Article

Identifying real differences in live birth rates between HMG and rFSH in IVF

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Abstract

Fertility treatment strives for the delivery of a healthy live birth. Human menopausal gonadotrophin (HMG) and recombinant FSH (rFSH) are the two types of gonadotrophin currently used for ovarian stimulation in assisted reproduction treatments. Although both HMG and rFSH have been shown to be effective, a number of studies have examined whether a potential difference in clinical benefit or outcome exists between treatments. Unlike rFSH preparations, HMG contains both FSH and LH activity (in the form of LH and human chorionic gonadotrophin, which are short- and long-acting, respectively). The beneficial effect of exogenous LH activity has been investigated in the Menotrophin versus Recombinant FSH in-vitro Fertilisation Trial (MERiT), which revealed differences in embryo quality and endometrial receptivity between rFSH and highly purified HMG. Current evidence suggests that HMG provides significantly higher live birth rates than rFSH in women undergoing ovarian stimulation for in-vitro fertilization/intracytoplasmic sperm injection cycles using long gonadotrophin-releasing hormone agonist protocol. Further studies will continue to provide data with which to expand these findings and optimize the chances of achieving a live birth following assisted reproduction treatment.

Keywords: *HCG, HMG, IVF, LH activity, ovarian stimulation*

Introduction

Live birth is considered the most relevant standard of success in assisted reproduction (Dickey *et al.*, 2004). Unfortunately, the vast majority of embryos produced *in vitro* and transferred during assisted cycles fail to develop into a live birth (Kovalevsky and Patrizio, 2005; Patrizio *et al.*, 2007). Therefore, efforts are ongoing to improve the efficiency of infertility treatment and to increase the likelihood of a successful, preferably singleton, live birth.

One area of focus for potential optimization has been the examination of the different marketed gonadotrophin preparations that are available for assisted reproduction.

Currently, human menopausal gonadotrophin (HMG) and recombinant FSH (rFSH) are the two types of gonadotrophin most commonly used for controlled ovarian stimulation in assisted reproduction procedures. The most important difference between these two gonadotrophins is that, unlike rFSH preparations, HMG contains both FSH and LH activity (Van Wely *et al.*, 2003). Furthermore, the LH activity of HMG derives from two sources: (i) LH itself, which is short-acting; and (ii) human chorionic gonadotrophin (HCG), which is long-acting (Wolfenson *et al.*, 2005).

While both HMG and rFSH have been shown to achieve follicular development in ovarian stimulation for IVF, much still remains to be understood about the differential effects between these two gonadotrophin preparations (Van Wely *et al.*, 2003). The clinical issue of whether there is any real difference in live birth rates between HMG and rFSH in ovarian stimulation for IVF, using the most commonly used protocol, has been widely debated.

Combining studies for analysis as a tool for understanding outcomes in assisted reproduction

Combining different studies for analysis is a useful tool for understanding outcomes and counteracts some of the problems associated with the small numbers of patients commonly seen in assisted reproduction trials (Stewart and Clarke, 1995; Al-Inany *et al*., 2008). For example, smaller trials are likely to show false-negative findings (Type II errors), and a theoretical sample size of >2400 participants would be required for an individual study to have 80% power to detect a difference of 5% (Coomarasamy *et al*., 2008). Achieving this large sample size presents a practical challenge in the real world.

An accepted method for identifying significant outcomes that may not otherwise be noticed in smaller, individual trials is to carry out a meta-analysis of several randomized studies of similar design. This approach increases the sample size for analysis, which can minimize the risk of a false-negative finding (Egger and Smith, 1997; Guyatt and Rennie, 2002). Notably, however, it can also accumulate more variability owing to diverse study design and varying clinical practice. While this offers the potential for generalization to other patients and clinical settings, too much clinical and/or methodological diversity between studies may yield a meaningless result (Higgins and Green, 2008).

HMG versus rFSH: a Cochrane review

A Cochrane meta-analysis conducted in 2003 compared the effectiveness of HMG with rFSH in ovarian stimulation protocols in IVF or intracytoplasmic sperm injection (ICSI) treatment cycles (Van Wely *et al*., 2003). This review analysed data from four randomized trials in over 1200 women using the most commonly used protocol of long down-regulation with a gonadotrophin-releasing hormone (GnRH) agonist. The results from this meta-analysis demonstrated a trend towards better ongoing pregnancy rates and live birth rates with HMG (27.3%) versus rFSH (23.1%), although the difference was not statistically significant (odds ratio [OR] 1.27; 95% confidence interval [CI] 0.98–1.64; $P = 0.08$) (**Figure 1**). The authors found that the clinical pregnancy rate per woman was of 'borderline' significance in favour of HMG (30.9%) compared with rFSH (26.2%) (OR 1.28; 95% CI 1.00–1.64; $P = 0.05$).

Van Wely *et al*. (2003) concluded that, until further clinical evidence became available, there was insufficient evidence of a difference between HMG and rFSH in terms of ongoing pregnancy or live birth, and recommended the prescription of the least expensive gonadotrophin for women undergoing ovarian hyperstimulation in IVF cycles.

Revisiting the European and Israeli Study Group trial on highly purified menotrophin versus rFSH

Since the publication of the Cochrane review (Van Wely *et al*., 2003), several studies and analyses have been performed that have increased understanding of the differences between HMG and rFSH.

The largest study included in the Cochrane meta-analysis was conducted by the European and Israeli Study Group (EISG) on highly purified menotrophin versus rFSH ($n = 781$), which reported comparable efficacy between highly purified HMG (HP-HMG) and rFSH with respect to ongoing pregnancy rate in patients undergoing IVF and ICSI cycles (25% versus 22%) (European and Israeli Study Group, 2002). Re-analysis of data from the EISG trial (Platteau *et al*., 2004), stratified according to either IVF or ICSI cycle, demonstrated that the ongoing pregnancy rate was significantly higher with HP-HMG than with rFSH in patients undergoing IVF cycles (31 versus 20%; $P = 0.037$). In contrast, there was no difference in this clinical endpoint between HP-HMG and rFSH in women undergoing ICSI (21 versus 23%).

Platteau *et al*. (2004) also showed that there was a statistically significant association between circulating HCG concentrations

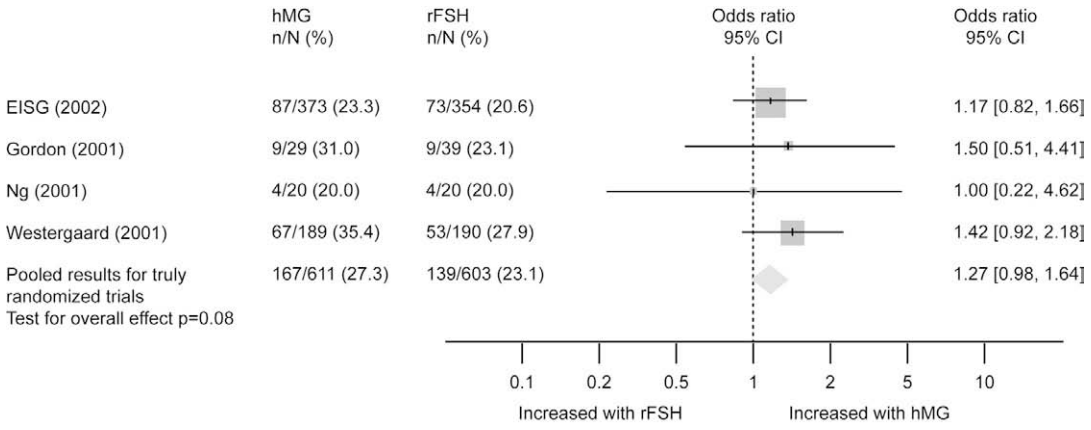

Figure 1. The Cochrane review demonstrated that live births or ongoing pregnancy rates were comparable between human menopausal gonadotrophin (HMG) and recombinant FSH (rFSH) (Van Wely *et al*., 2003. Reproduced with permission of John Wiley & Sons Ltd.) CI = confidence interval; EISG = European and Israeli Study Group.