ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Addition of neither recombinant nor urinary luteinizing hormone was associated with an improvement in the outcome of autologous in vitro fertilization/intracytoplasmatic sperm injection cycles under regular clinical settings: a multicenter observational analysis

Juan-Enrique Schwarze, M.D., M.Sc.,[a] Javier A. Crosby, Ph.D.,[b] and Fernando Zegers-Hochschild, M.D.[b,c]

[a] Reproductive Medicine Unit, Clinica Monteblanco, Santiago; [b] Reproductive Medicine Unit, Clinica Las Condes, Las Condes; and [c] Program of Ethics and Public Policies in Human Reproduction, University Diego Portales, Santiago, Chile

Objective: To determine whether the addition of either urinary or recombinant LH in patients undergoing routine clinical care improved the outcome in terms of the number of oocytes recovered for insemination or the delivery rate per initiated cycle.
Design: Cohort analysis.
Patient(s): Couples undergoing IVF/ICSI in 158 institutions in 15 countries in Latin America.
Setting: In vitro fertilization clinics.
Intervention(s): We compared the outcome of three different protocols of COH, including rFSH only, rFSH plus rLH, and rFSH plus hMG.
Main Outcome Measure(s): The number of mature oocytes recovered and inseminated; proportion of ETs at the blastocyst stage; clinical pregnancy, miscarriage, and delivery rates; proportion of cycles with embryo cryopreservation; and mean number of embryos cryopreserved.
Result(s): After correcting for the age of the female partner, body mass index, number of embryos transferred, and stage of embryo development at transfer, we found that LH addition was not associated with an increase in the mean number of metaphase II oocytes inseminated or with an increase in the delivery rate or changes in the miscarriage rate.
Conclusion(s): Our study strongly suggests that in routine clinical practice, the type of controlled ovarian stimulation—FSH alone or in combination with LH—has little impact on the outcome of assisted reproductive technology; therefore a more friendly and accessible alternative should be favored. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: COS, LH, rFSH, hMG

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/12241-22837

Received July 28, 2016; revised August 16, 2016; accepted September 2, 2016.
J.-E.S. has nothing to disclose. J.A.C. has nothing to disclose. F.Z.-H. has nothing to disclose.
Reprint requests: Juan-Enrique Schwarze, M.D., M.Sc., Rio Rotten 5229, Lo Barnechea, Santiago, Chile (E-mail: schwarze@monteblancoivf.cl).

Fertility and Sterility® Vol. ■, No. ■, ■ 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2016.09.003

Controlled ovarian stimulation (COS) is a fundamental step of assisted reproductive techniques (ART). Over the years, stimulation with antiestrogens was followed by the use of urinary gonadotropins containing a mixture of FSH and LH, generically referred to as human menopausal gonadotropin (hMG). Later, molecular biology technology introduced recombinant FSH (rFSH) and LH (rLH) (1, 2). Today it is possible to induce multifollicular development with a single gonadotropin such as rFSH or a mixture of FSH and LH, either combining rFSH and rLH or using urinary hMG.

In the last decades, there had been much discussion regarding the optimal protocol for COS (3–6). Several systematic reviews compared diverse outcomes when COS was performed with rFSH or with urinary gonadotropins (hMG, purified FSH, highly purified FSH). The interpretation of the data available is quite difficult, because each of these reviews used different inclusion and exclusion criteria. The latest systematic review and meta-analysis found no significant difference between different COS protocols and concluded that clinical choice of gonadotropins should depend on their availability, convenience, and costs. Furthermore, the investigators concluded that further research on these comparisons is unlikely to identify substantive differences in effectiveness or safety (3).

Although randomized controlled trials are the most accurate methodological design to determine the efficacy or superiority of any given intervention, interpretation of results needs to consider that this type of trials are performed under strict inclusion criteria, both for selecting patients and administering the drugs. Therefore, the results will be applicable only to those falling within certain selection criteria and not to the general population (7).

Thus, we decided to perform a cohort study to determine whether in nonselected patients, the addition of LH—either recombinant or urinary—to rFSH improved the outcome in women undergoing autologous IVF/intracytoplasmic sperm injection (ICSI).

MATERIALS AND METHODS

The Latin American Registry of ART collects multinational multicenter biomedical and social data in a cycle-based format, allowing the tracking of each treatment cycle performed in over 158 institutions in 15 countries in Latin America.

The data analyzed in our manuscript were proportioned by the Latin American Registry of ART procedures. As part of the accreditation procedure performed regularly by two independent professionals, all centers members of Red Latinoamericana de Reproducción Asistida (REDLARA) must state in their consent form that the data collected may be published in epidemiological studies that will keep the anonymity of patients. If they wish, patients can ask for their data to be removed from the database. Therefore, no Institutional Review Board/Ethics Committee approval was asked.

All cycles are registered from COS until birth or abortion (8). We extracted biomedical data of fresh autologous IVF/ICSI cycles initiated between January 1, 2012, and December 31, 2013. We restricted our analysis to cycles where premature LH rise was prevented by the use of GnrH antagonist, according to the practice of every center.

We compared the outcomes of three different protocols of COH, including rFSH only, rFSH plus rLH, and rFSH plus hMG. The outcomes included were number of mature oocytes recovered and inseminated; proportion of ETs at blastocyst stage; clinical pregnancy, miscarriage, and delivery rates; proportion of cycles with embryo cryopreservation; and mean number of embryos cryopreserved.

The Latin American registry uses the International Committee Monitoring Assisted Reproductive Technologies (ICMART)/World Health Organisation revised glossary of ART terminology (9). Informed consents acknowledge that the data will be used, anonymously, for epidemiological studies. Therefore, no other consent form was requested for the purposes of this study.

We used the χ^2-test to test for independence of association of categorical variables. To assess for normal distribution of variables, we used Shapiro-Wilk test. When variables were not normally distributed, we used Kruskal-Wallis one-way analysis. We performed linear regression analysis, adjusting for maternal age in completed years and body mass index (BMI), to determine the effect of COS protocol on the number of inseminated oocytes. To analyze the effect of COS protocol in the odds ratio of delivery and abortion, we performed logistic regression analysis adjusting for maternal age in completed years, number of embryos transferred, and stage of embryo development at transfer.

All statistical analyses were performed with STATA (Statacorp). $P<.05$ was considered statistically significant.

RESULTS

Overall, we analyzed 21,212 IVF/ICSI cycles, the majority of which (83%) were ICSI. COS protocols were distributed as follows: 11,431 cycles used rFSH and hMG; 2,463 cycles used rFSH and rLH; and 7,318 cycles used rFSH only.

Table 1 summarizes biomedical characteristics as well as the outcome of each COS protocol. The group undergoing COS with only rFSH were, on average, 1 year younger. The more frequent diagnoses were unexplained infertility and male factor in the case of rFSH alone; male factor and premature ovarian insufficiency in the case of rFSH/rLH; and male factor and unexplained infertility in the case of rFSH/hMG. There were no differences in terms of BMI distribution among the different groups.

The group receiving FSH alone recovered more oocytes and had therefore more oocytes inseminated and more embryos cryopreserved. In this group, a larger proportion of embryos were transferred at the blastocyst stage. The mean number of embryos transferred was similar in the three COS protocols. To determine the effect of the protocol for COS on the mean number of oocytes recovered, we performed linear regression analysis correcting for the age of the female partner and BMI. We found that, compared with the use of rFSH alone, cycles that included hMG or rLH were associated with a lower mean number of metaphase II oocytes inseminated (regression coefficient, –0.47, 95% confidence interval [CI], –.50 to –.4; $P<.001$; Supplemental Table 1).

We performed logistic regression analysis to determine the effect of COS protocol on the delivery rate per ET. Given that the three groups were not homogenous in several confounding