Cumulative newborn rates increase with the total number of transferred embryos according to an analysis of 15,792 ovum donation cycles

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Objective: To measure the success of in vitro fertilization (IVF) of donated ova according to cumulative newborn rates (CNBR) per number of embryos required to achieve at least one newborn (EmbR), considering in addition the relevance of age and infertility etiology.
Design: Survival curves and Kaplan-Meier methods were employed to analyze CNBR with respect to the number of EmbR in a retrospective cohort of oocyte donation recipients.
Setting: University-affiliated infertility center.
Patient(s): Infertile couples undergoing IVF with oocyte donation.
Intervention(s): None.
Main Outcome Measure(s): CNBR per EmbR.
Result(s): The CNBR increased radically (up to 64.8%) between 1 and 5 EmbR, moderately (85.2%) between 5 and 15, and slowly thereafter, reaching a plateau at 15 embryos (92.4%) and peaking after 25 EmbR (96.8%), thus demonstrating that the chances of success vary as failed attempts accumulate. Patient age was not a negative factor, and indication for oocyte donation was also irrelevant to the outcome. The data showed an overall mean number of 2.6 embryo transfers and 5.8 transferred embryos per newborn.
Conclusion(s): The relationship between CNBR and number of EmbR provides pragmatic and exact information about the probability of success with oocyte donation, which is of obvious relevance to patient counseling. (Fertil Steril® 2012;98:341–6. ©2012 by American Society for Reproductive Medicine.)
Key Words: Assisted reproduction, cumulative rates, IVF, newborn, number of embryos, ovum donation

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In many developed societies there is a trend among women to delay the age at which they wish to become mothers. As a result, reduced ovarian reserve and oocyte quality often affect women's chances of becoming pregnant (1), so the demand for donated oocytes has increased (2–8). It is assumed that oocyte donation (OD) yields higher pregnancy and implantation rates than standard in vitro fertilization/intracytoplasmic sperm injection (IVF-ICSI) cycles with the patients' own oocytes, as documented by both independent centers and public registries (2–4). The reason for this is undoubtedly linked to the selection of young, healthy women as donors, which would suggest that uterine receptivity is secondary.

Improvement in the results obtained with OD has been reported over the years (2, 5), but there have been few reliable studies investigating repeated treatments in cases of failure in general and the cumulative rates in particular. Moreover, the achievement of a newborn is not always evaluated as the end point in the studies published to date.

We have recently reported an innovative new approach to measuring the success of assisted reproduction treatment (ART) by analyzing, in IVF cycles using the patient's own oocytes,

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increases in cumulative newborn rates according to the total number of embryos replaced in consecutive embryo transfers (ETs) until a newborn is achieved (6). This analysis allow an accurate description of the rate at which newborns are attained, thus providing doctors with reliable information about the results that can be expected in the case of couples who have experienced several failed treatments. This would enable physicians to counsel patients about repeating or abandoning treatment, depending on their specific chances of success and an evaluation of cost effectiveness. In our cohort, the rate of newborns per transferred embryo increased substantially between the first and fifth embryo, slightly lowered between the fifth and tenth, and became even less thereafter; a plateau and different limits were detected that depended on the woman's age and the cause of infertility (6). We describe the changes in cumulative newborn rates (CNBR) per total number of embryos replaced until a newborn was achieved (EmbR) in over 15,000 ETs performed as part of our OD program since 1998, where each embryo transferred is considered a chance to achieve a newborn and the results are stratified according to age and infertility etiology.

MATERIALS AND METHODS

Patients

A retrospective cohort study was performed with the data from OD cycles performed between January 1998 and February 2010 at the Instituto Universitario IVI Valencia (Spain) that ended in ET. The inclusion criterion was a fresh or frozen-thawed ET without preimplantational genetic screening for embryo aneuploidies. Institutional review board approval was obtained for this study (#1110-C-093-NG). Given that the aim of the study was to evaluate the significance with respect to CNBR of the total number of embryos transferred that were required to achieve at least one newborn, we considered each of the consecutive OD cycles performed for each couple until treatment was discontinued (>2 years, considered statistically as a censored time) or until at least one newborn was delivered, which was the primary outcome measure.

Our study differs from others published until now in that our unit of analysis was the number of embryos transferred and that the cumulative rates per unit of analysis were measured rather than raw per transfer, stimulation, or patient rates. All patients failing to achieve a newborn (i.e., negative pregnancy test result or miscarriage) in a given cycle were eligible for a subsequent cycle. All patients achieving a newborn and who returned for additional OD treatments (to achieve a second pregnancy) were also included (7.7% of the total number of cycles analyzed). These new attempts were considered as new treatments. A separate analysis of only the patients who had yet to achieve their first child (Supplemental Fig. 1, available online) rendered very similar results, sustaining an extremely high statistical power even when approximately 8% of the cases were excluded.

Oocyte Donors and Recipients

Oocyte donor recruitment and management were performed following protocols previously described in detail elsewhere (2, 5, 7). Screening for sexually transmitted diseases (human immunodeficiency virus, hepatitis B virus, and hepatitis C virus included) was also performed.

In Vitro Fertilization and Fresh-Embryo Transfer

Once oocytes were obtained and matched with a recipient according to phenotypical characteristics, insemination was performed according to one of two IVF methods, namely, by means of microdrops containing the oocyte and sperm cells (classic IVF) or by mechanically introducing sperm into the oocyte by ICSI (8).

Embryo transfer (ET) took place between 2 and 6 days after oocyte retrieval. The number of embryos transferred complied with current national regulations and responded to the individual patient's needs, requests, and possibilities. This number ranged from 1 to 3 since 2006, at which time Spanish law established this limit.

Frozen-Thawed ET

Cryopreservation was performed 3 days after oocyte retrieval or during the blastocyst stage, and only with embryos that were considered viable according to morphologic criteria. Frozen-thawed cycles employing cryopreserved embryos were performed following a natural cycle in which ovulation was triggered with human chorionic gonadotropin (hCG) when the preovulatory follicle reached 18 to 19 mm or after an artificial cycle in which exogenous hormones were administered (9). In both types of cycles, the luteal-phase was supported with vaginal micronized progesterone. Thawed embryos were considered viable if more than 50% of the blastomeres and the zona pellucida were unaffected by the thawing process.

Data Collection

Data were obtained from donors and patient's clinical charts, and included age, body mass index (BMI) and basal serum follicle-stimulating hormone (FSH) levels. Other parameters recorded for each cycle were total dose of gonadotropins, serum estradiol (E_2) levels on the day of hCG administration, oocytes obtained per cycle, type of insemination (IVF and/or ICSI), embryos replaced, embryos cryopreserved, and outcome in terms of pregnancy, miscarriage and newborns. The primary outcome was the delivery of one or more live infants, confirmed by medical records. Indications for OD were as follows: low response to conventional controlled ovarian stimulation due to either diminished ovarian reserve or age (>38 years), ovarian failure due to premature or natural menopause, endometriosis, repeated IVF failure or recurrent miscarriage.

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences 17 (SPSS, Inc.). The cumulative probability of a first newborn for each woman undergoing treatment during the study period was estimated using the Kaplan-Meier method, according to the total number of EmbR in each set of treatments, defining a set of treatments as the total number of consecutive OD performed until a newborn was achieved or the patient abandoned treatment. Adjustments were made