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ARTICLE

GnRH agonist and GnRH antagonist protocols: comparison of outcomes among good-prognosis patients using national surveillance data

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Abstract Implantation and live birth rates resulting from IVF cycles using gonadotropin-releasing hormone (GnRH) agonist and (GnRH) antagonist IVF protocols were compared among good-prognosis patients using the Centers for Disease Control and Prevention's National Assisted Reproductive Technology Surveillance System 2009–2010 data (n = 203,302 fresh, autologous cycles). Bivariable and multivariable analyses were conducted between cycles to compare outcomes. Cycles were restricted as follows: age younger than 35 years, maximum FSH less than 10 mIU/mL, first assisted reproduction technology cycle and FSH dose less than 3601 IU. A subgroup analysis including only elective single embryo transfer was also carried out. Among good-prognosis patients, the GnRH-agonist protocol was associated with a lower risk of cancellation before retrieval (4.3 versus 5.2%; $P < 0.05$) or transfer (5.5 versus 6.8%; $P < 0.05$), and a higher live birth rate per transfer (adjusted odds ratio [OR] 1.13, confidence interval [CI] 1.03 to 1.25) than the GnRH-antagonist group. Among the elective single embryo transfer group, the GnRH-agonist protocol was associated with a higher implantation rate (adjusted odds ratio [OR] 1.36, CI 1.08 to 1.73) and a higher live birth rate (adjusted OR 1.33, CI 1.07 to 1.66) compared with the GnRH-antagonist protocol. The GnRH-antagonist group had lower rates of ovarian hyperstimulation

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syndrome. Among good-prognosis patients, agonist protocols decreased cancellation risk and increased odds of implantation and live birth. Antagonist protocols may confer decreased risk of hyperstimulation.

KEYWORDS: agonist, antagonist, implantation rate, live birth rate, good prognosis

Introduction

In assisted reproductive technology, GnRH analogues, agonists and antagonists, are widely used to prevent the endogenous LH surge and allow for well-timed oocyte retrieval (Al-Inany et al., 2006, 2011). Although GnRH agonists have been used for several decades (Cetel et al., 1983), antagonists have recently gained increased popularity, as their use provides more immediate pituitary suppression without an initial flare (shorter stimulation duration and fewer injections) and may confer decreased risk of ovarian hyperstimulation syndrome (OHSS) (Engmann et al., 2008). The effect of each protocol on implantation and live birth rates, however, remains controversial despite numerous studies, including randomized controlled trials (RCTs) involving heterogeneous, small study populations (Aboulghar et al., 2004; Albano et al., 2000; Barmat et al., 2005; Bodri et al., 2010; Marci et al., 2013). A 2006 Cochrane review including 27 RCTs found antagonists to be associated with a decreased live birth rate (odds ratio [OR] 0.82, 95% confidence interval [CI] 0.68 to 0.97 (Al-Inany et al., 2006). A 2011 Cochrane review including 45 RCTs, however, found no statistically significant difference in live birth rates between the agonist and antagonist groups (Al-Inany et al., 2011).

The 2009–2010 Centers for Disease Control and Prevention National Assisted Reproductive Technology Surveillance System (NASS), was used to compare cycle cancellation rates, implantation rates, and live birth rates per transfer between cycles using a GnRH agonist and a GnRH antagonist protocol in good-prognosis patients (defined as women younger than 35 years, with a maximum FSH less than 10 mIU/mL, undergoing their first assisted reproductive technology cycle, with a total FSH dose between 1200 and 3600 IU). An analysis including only elective single embryo transfers transfers (SET), in which only one embryo was transferred and at least one supernumerary embryo was cryopreserved, was also carried out to compare outcomes within an even more homogenous good-prognosis group.

Methods

Study population and participants

Data on 203,302 fresh, autologous IVF cycles initiated during 2009 and 2010 were taken from NASS (Sunderam et al., 2012), which receives mandatory cycle and demographic data on over 95% of all IVF cycles carried out in the USA. Collected data include patient demographics, medical and obstetric history, infertility diagnoses, detailed parameters of each assisted reproductive technology treatment cycle and, if applicable, the resultant pregnancy outcome.

Additionally, each year, 7–10% of reporting clinics are randomly selected for data validation, with slightly greater selection chances for larger clinics and clinics with a low cycle cancellation rate. During validation, a sample of assisted reproductive technology data reported by the clinics is compared with information recorded in medical records, and discrepancy rates are calculated. Overall, discrepancy rates for the variables evaluated in the present study were less than 5%, except for the diagnosis of infertility, which had higher discrepancy rates (up to 18%), mostly because of reporting of 'other' or 'unexplained' infertility instead of a specific cause.

To reduce selection bias, we restricted our analysis to cycles of women using either a GnRH antagonist or long GnRH agonist protocol, with a good prognostic profile, defined as female age younger than 35 years, maximum baseline serum FSH less than 10 mIU/mL, no prior history of IVF, and total FSH dose between 1200 and 3600 IU. No clomiphene citrate cycles were included in the analysis. Women who underwent antagonist stimulation and received an agonist trigger were excluded from the comparison. For women with body mass index less than 15 or greater than 50 kg/m^2, the values were set to missing. For the final model calculating the adjusted odds ratios, cycles with missing data for these criteria were excluded from the analysis.

Ovarian hyperstimulation can be reported as 'moderate,' characterized by ascites, enlarged ovarian volume, and abdominal distension accompanied by nausea, vomiting, diarrhoea, or both, or as 'severe', characterized by moderate characteristics and also haemoconcentration, laboratory abnormalities, or clinical evidence of ascites, hydrothorax, or dyspnoea.

Statistical analysis

Bivariable analyses were carried out to explore the relationship between stimulation protocol (GnRH agonist versus GnRH antagonist) and patient and cycle characteristics, including patient age, race, ethnicity, infertility diagnosis, obstetric history, and characteristics of the IVF cycle. The Pearson chi-squared test for categorical variables and *t*-test for numeric variables were used to assess differences between agonist and antagonist cycles. Mixed-effect logistic models with clinic as the random effect were used to estimate crude odds ratios and adjusted odds ratios for implantation of at least one embryo and live birth per embryo transfer, comparing the two protocols. We chose to report adjusted odds ratios comparable with the 2006 and 2011 Cochrane Reviews (Al-Inany et al., 2006). Implantation rate was defined as the percentage of embryo transfer cycles resulting in implantation of at least one embryo. Race and ethnicity were excluded from the final model, owing to a large percentage of missing values within this field.

To further reduce confounding and selection bias, a secondary analysis, including only cycles involving an elective SET (n = 2029 cycles) was carried out, as these cycles avoid