (with ovulation occurring in the corresponding ovary), mild male factor or ovulatory dysfunction, who initiated their first cycle of IUI/COH during the study period 2009–2013 and completed up to 3 cycles. Exclusion criteria included donor sperm and diminished ovarian reserve. Success factors and probabilities were determined based on live birth rates.

Results: Mean age was 33.8 ± 3.3 years and mean duration of subfertility was 2.28 ± 1.47 years. Independent associates of successful outcome factors were lower age (AOR 0.93; 95%CI 0.89–0.98, p = 0.007) and multiparity (AOR 1.72; 95%CI 1.17–2.52). Live-birth rates declined independently of other factors from 15.3% (n = 130/851) in cycle 1–7.0% (n = 19/273) in cycle 3 (AOR 0.76; 95%CI, 0.62–0.93, p = 0.008). Per cycle probabilities of live birth ranged from 21.4% to 5.1% dependent on age, cycle number and previous parity. The unadjusted cumulative pregnancy rate for live birth per cycle started, over three cycles, was 34.9% with a multiple live birth rate per cycle started of 5.4%. The associates of live birth amongst those with unexplained sub-fertility only (n = 632, first cycle attempt) were also analysed, yielding similar results.

Conclusions: IUI/COH is a simple treatment that produces good live birth rates, especially in younger patients and/or those with previous parity. More than 90% of total live births with IUI/COH is achieved during the first two cycles. As a retrospective, observational study, there is no comparator group and therefore we cannot comment on the relative efficacy of up to three IUI cycles over expectant management in a similar cohort. Our study suggests that probabilities of success can be used to individualise treatment decisions and that there is merit in continuing to offer IUI before resorting to IVF for certain patients.

Introduction

Intrauterine insemination (IUI) with controlled ovarian hyperstimulation (COH) is a frequently employed treatment for couples with subfertility including unexplained subfertility, mild endometriosis, ovulatory dysfunction and mild male factor subfertility. Data from the European Society of Human Reproduction (ESHRE) reports a live birth rate of 8.9% [1]. The per cycle success (frequently clinical pregnancy rather than live birth) of an IUI/COH cycle has been reported at 11–16.4% [2–5]. Recently the National Institute for Health and Care Excellence (NICE) released updated guidelines on fertility advising that couples with unexplained subfertility, mild male factor or mild endometriosis, who have failed to become pregnant after two years of expectant management should proceed directly to IVF treatment [6]. This guidance is based on low to very low quality evidence indicating that treatment with IUI (with or without COH) shows no significant increase in live birth over expectant management [7,8]. This update represents a dramatic shift in treatment algorithm for most fertility specialists, many of whom continue to recommend at least 3 cycles of IUI/COH for these patients [9]. A survey of British Fertility Society members demonstrated only 26.72% planning to change their practice in accordance with the updated guideline. A subsequent survey revealed that 54% of UK fertility clinics have made no alteration to their clinical practice [10,11]. Indeed, as well as increased risk of adverse effects related to high doses of follicle

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stimulating hormone (FSH), many couples find the prospect of IVF as a first-line treatment more daunting and more financially onerous than IUI treatment, particularly in jurisdictions where there is limited/no public funding for ART [11,12]. The aim of this study is to assess the per cycle chance of a live birth in a large, single centre cohort, to identify success factors and dependent probabilities of success in stratified subgroups that may support a more individualised application of IUI.

Materials and methods

Patient population

This is a retrospective cohort study of 851 couples who initiated their first cycle of IUI/COH treatment at Cork Fertility Centre, a tertiary care fertility centre, between 2009 and 2013 inclusive, and completed up to 3 cycles of IUI/COH. Follow up was extended to 6 months beyond the first cycle of the last included patient. 1688 completed cycles of IUI/COH, using FSH (Puregon®, MSD Ireland) were analysed. All couples with unexplained subfertility, mild endometriosis, one patent Fallopian tube (insemination only went ahead if ovulation occurred in the corresponding ovary), mild male factor or ovulatory dysfunction, who completed at least one cycle of IUI/COH during the study period, were included. Mild male factor was defined as an initial sperm count of 10–15 million/mL and motile count $\geq$40%, or an initial sperm count of 12–15 million/mL and motile count $\geq$30%, with a final sperm count of >5 million/mL following gradient preparation. Exclusion criteria were donor sperm and/or a diagnosis of diminished ovarian reserve (identified as FSH >10 IU/L and/or a combined antral follicle count of <5). FSH was commenced on day 2 of the menstrual cycle and follicular growth was monitored by transvaginal ultrasound until one mature follicle (18 mm) was present. Ovulation was triggered with human chorionic gonadotrophin (10,000 IU hCG, Pregnyl® MSD Ireland) and IUI performed the following day. If more than two follicles measuring $\geq$14 mm were present, they were aspirated at the time of IUI or the cycle was cancelled.

Data collection

The medical records of patients were reviewed for clinical and demographic data. Anti-Müllerian hormone (AMH) level, where available, was also recorded, however AMH testing was only introduced in 2012. The antral follicle counts of both ovaries were measured by transvaginal ultrasonography.

At each IUI cycle the following data were recorded: patient age; dose and duration (days) of FSH; endometrial thickness (mm) on day of hCG injection; the number of follicles measuring greater than 16 mm at the time of hCG trigger; the occurrence of aspiration of excess follicles and outcome of IUI attempt. Cumulative outcome rates were calculated per cycle started, with and without adjustment for patients who discontinued IUI treatment. Those who did not achieve a live birth continued with a subsequent IUI cycle(s), progressed to IVF/ICSI treatment or discontinued treatment at the fertility centre. The practice during the study period was to advise IVF treatment after up to three unsuccessful (no live birth) IUI cycles, in line with the NICE guideline on fertility (2004).

Semen analysis

The semen sample was collected by masturbation following a 3–5 day abstinence period and analysed according to World Health Organisation guidelines [13]. Sub-optimal semen samples were prepared using density gradient centrifugation technique and those that prepared poorly were deemed unsuitable for IUI.

Outcome measures

The primary outcome measure was live birth. We calculated univariable and multivariable predictors of achieving live birth as well as live birth probabilities in patient subsets stratified according to independent predictors of outcome.

Secondary outcome measures were: positive urinary pregnancy test; clinical pregnancy (fetal heart pulsation at eight weeks' gestation); miscarriage before or after 8 weeks' gestation; cumulative pregnancy and live birth rates and the rate of patient discontinuation of IUI treatment.

Statistical analysis

Continuous normally distributed variables were expressed as mean $\pm$ standard deviation and comparisons between patients were conducted using independent sample *t*-tests (two-tailed, $\alpha = 0.05$). Continuous non-normally distributed variables were expressed as median [interquartile range] and comparisons between patients were conducted using the Mann-Whitney *U* test. Categorical variables were summarised as frequencies and percentages and comparisons between patients were conducted using χ^2 analysis. Univariable and multivariable logistic regression analyses were carried out with determination of odds-ratios (OR) with 95%CI to determine the patient characteristic associated with the following outcomes: (i) positive pregnancy test, (ii) clinical pregnancy and (iii) live birth. The logistic regression model coefficients were used to calculate predicted probabilities.

Results

Study population

This study evaluated 851 patients who completed a total of 1688 cycles of IUI/COH. A total of 851, 564 and 273 couples completed the first, second and third IUI cycle respectively.

Clinical and demographic patient data is presented in Table 1. There were small but significant increases in average daily dose of FSH over the first three attempts with no significant associated increase in duration of therapy, endometrial thickness, number of follicles >16 mm or the requirement for aspiration of excess follicles.

Cycle characteristics and primary outcome measures

The cycle characteristics and livebirth per cycle attempt over the first three cycles are presented in Table 2. They show a progressive decline in per cycle success rates across all three measures (positive HCG, clinical pregnancy rate and live birth rate), with odds of live birth being 0.79 (95%CI, 0.65-0.94, p = 0.01) per additional cycle attempt. Following adjustment for age, previous parity, time trying to conceive, FSH dose and aetiology of subfertility, the adjusted OR of live birth per additional cycle attempt was 0.76 (95%CI, 0.62-0.93, p = 0.008). Using Bonferroni correction for multiple comparisons, there were no pairwise differences in outcome measures between attempts 1 and 2, or between attempts 2 and 3. However, there were significant differences between attempts 1 and 3 for live-birth rates (p = 0.003).

Other univariable associates of live birth were age (OR 0.95 (95% CI, 0.91-1.00, p = 0.03)), previous parity (OR 1.47 (95%CI, 1.05-2.06, p = 0.03)) and time trying to conceive (0.88 (95%CI, 0.78–1.00, p = 0.05)). Following adjustment for aetiology, length of time trying to conceive, age, previous parity, FSH dose and IUI attempt however, only age and previous parity persisted as significant factors. (Table 3). Implantation rates were 84.1% in cycle 1, 81.3%