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ARTICLE

Failure of intrauterine insemination as rescue treatment in low responders with adequate HCG timing with no oocytes retrieved

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Abstract In this retrospective study, the efficiency of carrying out rescue intrauterine insemination (IUI) in low-responder patients undergoing IVF when no oocytes were retrieved after follicular aspiration and when HCG timing was adequate was analysed. A historical control group was used. Over 13 years, women undergoing IVF with failure to obtain oocytes at follicular aspiration underwent rescue IUI if the following criteria were met: adequate HCG timing; one normal tube; motile sperm count after preparation over 3 million/ml; and ultrasound visualization of one to six follicles over 13 mm. The rescue IUI was carried out 1 h after follicular aspiration. Results were compared with those of a standard IUI population (5394 cycles) in the same period. Confidence intervals were calculated using Poisson 97.5% confidence upper tail limits when no event was observed in the study sample. No pregnancies were achieved among the 54 cases who underwent rescue IUI (confidence interval: 0 to 6.8%). This pregnancy rate was lower than that observed in the general IUI population (17.5%) (relative risk, 19.2). After adjusting for age and endometriosis, the relative risk was 11.7. The rescue IUI is an inefficient procedure. Its efficacy is unlikely to exceed 7% pregnancy rate per IUI.

KEYWORDS: empty follicle syndrome, IUI, IVF, low responders, oocyte, rescue

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Introduction

In the presence of dominant follicles, failure to obtain oocytes after follicular aspiration is an uncommon event, estimated to occur in 0.045–3.5% of women undergoing oocyte retrieval (Ben-Shlomo et al., 1991; Castillo et al., 2012; Driscoll et al., 1998; Zreik et al., 2000). A number of conditions may be responsible for this failure: premature ovulation; deficient or insufficient administration of human chorionic gonadotrophin (HCG); 'empty follicle' syndrome; technical problems in oocyte retrieval (Matorras et al., 2012a); impaired folliculogenesis (Ben-Shlomo et al., 1991); and, infrequently, genetic conditions (Yariz et al., 2011). Most cases of failure to obtain oocytes are related to problems with HCG dose or timing (Stevenson and Lashen, 2008).

Failure to obtain oocytes at aspiration is much more common in women with fewer dominant follicles (Zreik et al., 2000), and most investigators exclude such cases when reporting on what was previously called 'empty follicle' syndrome. Two different factors could be responsible for this higher rate of failure to obtain oocytes in low responders: a hypothetically increased rate of impaired folliculogenesis or oocyte quality (especially age-related) and a probabilistic phenomenon, as in 5–20% of dominant follicles no oocytes are retrieved (Nargund et al., 2001); therefore, the fewer the dominant follicles, the greater the likelihood of failing to obtain any oocytes.

In HCG-related cases, various strategies have been proposed, such as delaying the oocyte retrieval of the second ovary, administering HCG if it was not given previously or carrying out oocyte retrieval later (Yariz et al., 2011). To date, the only options in cases unrelated to HCG problems necessarily involve starting another cycle, perhaps with a different stimulation protocol. All these options are disappointing for the couple seeking fertility treatment and the clinical staff, as they preclude any possibility of pregnancy in the current cycle. It may be speculated, however, that non-recovered oocytes might be in the peritoneal fluid or retained in the follicular cavity and could later be picked up by the tubes (if patent); if so, carrying out intrauterine insemination (IUI) could be worthwhile, as, ovulation timing is not as important in IUI as it is in IVF (Osuna et al., 2004). The aim of the present study study was to analyse pregnancy rates obtained with rescue IUI carried out in women scheduled for IVF, in whom response to ovarian stimulation was poor and no oocytes were obtained, in the absence of any problems related to HCG administration.

Materials and methods

The study was conducted at the Human Reproduction Unit of the Cruces University Hospital between 2000 and 2012. During that period, a total of 6520 IVF cycles with own oocytes were started, all in women younger than 40 years of age, as this is a mandatory criterion in all Spanish public hospitals (Matorras et al., 2012a). Exclusion criteria for IVF were the same as the general criteria for patients in our public centre: age 40 years or older; three or more previous IVF failures; two previous cycles with poor response (less than four oocytes obtained in spite of an adequate stimulation protocol); poor ovarian reserve (FSH greater than 13 mUI/ml between 2000 and 2008, anti-Müllerian hormone less than 0.4 ng/mL and antral follicle count less than 6 between 2008 and 2012); infection risk; prenatal genetic diagnosis; or contraindication for pregnancy (Matorras et al., 2003, 2012a).

At that time, the clinic's policy in women with two or less follicles with a mean diameter greater than 13 mm was to recommend switching to IUI if at least one tube was patent (Matorras et al., 2003) or to cancel the cycle if no tube was patent.

Women reaching follicular aspiration not obtaining oocytes were offered rescue IUI if all the following inclusion criteria were meet: follicular ultrasound showing one to six follicles greater than 13 mm (mean diameter) on the day of HCG administration (all the cases showing only one to two follicles greater than 13 mm had previously refused to follow our standard policy of switching to an IUI instead of performing ooctye retrieval; HCG levels immediately after failure to obtain oocytes over 23 UI/ml, based on our previous research (Matorras et al., 2012a); at least one patent tube; and a motile sperm count after preparation over 3 million/mL, as in our general IUI programme. A total of 54 rescue IUIs were carried out. In patients in whom oocytes could not be retrieved, who had more than six follicles with a mean diameter of over 13 mm on the day of HCG administration were excluded to avoid the risk of high-order multiple pregnancy. The Clinical Research Ethics Committee of the University Hospital of Cruces approved the study on 14 November 2012 and informed consent was obtained. Our IVF management has previously been described (Matorras et al., 2009; Osuna et al., 2004).

Ovulation was triggered with 10,000 IU of urinary HCG intramuscularly during the first 6 years of the study period and 250 μg recombinant HCG subcutaneously for the rest of the study period. The HCG was administered when at least three follicles over 18.5 mm were observed or, in cases failing to develop, three mature follicles, when the leading follicle was 20 mm.

Transvaginal ultrasound-guided oocyte retrieval was scheduled 36 h after HCG administration. Oocyte aspiration was carried out under sedation with local anaesthesia, with a single-lumen 18-gauge needle (K-OPS-6035-RWH-B-ET; Cook, Spain) with a negative pressure of 115–120 mm Hg. All the follicles observed, even if less than 10 mm, were aspirated. Oocyte aspiration was always conducted by a staff gynaecologist with more than 20 years experience in the procedure. No follicle flushing was carried out. Immediately after follicle puncture, follicular fluids were transported to the IVF laboratory for oocyte collection. The fluids were observed at low magnification (40X–100X) under the stereomicroscope. When an oocyte–cumulus–complex was found, the stage of maturity was assessed by noting the volume, density and condition of the surrounding coronal and cumulus cells. In women in whom oocytes could not be obtained, blood samples were taken immediately after follicle puncture and submitted for analysis of HCG concentration. Serum concentrations of oestradiol (during ovarian stimulation) and of HCG (at oocyte retrieval) were measured using commercially available kits (Automated Chemiluminescence ACS-180 System, Bayer Corp., Tarrytown, NY). In cases in which no oocytes were retrieved, if HCG levels were greater than 23 mUI/ml at the time of attempted retrieval, insemination took place 1 h after sperm collection. Sperm samples were obtained at the moment of oocyte aspiration and preparation was started immediately.