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ARTICLE

The value of HCG serum concentrations after trigger in predicting pregnancy and live birth rates in IVF–ICSI

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Abstract The aim of this study was to determine if an association existed between serum human chorionic gonadotrophin (HCG) level at 12 h after trigger and IVF and intracytoplasmic sperm (ICSI) treatment outcomes. Women undergoing initial IVF–ICSI and embryo transfer treatment using the long luteal phase gonadotrophin-releasing hormone agonist protocol between April 2012 and March 2013 for tubal factor were included ($n = 699$). In the clinical pregnancy group, HCG after trigger was significantly elevated (276.0 ± 5.1 versus 198.5 ± 6.1 mIU/mL; $P < 0.001$). The optimal cut-off value proposed by the receiver operating characteristic analysis (area under curve = 0.730) for HCG was 201.2 mIU/ml. Compared with the lower HCG group, the clinical pregnancy rate in the higher HCG group was increased in obese and non-obese patients (77.8% versus 57.3%, $P < 0.05$; 85.6% versus 53.0%, $P < 0.01$, respectively). Adjusted for age and body mass index, an increase of HCG was associated with a better IVF–ICSI treatment outcome (OR 4.39, 95% CI 2.99 to 6.45). Clinical pregnancy rate was significantly higher across increasing quartiles of HCG. An elevated level of serum HCG at 12 h after trigger was associated with a better IVF–ICSI outcome.

KEYWORDS: HCG, ICSI, IVF, pregnancy

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Introduction

Successful implantation after IVF and embryo transfer depends on various factors related to the embryo, as well as the endometrial receptivity (von Grothusen et al., 2014). It is important that the embryo reaches the endometrial cavity during the period in which the endometrium is receptive, the 'implantation window'. It is estimated that about 50–70% of lost pregnancies are caused by implantation failure (Achache and Revel, 2006).

Implantation is a complex process that is regulated by many factors, the most important of which is human chorionic gonadotrophin (HCG) (Tsampalas et al., 2010). In primates, HCG is one of the early embryonic signals that is secreted by the embryo before its implantation. It is a glycoprotein from the same family as the pituitary gonadotrophins (FSH and LH), and shares marked structural similarity with LH. Because of its similarity to LH, HCG can act as a surrogate for LH surge to induce final oocyte maturation and ovulation in ovarian stimulation cycles. It stimulates similar periovulatory events, including softening of the connective tissue of follicle, which allows easy detachment of oocyte cumulus complex from the follicle wall, enabling aspiration during oocyte retrieval (Bjercke et al., 2000).

Studies have shown that early ovarian hyperstimulation syndrome (OHSS) was apparently caused by the administration of exogenous HCG, the more doses of HCG used, the earlier OHSS occurred (Nargund et al., 2007). One study reduced the dose of HCG to 4000 IU in triggering oocyte final maturation in IVF–ICSI. They found that the number or proportion of mature oocytes retrieved and the OHSS rate in the lower and higher doses groups were similar, but the reduced dose of HCG could obviously affect clinical pregnancy rates (Lin et al., 2011). It can be speculated that HCG might help embryo implantation.

Gonadotrophin-releasing hormone agonist (GnRHa) is also used as a trigger of final oocyte maturation to prevent OHSS. Compared with HCG triggering, GnRHa triggering reduced moderate to severe OHSS incidence, but also decreased the live birth rate and ongoing pregnancy rate, and increased ectopic pregnancy rate (Sahin et al., 2015; Youssef et al., 2014). Many involved genes known to play a role in implantation and the receptivity of the endometrium were highly up-regulated in HCG triggering compared with GnRHa triggering (Humaidan et al., 2012). Therefore, the reason for higher pregnancy rate and lower ectopic pregnancy rate in HCG-triggered cycles relative to GnRHa triggered cycles may be the increased receptivity of the endometrium (Sahin et al., 2015). Evans and Salamonsen (2013), however, also showed that, although acute high-dose HCG enhanced endometrial epithelial cell adhesion and elicited the maxim ERK1/2 phosphorylation response, chronic low-dose HCG exposure may detrimentally affect endometrial receptivity.

On the basis of these studies, we postulated that trigger with HCG contributes to final oocyte maturation and also plays an important role in modulating endometrial receptivity. Furthermore, to the best of our knowledge, no study has evaluated the association of the HCG levels after trigger with pregnancy rate. The aim of this study was to investigate the value of HCG serum levels after trigger in predicting pregnancy and live birth rates in IVF and intracytoplasmic sperm injection (ICSI) treatments.

Materials and methods

Study population

A cohort of couples who underwent initial IVF–ICSI and embryo transfer treatment using the long luteal phase GnRH agonist protocol between April 2012 and March 2013 at the IVF centre of Nanjing Drum Tower Hospital for tubal factor was included. Inclusion criteria were age 35 years or younger, regular cycles (24–35 days), basal FSH less than 10 mIU/ml, and antral follicle count 10 or over. Women with polycystic ovarian syndrome and poor ovarian reserve, immunological disease, endometriosis, uterine abnormality, endometrial thickness less than 8 mm before embryo transfer, fewer than two good-quality embryos available for transfer or patients with inadequate data for analysis were excluded. Poor responders were defined when one or more of the following criteria was present in the first or in at least one previous failed assisted reproduction technique cycle: fewer than four mature oocyte retrieved, level of oestradiol less than 500 pg/ml on the day of HCG administration, or a prior cancelled stimulation cycle owing to poor ovarian response. Independent ethical approval was obtained from the Nanjing Drum Tower Hospital Research Ethics Committee on 22 March 2014 (no. SZ200-802). Informed consent was provided by all couples at recruitment.

Ovarian stimulation protocol

All patients received standard ovarian stimulation with recombinent FSH under pituitary suppression with GnRH agonist according to a routinely used protocol (Ding et al., 2013). In all women, pituitary desensitization was achieved by subcutaneous administration of triptorelin (0.1 mg daily, which was reduced to 0.05 mg after ovarian arrest was confirmed) started in the mid-luteal phase of the previous cycle. Gonadotrophin stimulation of the ovaries was started when serum oestradiol concentrations declined to less than 40 pg/ml and a vaginal ultrasound scan showed an absence of follicles over 10 mm in diameter. Ovarian stimulation was started with 150–250 IU/day of recombinant FSH (Gonal F; Serono, Switzerland); the initial dose was determined by the treating clinician, based on the patient's age, body mass index (BMI), basal FSH and oestradiol. Transvaginal ultrasound and oestradiol measurement were used to monitor follicular growth, and gondotrophin doses were adjusted accordingly. Ovulation was triggered by intramuscular administration of 10,000 IU of HCG (Ferring Pharmaceuticals) when at least two follicles reached a diameter of 18 mm. Serum HCG concentrations were measured at 12 h after HCG trigger using the immunoassay (ARCHITECT i2000SR; Abbott, USA). Oocytes were retrieved 36 h after the injection of HCG.

Ovum pick-up, insemination and embryo incubation

After retrieval, oocytes were fertilized using IVF–ICSI. After IVF insemination for 6 h in droplets G-IVF™ (Vitrolife, Sweden) fertilization medium under mineral oil (Ovoil ®, Vitrolife) in a conventional incubator (37°C, 5% O_2, 6% CO_2), the cumulus and corona cells were removed by mechanical pipetting. Then,