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ARTICLE

Adjuvant gonadotrophin-releasing hormone agonist trigger with human chorionic gonadotrophin to enhance ooplasmic maturity

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Abstract This study investigates whether an adjuvant gonadotrophin-releasing hormone agonist (GnRHa) trigger with human chorionic gonadotrophin (HCG) improves fresh intracytoplasmic sperm injection (ICSI) cycle outcomes in patients with poor fertilization history after standard HCG trigger alone. This study compared 156 patients with <40% fertilization rate in a prior ICSI cycle with standard HCG trigger who underwent another ICSI cycle with a combined 2 mg GnRHa and 1500 IU HCG ovulatory trigger. There was no difference in the baseline demographics, ovarian stimulation outcomes or sperm parameters of the groups. More mature oocytes were retrieved in the combined trigger group compared with the HCG trigger group: 12 (9–14) versus 10 (7–12); $P = 0.01$. The fertilization rate in the combined trigger group (59.2%) was higher than the HCG group (35.3%); $P = 0.01$. The odds of clinical pregnancy and live birth were 1.8 and 1.7 times higher, respectively, when comparing the former group to the latter; $P = 0.03$. The results suggest that combined GnRHa and HCG trigger in ICSI cycles is a reasonable approach to increase oocyte maturity, specifically ooplasmic maturity, thereby increasing fertilization and improving ICSI cycle outcomes in patients with a history of poor fertilization after standard HCG trigger alone.

KEYWORDS: dual trigger, fertilization rate, gonadotrophin-releasing hormone agonist trigger, ICSI, oocyte maturity

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Introduction

The use of a single bolus of human chorionic gonadotrophin (HCG) has been the gold standard for triggering final oocyte maturation in IVF and intracytoplasmic sperm injection (ICSI) cycles (Casper, 2015). However, in 1990, triggering of oocyte maturation with gonadotrophin-releasing hormone agonists (GnRHa) was proposed as an alternative (Gonen et al., 1990). The GnRHa trigger is thought to induce an endogenous surge of FSH and LH, which resembles the physiologic surge occurring in natural menstrual cycles (Humaidan et al., 2009). This property of GnRHa is frequently harnessed in IVF and ICSI cycles to prevent ovarian hyperstimulation syndrome (OHSS) (Engmann et al., 2008; Griesinger et al., 2006; Griffin et al., 2012; Shapiro et al., 2008). Some studies have also postulated that the GnRHa mediated surge of FSH and LH increases the percentage of mature oocytes retrieved compared with standard HCG trigger during IVF cycles (Humaidan et al., 2005). More recently, Griffin et al. (2014) showed that utilization of a combined GnRHa and HCG trigger in patients with >25% immature oocytes in a prior IVF cycle with standard HCG trigger increased the odds of retrieving mature oocytes by 2.51 times. However, it is unknown whether a combined GnRHa and HCG trigger can improve fertilization rates, particularly in patients with a history of poor fertilization in ICSI cycles. This study questions whether an adjuvant GnRHa ovulatory trigger with HCG improves fresh ICSI cycle outcomes in patients with poor fertilization history after standard HCG trigger alone.

Materials and methods

Cycle inclusion criteria

The institutional review board at Weill Cornell Medical College approved this study protocol on 25 November 2014 (protocol number: 1307014154R001). Patients initiating fresh ICSI cycles at the Ronald O Perelman and Claudia Cohen Centre for Reproductive Medicine resulting in embryo transfer between January 2006 and October 2013 were analysed for potential inclusion. Paired-comparison of all patients with a fertilization rate of <40% in a prior fresh ICSI cycle with standard HCG trigger who subsequently underwent another ICSI cycle with a combined GnRHa and HCG trigger were included in the study cohort. In other words, all patients included in the study cohort underwent a prior ICSI cycle with standard HCG trigger and a subsequent ICSI cycle with combined GnRHa and HCG trigger at our center. Cycles that were cancelled prior to embryo transfer or utilized surgically retrieved spermatozoa were excluded from the analysis.

Ovarian stimulation protocols

Controlled ovarian stimulation (COS) and oocyte retrieval were performed as per our standard protocols (Huang and Rosenwaks, 2014). Patients requiring follicular synchronization were started on 0.1 mg oestradiol patches (Climara, Bayer Healthcare Pharmaceuticals, Berlin, Germany), or oral contraceptive (OC) pills (Ortho-Novum, Janssen Pharmaceuticals, Beerse, Belgium). Ovarian stimulation was carried out to maximize follicular response while minimizing the risk of OHSS. Patients were stimulated with gonadotrophins (Follistim, Merck, Kenilworth, NJ, USA; Gonal-F, EMD-Serono Inc., Rockland, MA, USA; and Menopur, Ferring Pharmaceuticals Inc, Parsippany, NJ, USA), with ovulation being suppressed with once daily 0.25 mg Ganirelix Acetate (Merck) or Cetrotide (EMD-Serono Inc.) injections based on a previously described flexible protocol (Huang and Rosenwaks, 2014). Gonadotrophin doses were generally based on patient age, weight, antral follicle count and previous response to stimulation.

HCG was used as the ovulatory trigger in the initial ICSI cycle. Novarel (Ferring Pharmaceuticals Inc, Parsippany, NJ, USA) or Pregnyl (Merck) was administered according to a sliding scale (10,000 IU for oestradiol <1500 pg/ml, 5000 IU for oestradiol 1501–2500 pg/ml, 4000 IU for oestradiol 2501–3000 pg/ml and 3300 IU for oestradiol >3001 pg/ml). In general, the HCG trigger was administered when the two lead follicles attained a mean diameter >17 mm. Luteal support was begun the day after retrieval with 50 mg of intramuscular progesterone. In the subsequent cycle, an ovulatory trigger of 2 mg leuprolide acetate (Lupron, Abbott Pharmaceuticals, Abott Park, Illinois, USA) in conjunction with 1500 IU HCG was administered (Engmann and Benadiva, 2012). Luteal support with two 0.1 mg oestradiol patches and 50 mg of intramuscular progesterone was initiated the day after oocyte retrieval. Oocyte retrieval was performed under conscious sedation anaesthesia using transvaginal ultrasound guidance approximately 35–36 h after the ovulatory trigger. Retrieved oocytes were exposed to 40 IU recombinant hyaluronidase (Cumulase, Halozyme Therapeutics Inc., San Diego, CA, USA) to remove the cumulus-corona complex (Neri et al., 2014; Palermo et al., 1995).

Sperm injection and laboratory protocols

Semen samples were generally produced after 2–5 days of abstinence. These samples were evaluated for volume, total count, concentration and motility using World Health Organization (WHO) criteria (World Health Organization, 2010). Sperm micro-injection, including selection and immobilization of the spermatozoa was carried out based on previously described protocols (Palermo et al., 2014a). Oocytes were examined 12–17 h after ICSI for normal fertilization, i.e. the presence of two distinct pronuclei (PN) and two clear polar bodies (Palermo et al., 2014b). Embryos were incubated in in-house culture media. All patients underwent embryo transfer at cleavage-stage, i.e. on day 3. Embryo transfers were performed with Wallace catheters (Smiths Medical Inc., Norwell, MA, USA) at approximately 1 cm less than the uterine depth identified at prior trial transfer. Ultrasound guidance was utilized only when the transfers were deemed difficult based on the prior trial transfer.

Outcome variables

Demographic characteristics analysed included age, gravidity, body mass index (BMI) (kg/m^2) and infertility diagnosis.

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