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Dropout rates in couples undergoing in vitro fertilization and intrauterine insemination

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ABSTRACT

Objective: To compare dropout rates in couples undergoing conventional in vitro fertilization with single embryo transfer (IVF-SET), in vitro fertilization in a modified natural cycle (IVF-MNC) or intrauterine insemination with ovarian stimulation (IUI-OS).
Study design: Secondary analysis of a multicentre randomized controlled trial between January 2009 and February 2012. 602 couples with unexplained or mild male subfertility, allocated to IVF-SET ($N = 201$), IVF-MNC ($N = 194$) and IUI-OS ($N = 207$).
Main outcome measures: Dropouts, defined as couples who discontinued their allocated three cycles of IVF-SET, six cycles of IVF-MNC or IUI-OS, without having achieved a pregnancy. We classified dropouts as "following medical advice" or "patient initiated".
Result(s): Thirty couples (15%) allocated to IVF-SET dropped out and 45 couples (23%) allocated to IVF-MNC, compared to 26 couples (13%) allocated to IUI-OS; relative risk (RR) 1.2 (95%CI; 0.73–1.9) for IVF-SET and 1.9 (95%CI; 1.2–2.9) for IVF-MNC, both compared to IUI-OS.
Nine couples (4.5%) allocated to IVF-SET, 14 (7.2%) allocated to IVF-MNC and 14 (6.8%) allocated to IUI-OS dropped out following medical advice; RR of 0.51 (95%CI; 0.21–1.2) for IVF-SET and 0.84 (95%CI; 0.39–1.80) for IVF-MNC, both versus IUI-OS. Twenty-one couples (10%) allocated to IVF-SET were patient initiated dropouts, as were 31 (16%) allocated to IVF-MNC and 12 (5.8%) allocated to IUI-COS; RR 1.8 (95% CI; 0.91–3.6) for IVF-SET and 2.8 (95%CI; 1.5–5.2) for IVF-MNC both versus IUI-OS.
Conclusion(s): IVF-SET and IUI-OS result in comparable drop-out rates, while drop-out rates after IVF-MNC are almost twice as high, mainly driven by patient preferences.

Introduction

Up to 50% of couples receiving medically assisted reproduction (MAR) are diagnosed with unexplained or mild male subfertility [1]. Traditionally, intrauterine insemination with ovarian stimulation (IUI-OS) has been the first line treatment for couples with

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unfavourable chances of natural conception, as it is not invasive and relatively inexpensive. In vitro fertilization (IVF) with single embryo transfer (SET) is also widely accepted as a first line treatment as it may be equally effective as IUI-OS with lower multiple pregnancy rates [2–6]. IVF with minimal ovarian stimulation, such as IVF in the modified natural cycle (IVF-MNC), has been suggested as a less burdensome alternative than conventional IVF [7].

There is ample evidence that the IVF procedure and its unpredictable outcome are multidimensional stressors which may evoke feelings of anxiety and depression [8–10]. These feelings decrease once pregnancy is achieved, but are further increased when treatment is unsuccessful [11–13].

The burden associated with IVF is one of the main reasons for couples to stop treatment, and is categorized as either physical, i.e. the daily administering of injections and concurring side effects, recurrent visits to the clinic, or psychological i.e. the frustration when the cycle is cancelled, or when fertilization or implantation fails [14–18]. Levels of anxiety and depression are even further increased when couples are advised to discontinue treatment for medical reasons or because of poor response [16].

Thus, discontinuing or dropping out of IVF – irrespective of the underlying reason – is associated with burden. Dropout is either the symptom of considerable burden suffered by a couple while receiving treatment, or is the cause of burden as the couple has no longer a prospect of parenthood [16,19]. Already in 2004, the UK National Institute for Clinical Excellence (NICE) emphasized the effect of dropout rates by recommending the use of treatment compliance as a means of auditing treatment performance of clinics [20].

Cumulative dropout rates have been reported to vary between 7% and almost 90% in cohort studies after conventional IVF but they mostly vary between 20–35%, and are commonly reported after three cycles [15–17,21,22].

While there is substantial evidence that IVF is a burdensome treatment, there are less data available on dropouts during an IVF-MNC or IUI-OS treatment program. There is one retrospective study that reported cumulative dropout rates of 48% after nine cycles of IVF-MNC and reasons for dropping out were associated with repetitive cycle cancellation or fertilization failure [23]. Only one retrospective study specifically examined dropouts during IUI-OS treatment program, and reported a 28% dropout rate after six cycles [24].

Since there is no comparative data on burden of conventional IVF, and IVF-MNC, in relation to IUI-OS, we aimed to compare dropout rates and the underlying reasons in couples with unexplained and mild male subfertility and unfavourable chances of natural conception. We used data available from a randomized controlled trial comparing these very interventions.

Methods

We performed an open-label, randomized controlled multicentre non-inferiority trial. The design and clinical outcomes of this study have been described in detail in a previous publication [25,26].

All couples underwent a basic fertility work-up, which included semen analysis, evaluation of ovulation and tubal patency testing (Chlamydia antibody test, hysterosalpingography or laparoscopy). We included couples with unexplained or mild male subfertility, with the female partner between 18 and 38 years, and an unfavourable prognosis for natural conception. Couples were classified as having unexplained subfertility when the fertility work-up showed at least one patent fallopian tube, an ovulatory menstrual cycle, and a normal semen analysis (pre-wash total motile sperm count above 10 million) [26]. Mild male subfertility was diagnosed when the semen analysis showed a pre-wash total motile sperm count between three and 10 million (according to the Dutch guidelines).

We defined an unfavourable prognosis for natural conception as a probability of natural conception within the next 12 months below 30%, calculated with the prognostic model of Hunault [27,28]. The trial was approved by the ethics committee of the Academic Medical Centre, and registered as NTR 939.

After informed consent, we randomly allocated consenting couples in a 1:1:1 ratio to receive to receive either three cycles of IVF-SET plus subsequent frozen thawed embryo transfers, six cycles of IVF-MNC or six cycles of IUI-OS all to be performed within a time frame of 12 months. Randomisation was performed with an online randomisation program, using biased coin minimisation, stratified for study centre. A unique number with allocation code was generated with a web-based program after entering patient initials and date of birth. We recorded all interventions within 12 months after randomization.

In couples allocated to IVF-SET, participating hospitals could follow local IVF regimens for ovarian down regulation and hyper stimulation. We performed SET when there was one good quality embryo available. If more than one supernumerary good quality embryo was obtained, suitable surplus embryos were cryopreserved. Cycles were cancelled if there were more than 30 follicles or if estradiol levels were higher than 13 nmol/l.

In couples allocated to IVF-MNC, the oocyte that developed spontaneously was used for IVF. The cycle was monitored by transvaginal ultrasound from cycle days eight to 10 onward modified after from day 8 or 10 onwards and modified with daily injections,of a gonadotrophin-releasing hormone (GnRH) antagonist to prevent untimely ovulations, and follicle stimulating hormone (FSH) to prevent collapse of the follicle and a concomitant fall in estradiol levels. Human chorionic gonadotropin hormone (hCG) was given for luteal support. Oocyte retrieval was planned 34 h thereafter and was performed without anaesthesia or sedation. If an oocyte was obtained and fertilised, transfer of the embryo was performed on day three. For luteal support, human chorionic gonadotropin 1500 IU (Pregnyl®, Merck Sharp & Dohme) was given by subcutaneous injections on days five, eight and 11 after oocyte retrieval. The next treatment cycle could start immediately after the previous cycle. Cycles were cancelled if luteinizing hormone levels were above 30 IU/L, at a follicle size less than 15 mm.

In couples allocated to IUI-OS, women received controlled ovarian stimulation according to local protocol with either clomiphene citrate (CC) or FSH. Cycles were cancelled when there were more than three follicles with a diameter of at least 16 mm, or more than five follicles with a diameter of 12 mm.

All treatments, including the use of the prescribed medication, were reimbursed. After the allocated IVF-MNC and IUI-OS cycles, couples were still entitled to three conventional IVF cycles which were also reimbursed.

Research assistants in participating hospitals recorded the dropouts and corresponding reasons in the case record file. If the information or reasons behind dropouts were unclear from the case record form we searched the medical file.

We defined couples as dropout if they had not completed their allocated three cycles of IVF-SET, including frozen thawed cycles or their allocated six cycles of IVF-MNC or IUI-OS. If couples were still actively enrolled in the treatment program because they had experienced a delay or had taken a break, or if they achieved pregnancy in between treatment cycles, we did not label them as dropout. We recorded all started cycles as treatment cycles. Transfers of frozen thawed embryos were not analysed as independent treatment cycles.