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ASSISTED REPRODUCTION

Stimulated intrauterine insemination (SIUI) and donor insemination (DI) as first line management for a selected subfertile population: the Manchester experience

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Abstract

Purpose The objective of our study is to investigate the optimum number of stimulated intrauterine insemination (SIUI) or donor insemination (DI) cycles that can be offered to the couples prior to in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) in a tertiary referral unit for assisted reproduction.

Methods This is a retrospective analysis of 408 SIUI and 704 DI cycles performed in a tertiary referral unit for assisted reproduction. SIUI's were performed by controlled ovarian hyperstimulation and ovulation induction followed by insemination 36 h later. DI's were performed in natural or stimulated cycles after thawing frozen donor sperm. The main outcome measured was cumulative live birth rate (CLBR) per couple.

Results A maximum CLBR of 26.1% was achieved after the fourth cycle of SIUI. The CLBR of DI increased to 60.1% in the sixth cycle.

Conclusions This study, in line with a number of other studies, is unable to demonstrate unequivocally whether increasing numbers of IUI or DI cycles are justified clinically or financially. There is a need for larger datasets from multiple centres along with rigorous randomised trials to compare treatment pathways. Until then, the resources spent on the provision of extra SIUI cycles may be better utilized by early referral to IVF.

Keywords Cumulative live birth · Donor insemination · In vitro fertilization · Stimulated insemination · Intracytoplasmic sperm injection

Introduction

Stimulated intrauterine insemination (SIUI) is a form of assisted reproductive technology that is widely used in treating couples with infertility due to mild male factor, minimal to mild endometriosis and unexplained infertility. Intrauterine insemination (IUI) gained popularity because of its simplicity, non-invasiveness and reported cost-effectiveness. There is no consensus regarding the optimum number of SIUI cycles that can be offered to couples before they move on to in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI). Some authors advocate that after three to four cycles of IUI the pregnancy rates decline [1–8], while others have suggested that there are still acceptable pregnancy rates achievable after the sixth cycle [9, 10]. Only two studies clearly identified their objective as determination of the optimal number of IUI [11] or SIUI [12] cycles for the subfertile couple before resorting to IVF with or without ICSI.

The National Institute for Clinical Excellence (NICE) recommended offering up to six cycles of unstimulated IUI for couples with unexplained fertility problems, slightly abnormal sperm count or mild endometriosis before moving to IVF [13]. Although the recommendation was based on one systematic review comprising five random-

Capsule Compared to donor insemination cycles, higher order stimulated intrauterine insemination (SIUI) cycles do not increase the cumulative pregnancy rates.

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ized controlled studies (RCTs) [14], there was only one RCT comparing IVF with stimulated and unstimulated IUI in couples with unexplained or mild male factor infertility [15]. There were no significant differences in live birth rates between IVF and either unstimulated or stimulated IUI. The cost of pregnancy resulting in a live birth was 2–3 times higher in IVF than IUI. Using a mathematical model, Pashayan and colleagues [16] concluded that for couples with unexplained and mild male factor subfertility, primary offer of a full IVF cycle (including frozen cycles) is less costly and more cost effective than providing IUI (of any modality) followed by IVF. The cost of IUI, as first line treatment, increases and its cost-effectiveness decreases when increasing number of IUI cycles are offered. Therefore, the issue surrounding the optimum number of IUI cycles that can be offered to couples remains unresolved. In view of this uncertainty, we have performed a retrospective analysis for a cohort of couples treated at our centre in order to determine the optimum number of SIUI or DI cycles that can be offered to couples prior to IVF or ICSI.

Materials and methods

The electronic database of the IVF Unit at Saint Mary's Hospital, Manchester, was searched for all SIUI and DI cycles between January 2000 and December 2006. All women were between 22–39 years old, with body mass index (BMI) between 19–30 kg/m^2. Couples were offered treatment until they had a live-birth with a maximum of 6 SIUI or 6 DI cycles. All subjects had undergone routine investigations including measurement of day-2 serum follicle stimulating hormone (FSH), luteinizing hormone (LH), oestradiol (E_2) and day-21 serum progesterone, Laparoscopy and dye test and baseline transvaginal ultrasound scan (TVS). In our department, we offer SIUI mainly to couples with unexplained infertility for a minimum of 2 years and a maximum of 3 years duration and occasionally to couples with mild male factor or women with minimal to mild endometriosis (revised AFS I–II). DI was offered for couples with severe male factor infertility, in the form of azoospermia. Unexplained infertility was diagnosed when all the above investigations, in addition to semen analysis (SA) were normal. Mild male factor was defined as sperm count of 10–19 million/ml and at least 20% progressive motility. The study received favorable ethical opinion by the Local Research Ethics Committee (Reference no. 07/H1003/200, UK-SMREC).

Sperm preparation

Semen specimens from partners were collected by masturbation on site, evaluated according to standardized methods, and prepared for intrauterine insemination within 1 h of collection. Sperm was prepared using discontinuous density gradient (Suprasperm System, Medicult Ltd., UK). After centrifugation at 300 g for 20 min the pellets were removed and combined in 3 ml of sperm preparation medium (Medicult Ltd., UK). The sperm suspension was washed twice by centrifugation for 5 min at 600 g and the final pellet was re-suspended in 0.4 ml of sperm preparation medium. Approximately 60 μl was used to determine the concentration and motility of the sperm. The remaining sample was drawn into an IUI catheter (Rocket Medical, Watford, UK) attached to a 1-ml syringe.

Protocol for SIUI and DI

A baseline TVS was performed on cycle day 2 to exclude ovarian cysts larger than 20 mm. Thereafter, the women started daily subcutaneous injections of human menopausal gonadotrophin (HMG, Merional, IBSA Institut Biochimique SA, Lugano, Switzerland) in mean doses of 75 IU, ranging from 37.5 IU to 150 IU, until TVS showed at least one follicle of at least 16.5 mm in diameter. Ovulation was then induced with 5000 IU of human chorionic gonadotrophin (hCG) and the women were inseminated 36 h later. We withheld hCG and IUI if there were more than two follicles of ≥16 mm diameter. If cycle was cancelled because of over response, a new cycle was offered with lower starting dose of gonadotrophins.

All DI cycles were performed after thawing frozen donor sperm that was prepared using the same sperm preparation method, then used in unstimulated cycles or stimulated cycles depending on whether the woman was ovulating or not. In unstimulated cycles, serum LH levels were measured daily starting from day 6–7 of a spontaneous menstrual cycle and plotted on a chart. Insemination was performed 24 h after the LH surge.

Outcomes

The primary outcome measure was cumulative live birth rate (CLBR) per couple. Other outcomes included live birth rate (LBR) per cycle, pregnancy (PR) and clinical pregnancy (CPR) rates per cycle, first trimester loss per total pregnancies, dropout and cycle cancellation rates. We defined pregnancy as a positive urine pregnancy test 17 days after insemination and clinical pregnancy as the presence of a viable intrauterine pregnancy with fetal heart beat seen on ultrasound scan performed at ≥6 weeks gestation.

Statistical analysis

Live birth rates are summarised by the percentages with associated 95% confidence intervals based on the Wilson method [17] and these are propagated through to the CLBR

estimates. CLBR (C_i) for each successive cycle (i), is estimated for those who continued treatment as $C_i = C_{i-1} + (1 - C_{i-1})b_i/n_i$, where there are live births (b_i) from couples (n_i) treated in the i cycle. Logistic regression is used to quantify the drop in LBR over multiple cycles. The beta-binomial selection model of Weinberg and Gladen [18] is used to formally test for a decline in LBR with increasing numbers of cycles.

Results

One hundred and sixty-two couples underwent a total of 408 cycles of SIUI with an average of 2.5 cycles per couple. The majority of these couples had unexplained infertility (92%). The rest of the couples were treated for either mild male factor (5%) or minimal to mild endometriosis (3%). The mean age of the women in this group was 33 years with a range between 22–39 years. The overall cancellation rate was 5.3% per cycle, mostly due to over response to gonadotrophins stimulation, but occasionally due to inappropriate response. The majority of the couples who had cancelled cycles continued treatment with further cycles.

Thirty-one clinical pregnancies and 26 live births were reported, with overall clinical pregnancy and live birth rates per couple of 19.1% and 16.0%, respectively. No clinical pregnancies were recorded after the fourth treatment cycle of SIUI, with CLBR of 26.1% (Table 1). However, very few couples (n=32) had more than 4 treatment cycles. Although the LBR declined with increasing cycles, this decline was not statistically significant, with an odds ratio of 0.84 (95%CI: 0.55 to 1.30) per cycle. There were two set of twins (6.5%) in the SIUI group: the first ended in a mid-trimester miscarriage at 20 weeks gestation and the second resulted in delivery of two live births at 38 weeks of gestation. There were no recorded cases of ovarian hyperstimulation syndrome (OHSS) requiring hospital admission. No significant differences were found between the group of patients who had one to four cycles and the group who had more than four cycles with respect to their demographic characteristics including the woman's age, BMI, duration and cause of infertility.

Two hundred and thirty-five couples underwent a total of 704 DI cycles with an average of 3.0 cycles per couple. Sixty-six inseminations (9.4%) were performed after controlled ovarian hyperstimulation using HMG and the rest were performed in unstimulated natural cycle. The overall cycle cancellation rate was 3.4%. The reason for cancellation of the cycle was the inability to detect LH surge in the majority of cases with over response to gonadotrophin stimulation occurred in only 2 cycles when COH was also employed. Donor insemination treatment resulted in 121 clinical pregnancies and 102 live births, with overall clinical pregnancy and live birth rates per couple of 51.5% and 43.4%, respectively. There was no significant decline in LBR with increasing cycle number. In the DI group, CLBR progressively increased from 18.3% after the first cycle to 60.1% after the sixth cycle (Table 2). Figure 1 represents the cumulative live birth rates of SIUI and DI treatment cycles.

The beta-binomial selection model showed no significant heterogeneity between patients for either SIUI or DI, and the data was consistent with the cycles being independent.

Many of the couples were lost to follow-up despite efforts made to contact them and their general practitioners, and therefore it was not possible to determine the exact reason for discontinuation of treatment. About 1/3 of couples in both groups could not continue treatment because of pressure from work and 7–11% felt that they could not cope with further treatment cycles. One couple in the SIUI group was converted to IVF after their first treatment cycle ended in an ectopic pregnancy with unilateral salpingectomy.

Discussion

The optimum number of IUI cycles that can be offered to couples before resorting to IVF is debatable and findings from previous studies are inconsistent. This study was set to answer this question locally by calculating the cumulative live birth for a cohort of 162 couples undergoing SIUI and

Table 1 Outcome of SIUI cycles

Cycle No. (No. of couples)	Cancelled cycles n (%)	Dropout n (%)	PR/couple n (%)	First trimester loss per total pregnancies (%)	CP/couple n (%)	LB/couple % (95% CI)	CLBR % (95% CI)
1 (162)	9 (5.5)	0	17 (10.5)	4/17 (23.5)	16 (9.9)	13 (8.0) (4.7–13.2)	8.0 (4.7–13.2)
2 (112)	5 (4.5)	37 (24.8)	7 (6.3)	3/7 (48.9)	4 (3.6)	4 (3.6) (1.4–8.8)	11.3 (7.5–18.4)
3 (66)	5 (7.6)	42 (38.8)	11 (16.6)	4/11 (36.4)	9 (13.6)	6 (9.1) (4.2–18.4)	19.4 (13.5–30.4)
4 (36)	2 (5.5)	24 (40)	4 (11.1)	1/4 (25)	2 (5.5)	3[a] (8.3) (2.9–21.8)	26.1 (18.6–41.9)
5 (22)	1 (4.5)	12 (35.3)	0 (0)	0	0 (0)	0 (0–14.9)	26.1 (18.3–45.7)
6 (10)	0 (0)	12 (54.5)	0 (0)	0	0 (0)	0 (0–27.7)	26.1 (18.1–55.0)

PR Pregnancy rate, *CP* clinical pregnancy, *LB* live birth, *CLB* cumulative live birth, *CI* confidence interval.
[a] Including one set of twins

Table 2 Outcome of DI cycles

Cycle No. (No. of couples)	Cancelled cycle *n* (%)	Dropout *n* (%)	PR/couple *n* (%)	First trimester loss per total pregnancies (%)	CP/couple *n* (%)	LB/couple% (95% CI)	CLBR % (95% CI)
1 (235)	9 (3.8)	0	55 (23.4)	5/55 (9.1)	52 (22.1)	43 (18.3) (13.9–23.7)	18.3 (13.9–23.7)
2 (173)	7 (4)	19 (9.9)	26 (15)	7/26 (26.9)	21 (12.1)	18 (10.4) (6.7–15.8)	26.8 (21.3–34.0)
3 (138)	5 (3.6)	17 (11.0)	27 (19.6)	4/27 (14.8)	25 (18.1)	20 (14.5) (9.6–21.3)	37.4 (30.5–46.6)
4 (93)	0 (0)	25 (21.2)	13 (14)	1/13 (7.7)	12 (12.9)	11 (11.8) (6.7–19.9)	44.8 (36.6–56.1)
5 (51)	2 (3.9)	31 (37.8)	12 (23.5)	4/12 (33.3)	8 (15.7)	8 (15.7) (8.2–28.0)	53.5 (43.3–67.9)
6 (14)	1 (7.1)	29 (67.4)	3 (21.4)	1/3 (33.3)	3 (21.4)	2 (14.3) (4.0–39.9)	60.1 (47.3–80.8)

R Pregnancy rate, *CP* clinical pregnancy, *LB* live birth, *CLB* cumulative live birth

235 couples undergoing DI. The results of this study will enable us to counsel our own patients with regard to the anticipated cumulative live birth rate after SIUI and DI. More importantly, we will be able to advise our patients when to move on to IVF or ICSI.

Although the European registers hold a large database on women undergoing IUI using husband or donor sperm, the European Society of Human Reproduction and Embryology (ESHRE) reported only on pregnancy rate per procedure rather than cumulative live birth rate per couple [19]. Unfortunately, the ESHRE report does not help subfertile couples and their fertility specialists in making a decision on how many IUI cycles they should try before they move on to IVF or ICSI.

Previous studies have evaluated some or all of the prognostic factors influencing the success rate of IUI including the age of the woman [2], the sperm count and quality [4, 20, 21] or combined factors including the cycle's number [1, 3, 5, 7, 10, 22, 23]. All these studies were retrospective except one [21], which was a prospective observational study and included 1,624 couples who underwent 3,381 clomiphene citrate-stimulated IUI cycles using either husband or donor sperm. The results of our study as well as those of others [2, 6, 7] showed that most of the pregnancies occurred in the first four treatment cycles, although few patients received more than 4 cycles. Other authors found that SIUI has the highest pregnancy rate within the first two [20, 21, 23] or three [1, 3–5, 8] treatment cycles. Lalich and colleagues [9] reported no pregnancies after six cycles of SIUI in couples with unexplained or male factor infertility. A retrospective analysis of 260 couples with anovulation, cervical factor or unexplained infertility who underwent SIUI after pituitary down-regulation with GnRH-analogue for 4 weeks showed a pregnancy rate of 22.4%, 17.8% and 13.9% in the first, second and third cycles respectively [24]. It is not possible to draw any conclusion regarding the optimum number of SIUI attempts from this study as couples were offered a maximum of three treatment cycles. Only two studies aimed to determine the optimal number of IUI cycles before referring patients to IVF [11, 12]. In the first study [11] that included couples undergoing unstimulated IUI, 98% of the pregnancies occurred within the first four treatment cycles. More recently, Aboulghar and colleagues [12] reported an overall cycle fecundity rate (CFR) and cumulative pregnancy rate of 16.4% and 39.2% respectively, in a group of 594 couples with unexplained infertility that underwent three cycles of SIUI. The CFR dropped to 5.6% in a subgroup of 91 couples who underwent a further three cycles of SIUI. This was much lower than the CFR from a historical control group (36.6%) who underwent IVF after they had three unsuccessful cycles of SIUI. The authors concluded that patients should be offered IVF if they fail to conceive after three cycles of SIUI.

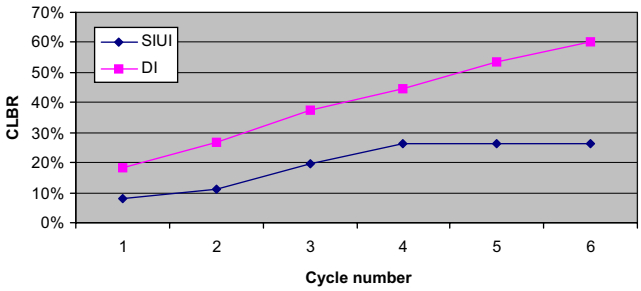

Fig. 1 CLBR for women having S-IUI and DI

In our data, we have not reported a single pregnancy in 32 SIUI attempts carried out after the fourth treatment cycle. The live birth rate was maintained through the first four cycles with a constant increase in the cumulative live birth rate from 8% to 26.1%. However, the apparent decline in live birth rate over time may be an artifact of the very small number of couples getting many treatment cycles and overall, the data are consistent with both a clinically significantly decline in LBR and with a constant LBR across cycles. In agreement with these results, Khalil and colleagues [7] reported a CLBR of 25.1% after four attempts and 27% after more than six attempts. Other authors [25] found similar CLBR for couples who had four attempts of SIUI using either clomiphene citrate or recombinant FSH for ovarian stimulation (26.9% versus 28.2%, respectively). Werbrouck and colleagues [26] reported an equally high CLBR after four cycles of SIUI

in couples with unexplained infertility and in women with minimal and mild endometriosis that had been laparoscopically removed before SIUI (66.5%, 70.2% and 68.2%, respectively). It is plausible that variation in the reported effectiveness of IUI could be due to differences in study populations, ovarian stimulation regimens, the number of inseminations per cycle, the timing of insemination and methods of sperm preparation. Recently, a large multicentric retrospective study performed by Custers and colleagues [27] concluded that higher order IUI cycles are justified up to nine cycles as they found acceptable ongoing cumulative clinical pregnancy rates after 3rd, 6th and 9th cycle. However, this study [27] did not report separate pregnancy rates for SIUI and DI.

Multiple pregnancies and OHSS are the commonest complications of assisted conception. In this series we had only two twin pregnancies (6.5%), no triplets or higher order multiple gestations and no case of OHSS. The low rate of multiple pregnancies and the absence of OHSS are likely to be dependent on our guidelines for cycle cancellation (more than 2 follicles >16 mm in diameter) and the low-dose, step-up regime for controlled ovarian hyperstimulation.

With regard to DI cycles, our data, like other reports [27–29, 30, 31], have shown a constant increase in the CLBR with the increasing number of cycles. Of note, Khalil and colleagues [31] used ovarian stimulation for all DI cycles, which may account for the 20.6% multiple pregnancy rates. As DI is usually offered to couples with male factor being the only cause for subfertility, pregnancy and live birth rates are higher than with SIUI, which is usually offered for couples with unexplained subfertility.

In the modern healthcare system cost-effective treatment relies on the best use of available resources to reach successful outcomes. Costs involved in the IUI and DI cycles are therefore important to optimize decision-making and success. In our unit, the average costs of one cycle of SIUI and DI are £1000 and £700, respectively. Phillips and colleagues [32] in their evaluation of relative cost-effectiveness in the treatment of infertility in the United Kingdom stated that to make a break even value for IUI the CPR should be more than 8.3% per treatment cycle. The overall clinical pregnancy rate per couple in our study was 19.1% for SIUI and 52.8% for DI.

Furthermore, the time-to-live birth must also be taken into consideration when trying to explore the cost-effectiveness of a therapeutic model. Many of those couples who had failed SIUI treatment had been subjected to enormous stress to the extent that some of them had decided to withdraw completely from assisted conception treatment. Data based on face-to-face patient interviews demonstrate that decreasing the probability of ongoing pregnancy with SIUI lead to an increasing number of couples switching their preference from SIUI to IVF, especially after six cycles of treatment [33]. A recent report by Reindollar and colleagues [34] in the USA showed a shorter median time to pregnancy in women who had three cycles of clomiphene-stimulated IUI followed by up to six cycles of stimulated IVF compared to those who had three cycles of clomiphene-stimulated IUI, then three cycles of FSH-stimulated IUI and up to six cycles of IVF.

Using a mathematical model to estimate comparative clinical-efficiency and cost-effectiveness of either one full IVF cycle (including frozen cycles) or IUI followed by IVF, Pashayan and colleagues [16] concluded that offering an IVF cycle straight away is less costly and more effective than providing IUI (stimulated or unstimulated) followed by IVF. However, the cost associated with complications such as multiple pregnancies and OHSS was not included in their original analysis.

In conclusion, this study, in line with a number of other studies, is unable to demonstrate unequivocally whether increasing numbers of IUI or DI cycles are justified clinically or financially. There is a need for larger datasets from multiple centres along with rigorous randomised trials to compare treatment pathways. Until then, the resources spent on the provision of extra SIUI cycles may be better utilised by early referral to IVF. We recommend that couples should be fully informed of all their options and should be given realistic up-to-date information about the chance of success as well as the costs and complications before they can decide which treatment option is better for them. All centres should be encouraged by higher regulatory authorities to calculate their own CLBR after SIUI and DI as this will certainly help the couples to choose their best treatment options.

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