Cumulative live birth rates according to the number of oocytes retrieved after the first ovarian stimulation for in vitro fertilization/intracytoplasmic sperm injection: a multicenter multinational analysis including ~15,000 women

Nikolaos P. Polyzos, M.D., Ph.D.,[a,b,c] Panagiotis Drakopoulos, M.D., Ph.D.,[b,d,e] Jose Parra,[f] Antonio Pellicer, M.D., Ph.D.,[g] Samuel Santos-Ribeiro, M.D., Ph.D.,[b,d,h] Herman Tournaye, M.D., Ph.D.,[b,d] Ernesto Bosch, M.D., Ph.D.,[i] and Juan Garcia-Velasco, M.D., Ph.D.[j,k]

[a] Department of Reproductive Medicine, Dexeus University Hospital, Barcelona, Spain; [b] Faculty of Medicine and Pharmacy, Department of Surgical and Clinical Science, Vrije Universiteit Brussel, Brussels, Belgium; [c] Department of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark; [d] Center for Reproductive Medicine, UZ Brussel, Brussels; [e] Department of Reproductive medicine, University of Liège, Liège; and [f] CleanicData, Leuven, Belgium; [g] Instituto Valenciano de Infertilidad, IVI-RMA Roma, Rome, Italy; [h] Department of Obstetrics, Gynaecology and Reproductive Medicine, Santa Maria University Hospital, Lisbon, Portugal; [i] Instituto Valenciano de Infertilidad, IVI-RMA Valencia, Valencia; [j] Instituto Valenciano de Infertilidad, IVI-RMA Madrid, Madrid; and [k] Rey Juan Carlos University, Madrid, Spain

Objective: To evaluate the association between the number of oocytes retrieved and cumulative live birth rates.
Design: Retrospective multicenter analysis using individual patient data.
Setting: Tertiary referral hospitals.
Patient(s): In total, 14,469 patients were analyzed. The study included the first cycle of patients stimulated for IVF/intracytoplasmic sperm injection (ICSI) from 2009 to 2014. All patients included in the analysis had either delivered a baby or had used all their embryos after their first stimulated cycle. All patients had vitrification as cryopreservation method. All women were followed up for at least 2 years.
Intervention(s): Ovarian stimulation with GnRH antagonist protocol for IVF/ICSI.
Main Outcome Measure(s): The primary outcome was the cumulative live birth rate defined as the delivery of at least one live-born infant (>24 weeks of gestation) in the fresh or in the subsequent frozen-thawed cycles in relation to the number of oocytes retrieved. Only the first delivery was considered in the analysis. The secondary outcome was live birth after the fresh IVF/ICSI cycle only.
Result(s): Cumulative live birth rates steadily increased with the number of oocytes, reaching 70% when ≥25 oocytes were retrieved. Interestingly, no plateau in cumulative live birth rates was observed, but a moderate increase of 5.1% on average was detected beyond 27 oocytes. Regarding the fresh cycle outcome, live birth probability increased up to seven oocytes retrieved and remained relatively unchanged (increase or decrease of ≤5%) between seven and 20 oocytes retrieved. However, a drop in fresh live birth rates was identified thereafter, which could be attributed to the progressive increase in "freeze-all" cycle rate with the number of oocytes retrieved, exceeding 20% in patients with >20 oocytes retrieved.
Conclusion(s): This is the largest multicenter study evaluating for the first time the impact of ovarian response on cumulative live birth rate. The significant progressive increase of cumulative live birth rate with the number of oocytes in our study suggests that ovarian stimulation may not have a detrimental effect on oocyte/embryo quality in good-prognosis women less than 40 year old. Nevertheless, although very high ovarian response may further increase cumulative live birth rates, ovarian stimulation should be

Received February 10, 2018; revised April 4, 2018; accepted April 25, 2018.
N.P.P. has nothing to disclose. P.D. has nothing to disclose. J.P. has nothing to disclose. A.P. has nothing to disclose. S.S.-R. has nothing to disclose. H.T. has nothing to disclose. E.B. has nothing to disclose. J.G.-V has nothing to disclose.
Reprint requests: Nikolaos P. Polyzos, M.D., Ph.D., Dexeus University Hospital, Department of Reproductive Medicine, Gran Via Carles III, 71-75, Barcelona, Spain (E-mail: nikpol@dexeus.com or n.polyzos@gmail.com).

Fertility and Sterility® Vol. 110, No. 4, September 2018 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2018.04.039

rational and avoid extreme response in terms of oocytes retrieved to preserve patients' convenience and safety and avoid ovarian hyperstimulation syndrome or other iatrogenic complications. (Fertil Steril® 2018;110:661–70. ©2018 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Key Words: Cumulative live birth, live birth rates, ovarian response, oocytes, IVF/ICSI outcome

Assisted reproductive technologies have substantially advanced since the birth of the first IVF baby (1), and innovations within the IVF lab have been of paramount importance for the overall assisted reproductive technologies success rates. Nevertheless, one of the milestones in the history of IVF is undeniably the introduction of ovarian stimulation (2), which resulted in a significant increase in pregnancy rates as compared with the very low 6% rates after the first unstimulated IVF cycles (3).

Although conventional ovarian stimulation is a key component of IVF treatment, allowing for multifollicular development, collection of multiple oocytes, and development of more than one embryo, no consensus has been reached regarding the optimal number of oocytes that clinicians should aim to retrieve in a stimulated IVF cycle.

Large registry analyses unanimously supported that live birth rates (LBRs) plateau when 10–15 oocytes are harvested and that further increase in the number of oocytes may only contribute to an increase in the risk of ovarian hyperstimulation syndrome (OHSS) (4, 5). However, both studies included IVF cycles and not patients (allowing for patients to be included more than once in the analysis) and analyzed only the results of the fresh IVF cycle, not accounting for the potential benefit of the transfer of supernumerary frozen embryos in a subsequent cycle and thus the cumulative LBR after the transfer of all fresh and frozen-thawed embryos after one ovarian stimulation protocol. Taking into account the increasing use of embryo freezing in the era of "OHSS-free" clinics and the significant progress in the cryopreservation techniques including vitrification (6–8), cumulative LBR appear to be considered a more complete measure of success of an IVF treatment (9); in this context, the delineation of the optimal number of oocytes retrieved needs to be determined in terms of cumulative LBR.

Up till now, the association between cumulative LBR and the number of oocytes retrieved has been evaluated in several studies to provide the most meaningful number of oocytes needed. A large registry analysis of the Human Fertilisation and Embryology Authority (HFEA) data has shown that cumulative LBRs follow the same pattern as fresh LBRs, reaching a plateau after 15 oocytes (10). Nevertheless, these results, referring to historical data before the introduction of embryo vitrification, were completely discordant with all single-center studies, which demonstrated that, despite the plateau reached for fresh LBRs between 10 and 15 oocytes, cumulative LBRs continue to increase with the number of oocytes retrieved (11–13).

Owing to this discrepancy in the literature, we set out to analyze available data from a very large number of patients across 15 different IVF centers in Europe to provide strong clinical evidence regarding the optimal number of oocytes after ovarian stimulation for IVF/intracytoplasmic sperm injection (ICSI).

MATERIALS AND METHODS

This is a retrospective multicenter cohort study using individual patient data, conducted in 15 tertiary referral hospitals in Europe.

The study included all consecutive women attending the Centre for Reproductive Medicine of the University Hospital of Brussels in Belgium and the 14 centers from the IVI group in Spain from January 2009 to December 2014. The study was approved by the institutional review boards.

Patients' Eligibility Criteria

All consecutive women between 18 and 45 years old undergoing their first ovarian stimulation cycle, in a GnRH antagonist protocol, were considered eligible patients. Each patient was included only once in the analysis.

Patients were excluded from the study if they had planned to undergo ovarian stimulation for preimplantation genetic diagnosis or screening, oocyte donation, and social or medical freezing of oocytes. In addition, we excluded women who planned to undergo natural cycle IVF/ICSI, given that in such cases no ovarian stimulation was used, as well as women with cycle cancellation or zero oocytes retrieved. Finally, all patients included in the study had a known fresh cycle outcome (live birth or not), and in case they did not deliver a live-born baby in the fresh cycle, they were followed for at least 2 years (irrespective of the date of study entry), to assess the frozen-thawed cycles outcome (including exclusively those having used all the supplementary frozen embryos during this time interval).

Treatment Protocol

IVF and fresh ET. Patients received daily injections of gonadotropins starting on day 2/3 of their menstrual cycle or 5 days after discontinuation of oral contraceptive pill. From day 6 of stimulation, gonadotropin doses could be adjusted according to serum E_2 levels and ovarian response, which was assessed by vaginal ultrasound, every 2 days. The GnRH antagonist was introduced on day 6 of stimulation or when the leading