ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Intrauterine insemination with gonadotropin stimulation or in vitro fertilization for the treatment of unexplained subfertility: a randomized controlled trial

Anupa Nandi, M.R.C.O.G.,[a] Priya Bhide, M.R.C.O.G.,[a] Richard Hooper, Ph.D.,[b] Anil Gudi, M.R.C.O.G.,[a] Amit Shah, M.R.C.O.G.,[a] Khalid Khan, Ph.D.,[b] and Roy Homburg, F.R.C.O.G.[a]

[a] Fertility Unit, Homerton University Hospital and [b] Women's Health Research Unit, The Blizard Institute, London, United Kingdom

Objective: To evaluate the best first line management option for the treatment of unexplained subfertility-controlled ovarian hyperstimulation (COH) with gonadotropins and IUI or IVF.
Design: Randomized controlled trial.
Setting: Single center trial in a tertiary referral unit.
Patient(s): Couples with unexplained subfertility.
Intervention(s): Couples were randomized to receive either three cycles of IUI + COH or one cycle of IVF.
Main Outcome Measure(s): Singleton pregnancy rate (PR) per couple.
Result(s): A total of 207 couples were randomly assigned to three cycles of IUI + COH (n = 101) or one cycle of IVF (n = 106). There were 25 (24.7%) singleton live births for the IUI + COH group and 33 (31.1%) for the IVF group (relative risk, 1.3; 95% confidence interval [CI] 0.81–1.96) with an absolute risk difference of 6.4% (95% CI −5.8% to 18.6%). The multiple pregnancies per live birth were 4 (13.8%) for the IUI + COH group and 3 (8.3%) for the IVF group (relative risk, 0.6; 95% CI 0.14–2.4). There were no cases of ovarian hyperstimulation syndrome (OHSS) in the IUI group and three cases of OHSS (3.7%) in the IVF group. There were 17 live births from spontaneous conception in between treatment cycles (8.2%).
Conclusion(s): The singleton live birth rate with one cycle of IVF was not significantly different than three cycles of IUI + COH.
Clinical Trial Registration Number: ISRCTN43430382. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: In vitro fertilization, intrauterine insemination, unexplained subfertility, unexplained infertility

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Unexplained subfertility refers to couples where standard investigations (tests for ovulation, tubal patency, and semen analysis) are all normal. Of infertile couples 30%–40% come within this category (1). During the past decade, interest has been shown in offering IVF as the first line treatment for couples with unexplained subfertility. Although the success rate of IVF has increased during the past decade, it comes at a considerable cost and is more invasive. On the other hand, IUI + controlled ovarian hyperstimulation (COH) is less invasive and less stressful for the patients and with better perinatal outcomes for singleton pregnancies (2).

At present, there is a lack of agreement among fertility specialists with regard to the first line treatment of couples with unexplained subfertility (3) and in spite of being aware of the The National Institute for Health and Care Excellence (NICE) guidelines (4), >90% of clinics in UK continues to offer IUI + COH to couples with unexplained subfertility as first line treatment (5). The evidence available so far on the best first line

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Reprint requests: Anupa Nandi, M.R.C.O.G., Fertility Unit, Homerton University Hospital, London E9 6SR, United Kingdom (E-mail: anupa.nandi@gmail.com).

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management for couples with unexplained subfertility is inconsistent, controversial and differs considerably in their study design (6). We performed a randomized controlled trial to examine the effectiveness of three cycles IUI + COH with gonadotropins versus one cycle of IVF as the first line approach to the treatment of unexplained subfertility.

MATERIALS AND METHODS

This is a single center parallel group randomized controlled trial with a balanced randomization (1:1), conducted at a tertiary referral unit in London, UK. Local institutional review board approval was achieved.

Participants

Eligible participants were couples with primary or secondary subfertility, of minimum one-year duration, where the female partner was aged between 23 and 37 completed years, body mass index (BMI) of 19–30, a regular menstrual cycle of 21–35 days, day 2 FSH <10 IU/L, and confirmed bilateral patent tubes. A midluteal serum P level was used to confirm ovulation. The male partner with normal semen parameters (i.e., sperm density >15 million/mL, progressive motility >40% and normal forms >4% [World Health Organization criteria], or total progressive motile sperm count >5 million) (7, 8) was included in the trial.

Couples not fulfilling the inclusion criteria, with known uterine anomaly, physical disability, or having difficulty in achieving vaginal intercourse, and couples using donor sperm or previous fertility treatment like IUI or IVF were excluded. Those with confirmed endometriosis of grade II-IV (9) were also excluded from the trial. However, routine laparoscopy was not performed in all cases to diagnose endometriosis (10). Self-funded patients were excluded from the trial due to lack of research funding.

Eligible couples were allocated to treatment strategies consisting of three cycles of IUI + COH with gonadotropins or one cycle of IVF within a time frame of 6 months from randomization. All patients were followed until the end of the time horizon. Those who conceived spontaneously in the time frame were noted. All randomized couples were analyzed in their allocated group as per intention-to-treat analysis.

IUI + COH Group

The COH was performed with daily SC injections of 75 IU FSH (Fostimon-, a highly purified urofollitropin, Pharmasure) starting from days 2–5 of the menstrual cycle onward. When at least two follicles with a diameter of 17–18 mm were present, final oocyte maturation was induced by SC administration of 250 μg of hCG (Ovitrelle, Merck Serono) and 24 hours later IUI was performed. If ≥3 follicles of ≥14 mm developed, then the cycle was cancelled by withholding hCG and IUI and recommending avoiding sexual intercourse due to risk of multiple pregnancies. Semen samples were processed within 1 hour of ejaculation using density gradient centrifugation followed by washing with culture medium. Single insemination was done by either nurse or an on-duty doctor (11).

IVF Group

In the IVF group of women underwent down-regulation with GnRH agonist in a long protocol, starting on day 21 of the previous cycle. The COH was started with FSH (either hMGs or recombinant FSH) with a dose ranging from 150–450 IU depending on the woman's ovarian reserve (as tested by anti-mullerian hormone level, basal antral follicle count, and day 2 FSH level) and decided by the attending clinician. When most follicles were ≥18 mm, ovulation was triggered with 250 μg recombinant hCG (Ovitrelle, Merck Serono) and cumulus-oocyte complexes were retrieved by transvaginal ultrasound-guided oocyte retrieval 36 hours later.

Women who were deemed high risk for ovarian hyperstimulation syndrome (OHSS) (antimullerian hormone >25 pmol/l, antral follicle count > 20) underwent a GnRH antagonist protocol for stimulation when COH was achieved with low dose FSH (150 IU) and starting GnRH antagonist on day 6 of stimulation. Ovulation was induced by GnRH agonist (Buserelin 0.5 mg SC) (12) and oocyte retrieval was performed after 36 hours. If >20 oocytes were collected, embryos were frozen and transferred at a later date in a frozen embryo replacement cycle. In that case, the first frozen ET cycle was considered as the first cycle and included in the analysis. We did not collect data for additional frozen ET cycles, as this was not in our study design. For the frozen ET cycle, down-regulation was achieved with GnRH agonist starting from day 21 of the previous cycle followed by endometrial preparation with daily E_2 valerate of 8 mg for 10–14 days or until the endometrial thickness of >8 mm was achieved.

If at least one top grade embryo was available, then only one embryo was transferred on either day 3 or day 5. If no top grade embryos were available, then couples were given the option to transfer up to two embryos. Luteal phase support was provided with P vaginal pessaries (Cyclogest 400 mg twice daily, Actavis UK, Ltd.). For frozen ET cycle or GnRH agonist trigger cycle where a fresh embryo was transferred, daily E_2 valerate of 8 mg and P gel (Crinone gel, Allergan) were given in addition to P vaginal pessaries for luteal support.

Outcomes

The primary outcome was singleton live birth/couple. Secondary outcome measures were the live birth rate, clinical pregnancy, multiple pregnancy and OHSS rates. We also noted the spontaneous conception rates in between treatments.

Sample Size

Assuming an absolute difference of 15% in live birth rate in favor of IVF with a live birth rate of 30% for one cycle of IVF and 15% for three cycles of IUI (13, 14), 80% power and significance of $P<.05$, 125 couples were considered to be required in each arm of the study. Following the introduction of the 2013 NICE guideline, there was a