# How many oocytes are optimal to achieve multiple live births with one stimulation cycle? The one-and-done approach

Denis A. Vaughan, M.D.,[a] Angela Leung, M.D.,[a] Nina Resetkova, M.D.,[b,c] Robin Ruthazer, M.P.H.,[d,e] Alan S. Penzias, M.D.,[b,c] Denny Sakkas, Ph.D.,[b] and Michael M. Alper, M.D.[b,c]

[a] Department of Obstetrics and Gynecology, Tufts Medical Center, Boston; [b] Boston IVF, Waltham; [c] Beth Israel Deaconess Medical Center, Harvard Medical School, Boston; [d] Research Design Center, Biostatistics Research Center, Tufts Clinical and Translational Science Institute, Tufts University, Boston; and [e] Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, Massachusetts

**Objective:** To study how many infertility patients would complete an average-sized family (achieve ≥2 live births) after a single, complete in vitro fertilization (IVF) cycle.
**Design:** A retrospective cohort study.
**Setting:** University-affiliated private infertility practice.
**Patient(s):** Women undergoing IVF.
**Intervention(s):** None.
**Main Outcome Measure(s):** The outcome of 1 or ≥2 live births after a single retrieval cycle, followed by use of all embryos in subsequent frozen cycles in relation to oocyte number.
**Result(s):** The pregnancy rate was statistically significantly higher when ≥15 oocytes were retrieved (289 of 699, 41.3%) than <15 oocytes (518 of 1,419, 36.5%). When investigating the outcome of ≥2 live births and assuming that all remaining frozen embryos were used, we found that 498 of 2,226 (22.4%) patients would achieve ≥2 live births. We performed multivariate analysis, and the area under the receiver operating characteristic curve for the model was 0.802. When controlling for multiple factors we found that as the number of oocytes retrieved increased, the chance of at least two live births increased, with odds ratio 1.08 (8% live birth increase per additional oocyte).
**Conclusion(s):** We demonstrate that one fresh cycle with high oocyte yield is an optimal way to plan IVF treatment. With modern cryopreservation methods, the concept of "one-and-done" could safely achieve ≥2 live births with just one stimulation cycle in almost a quarter of our patients. (Fertil Steril® 2017;107:397–404. ©2016 by American Society for Reproductive Medicine.)
**Key Words:** Family completion, IVF, live birth, ovarian hyperstimulation

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The true measure of overall fertility treatment success relates to the ultimate reproductive goals of the infertile couple. The fertility of women in the United States has fluctuated from approximately seven children at the beginning of the 19th century to 1.7 children in 1976, but has remained stable at 2.1 children since then (1). Similar patterns are seen in Europe with recent large surveys demonstrating that most respondents consider a two-child family to be as ideal (2). In relation to the success of an in vitro fertilization (IVF) cycle, it could therefore be deduced that the average infertility patient would consider two children as a successful achievement of their reproductive goals. Of course, distinct ethnic, cultural, and social differences may exist.

In vitro fertilization, however, is not without its problems, and there may be significant barriers to achieving this goal. The most commonly cited risk is related to controlled ovarian hyperstimulation (COH). Controlled ovarian hyperstimulation protocols aim to produce a cohort of oocytes, allowing the transfer of the best embryo(s) derived

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Reprint requests: Denny Sakkas, Ph.D., Boston IVF, 130 Second Avenue, Waltham, Massachusetts 02451 (E-mail: dsakkas@bostonivf.com).

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from these oocytes and cryopreservation of any surplus, high-quality embryos (3, 4). This has led to the question: What is the optimal target number of oocytes in a fresh IVF cycle? In cycles with high oocyte yield (>15 oocytes), debate exists surrounding the possibility that both endometrial and oocyte quality could be jeopardized (5, 6). Of greatest concern is that high oocyte yield cycles are also associated with ovarian hyperstimulation syndrome (OHSS), which can have potentially serious consequences (7).

In an effort to minimize the adverse effects associated with COH, it has been argued that mild stimulation may be more appropriate (8). The theory behind milder stimulation is that oocyte and embryo quality would improve and there would be fewer adverse affects on the endometrium from markedly elevated estradiol ($E_2$) and progesterone levels (9, 10). In addition, clinicians have been wary of potential complications with increasing doses of gonadotropins, particularly OHSS (11, 12). There is also concern about the potential association between the use of ovarian stimulants and cancer (13–15), although, reassuringly, a recent large Dutch study did not find an association between breast cancer and IVF (16).

The measure of IVF success has classically been defined as the live-birth rate per fresh stimulated cycle (17, 18). However, major advances have now been made that allow the successful freezing and thawing of embryos. This success is now either equivalent to, or better than, fresh embryo transfer (Center for Disease Control and Prevention) (19). A prime reason behind this is the advent of the vitrification process. Numerous publications (20, 21) have now demonstrated a higher clinical pregnancy rate as well as a statistically significantly higher live-birth rate with blastocysts cryopreserved using vitrification compared with those cryopreserved using slow-freeze methods. The success of frozen transfers has strengthened the argument, made by IVF pioneer Howard Jones (22), that IVF success should be measured by cumulative live births resulting from a completed, stimulated IVF cycle. This is defined as a single ovarian stimulation followed by transfer, either fresh or frozen, of all embryos resulting from that initial stimulation. When expressed in this manner, the cumulative success from a single stimulated IVF cycle is high (23, 24).

In this study, we investigated how many infertility patients would achieve $\geq 2$ live births, thereby potentially completing an average-sized family, using conventional ovarian hyperstimulation protocols after a single, complete IVF cycle. In contrast to the argument for the use of milder stimulation protocols, we propose that the concept of "one-and-done"—one egg retrieval—could actually result in limiting the adverse effects of multiple fresh IVF cycles, which carry most of the risks (and costs) of IVF.

## MATERIALS AND METHODS

### Patients

A retrospective cohort study was performed using an established and validated IVF database (eIVF, PracticeHwy.com, Inc) from Boston IVF in Waltham, Massachusetts. We reviewed all homologous cycles with oocyte retrieval from January 1, 2012, to December 31, 2014. We included only patients in whom at least one oocyte was retrieved after the stimulation cycle. All analyses were conducted using oocyte number as a continuous variable. Oocyte groups were, however, presented based on what one would typically consider very low, low, average, good, and high oocyte yield. Therefore, we divided the patients into five groups, based on the number of oocytes retrieved on the initial stimulation (index) cycle: 1–3, 4–9, 10–14, 15–25, >25 oocytes. These will be referred to as groups 1 to 5, respectively.

We tracked embryos created from the index (fresh) cycle to assess outcomes in subsequent (frozen) cycles using those particular embryos. We defined "usable blastocysts" as blastocysts that were either transferred during the fresh cycle or frozen, as we have strict freezing quality criteria based on embryo morphology. Blastocysts are frozen when they are graded as 3BB or better on day 5 or 6 according to the Gardner protocol (25).

We performed two separate analyses: one for those patients who underwent a single ovarian stimulation cycle with retrieval and subsequently used all embryos resulting from that cycle, and a second analysis for those patients who had frozen embryos remaining at the conclusion of our study period.

For patients in whom a complete oocyte utilization account was not available because of remaining frozen embryos, the additional potential yield of live birth (live babies born) from the use of these embryos was estimated, as previously described by Patrizio and Sakkas (26). We first predicted whether each unused frozen embryo would yield a live birth if transferred based on the binomial distribution with the probability of a live birth estimated from the observed live-birth rate among frozen embryos transferred at our center, stratified by age group: 21–30, 30–35, 36–40, and 41–46 years. We then added these estimated additional live births (assuming all frozen embryos would be used) to the observed cumulative live births (from all embryos already transferred) to get an overall potential cumulative live-birth rate.

Our primary outcome was $\geq 2$ live births across the index cycle plus any subsequent frozen transfers, assuming all frozen embryos were transferred using methodology described in the preceding paragraph. We hypothesized that this could be considered family completion based on the reported average family sizes in the United States and Europe (1, 2), as previously mentioned. Secondary outcomes were $\geq 1$ live births in the fresh (index) cycle, $\geq 1$ true live births across all observed cycles (both fresh/frozen cycles), number of usable blastocysts (transferred plus frozen), and clinical pregnancy rate. Medical records were reviewed and demographic and clinical data abstracted, including the subsequent ultrasound reports, particularly to identify patients who developed OHSS.

### Protocols

Patients underwent ovarian stimulation protocols with gonadotropins and either a gonadotropin-releasing hormone (GnRH) agonist or antagonist as previously described elsewhere (27). Cycles were monitored with measurements of

daily serum $E_2$ levels and transvaginal ultrasound examinations beginning on treatment days 6 to 8. When at least three follicles measured 15 to 20 mm, either 250 $\mu$g of recombinant human chorionic gonadotropin (hCG, Ovidrel; EMD Serono) or 10,000 U of urinary hCG (Novarel; Ferring Pharmaceuticals) was administered subcutaneously. More recently, a GnRH-agonist trigger (leuprolide acetate) has been used to mitigate the risk of OHSS. Ultrasound-guided oocyte retrieval was performed 36 hours after hCG administration.

Embryos were transferred either on day 3 (cleavage stage) or day 5 (extended culture/blastocyst stage) on a case-by-case basis, per provider preference and institution protocol. Throughout the course of our study there was a progressive trend toward increasing the proportions of blastocyst transfers. All freezing, however, was performed at the blastocyst stage on either day 5 or 6 of development. Of note, in September 2011 our practice changed from slow-freeze cryopreservation to vitrification. Luteal support consisted of either progesterone vaginal cream in one application daily (Crinone 8%, Activis USA), vaginal progesterone at two to three times per day (Endometrin, Ferring USA), or, less frequently, intramuscular progesterone at 50 mg, once daily.

## Statistical Analysis

As stated previously, all analyses were conducted using oocyte number as a continuous variable. For descriptive purposes, the patient characteristics and outcomes were summarized separately for the subgroups based on the number of oocytes retrieved. Logistic regression analysis was used to estimate the unadjusted and adjusted associations of patient characteristics with the outcome of $\geq 1$ live births in the fresh cycle. Variables with unadjusted associations with corresponding $P$ values of $P < .05$ together with variables identified based on prior literature were included in the final multivariable logistic regression model for the outcome of $\geq 1$ live births in the fresh cycle. Unadjusted and adjusted odds ratios (OR) together with 95% confidence intervals (CI) were used to describe associations with outcomes.

Restricted cubic splines were used to explore potential nonlinear unadjusted associations with continuous predictor variables and the outcome. Some continuous variables were truncated to improve model fit. We used the Akaike information criterion to compare the statistical fit of our multivariable model with the number of oocytes as a linear term compared with a restricted cubic spline fit. This modeling was repeated separately for $\geq 1$ live births across all cycles and $\geq 2$ expected cumulative live births across all cycles.

All statistical analyses were done using SAS for Windows, SAS 9.4 TS Level 1M1 (SAS Institute). For the statistical analyses, an $\alpha$-error of $< .05$ was considered statistically significant. This retrospective cohort study was approved by the institutional review board at Beth Israel Deaconess Medical Center (Protocol 2015P000345).

# RESULTS

## Pregnancy Outcomes Per Patient

The patient demographics and cycle characteristics are shown in Table 1. Overall, 2,226 patients (2,987 of 8,959 cycles) met the inclusion criteria. Of the 2,226 patients, 1,874 (84.2%) underwent a fresh transfer on the index cycle. Of these 1,874 patients, 665 (35.5%) had at least one live birth on the fresh cycle. Of note, 136 (20.4%) of the 665 births were multiples in the fresh cycle. An additional 761 thaw cycles were performed among the same cohort, of which 225 (29.6%) resulted in at least one additional live birth. In total, 890 (40%) of 2,226 patients among our cohort achieved at least one live birth. The outcome data are summarized in Table 1.

The mean age of patients in each group was 38.0, 36.6, 35.3, 34.5, and 33.8 years in groups 1–5, respectively. The mean body mass index (BMI) was highest in group 1 (27 kg/m$^2$) and decreased in each subsequent group. The mean day-3 follicle-stimulating hormone level was highest in group 1 (9.7 IU/mL) and lowest in group 5 (5.9 IU/mL). Total gonadotropin doses administered were highest in group 1 and decreased progressively to group 5 (see Table 1). The peak $E_2$ level was lowest in group 1 (mean 1,041 pg/mL) and gradually increased across all groups (mean 4,203 pg/mL in group 5). The level of progesterone on the day of trigger was highest in group 5 (mean 1.7 ng/mL) and lowest in group 1 (mean 0.8 ng/mL). The rates of any signs of OHSS are summarized in Table 1.

Next, we investigated differences in fertilization rates, blastocyst rates, and clinical pregnancy rates between each group (see Table 1). The mean fertilization rates were 0.58, 0.61, 0.62, 0.61, and 0.58 for groups 1–5, respectively. In the index (fresh) cycle, the blastocyst transfer rates were highest in group 4 (62.3%) and lowest in group 1 (0.01%). However, the number of usable blastocysts was highest in group 5 (mean 6.7) and lowest in group 1 (mean 0.1). Supplemental Figure 1 (available online) illustrates the number of usable blastocysts per oocyte retrieved with a superimposed smoothed curve.

The clinical pregnancy rates for the index cycle were highest in group 4 (42.8%). Regarding clinical pregnancy rates in subsequent thaw cycles, we noted the lowest clinical pregnancy rate in group 1 at 2 (33%) of 6, rising to 62 (78%) of 88 in group 5. When we assessed live-birth rates in the index cycle among each group, we noted an increase from 12.8% (group 1), peaking in group 4 (37.1%), while the live-birth rate in the index cycle was lower among patients in group 5 (30.9%). Among our cohort, we noted that more patients in group 5 achieved $\geq 1$ live births across all cycles (88 of 152 patients, 57.9%) and $\geq 2$ live births across all cycles (23 of 152 patients, 15.1%) than in any other group. Figure 1 illustrates the relationship of live-birth rate in the index cycle and also the cumulative live-birth rate across all cycles per oocyte retrieved. The superimposed smoothed curved lines show an increase in both the index and cumulative live-birth rate as the oocytes retrieved increases, although the slope of the line lessens at higher numbers of oocytes retrieved.

In the subset of patients who used all their embryos (1,292 of 2,226, 58% patients; see Supplemental Table 1, available online), we noted lower fertilization rates (0.59, 0.57, 0.56, 0.53, 0.43, 0.53, respectively) across groups 1–5, when compared with all patients, indicating that a smaller number of embryos was most likely the reason they had used all

**TABLE 1**

**Demographic and outcomes data on patients undergoing in vitro fertilization with patients grouped by number of oocytes retrieved.**

| | Oocyte yield | | | | |
|---|---|---|---|---|---|
| **Variable** | **1–3** | **4–9** | **10–14** | **15–25** | **>25** |
| Patient number (n) | 196 | 798 | 533 | 547 | 152 |
| Mean age (y) at 1st cycle start | 38.0 ± 4.3 | 36.6 ± 4.5 | 35.3 ± 4.3 | 34.5 ± 4.1 | 33.8 ± 4.3 |
| BMI (kg/m$^2$) | 27 ± 6.7 | 26.1 ± 5.7 | 26.0 ± 5.5 | 25.5 ± 5.7 | 25.1 ± 5.6 |
| Day-3 FSH (IU/mL) | 9.7 ± 4.5 | 7.8 ± 3.4 | 7.1 ± 2.5 | 6.7 ± 2.6 | 5.9 ± 2.2 |
| Peak $E_2$ (pg/mL) | 1,041.0 ± 604.5 | 1,760.7 ± 836.4 | 2,398.2 ± 1,203.1 | 3,119.6 ± 1,513.4 | 4,202.9 ± 2,119.6 |
| P4 on day of trigger (ng/mL) | 0.8 ± 0.4 | 1 ± 0.5 | 1.2 ± 1 | 1.3 ± 1.2 | 1.7 ± 1.8 |
| Assisted hatching | 18 (9.8%) | 61 (7.6%) | 13 (2.4%) | 10 (1.8%) | 1 (0.7%) |
| ICSI | 43 (21.9%) | 241 (30.2%) | 176 (33%) | 175 (32%) | 65 (42.8%) |
| PGS | 5 (2.6%) | 45 (5.6%) | 55 (10.3%) | 65 (11.9%) | 30 (19.7%) |
| OHSS | | | | | |
| Mild | 0 | 0 | 0 | 1 | 4 |
| Moderate | 0 | 1 | 1 | 17 | 11 |
| Patients with Paracentesis | 0 | 1 | 1 | 15 | 9 |
| Patients with repeat paracentesis | 0 | 0 | 0 | 3 | 2 |
| Froze all embryos | 0 | 0 | 0 | 8 | 10 |
| Cabergoline | 0 | 0 | 0 | 0 | 3 |
| Severe/hospitalized | 0 | 0 | 0 | 1 | 2 |
| Outcome | | | | | |
| Fertilization rate | 0.6 ± 0.4 | 0.6 ± 0.2 | 0.6 ± 0.2 | 0.6 ± 0.2 | 0.6 ± 0.2 |
| Blastocyst transfer in cycle 1 | 1 (0.8%) | 184 (25.5%) | 263 (56.3%) | 341 (73.1%) | 94 (87%) |
| Usable blastocysts | 0.1 ± 0.4 | 1 ± 1.4 | 2.5 ± 2.2 | 4.1 ± 3.3 | 6.7 ± 4.7 |
| Clinical pregnancy (cycle 1) | 34 (17.3%) | 283 (35.5%) | 201 (37.7%) | 234 (42.8%) | 55 (36.2%) |
| Clinical pregnancy (frozen) | 2 (33%) | 43 (38%) | 89 (55%) | 133 (67%) | 62 (78%) |
| ≥1 live birth rate cycle 1 | 25 (12.8%) | 222 (27.8%) | 168 (31.5%) | 203 (37.1%) | 47 (30.9%) |
| ≥1 live birth across all cycles | 26 (13.3%) | 247 (31%) | 234 (43.9%) | 295 (53.9%) | 88 (57.9%) |
| ≥2 live births across all cycles | 4 (2.0%) | 53 (6.6%) | 54 (10.1%) | 67 (12.2%) | 23 (15.1%) |

*Note:* BMI = body mass index; $E_2$ = estradiol; FSH = follicle-stimulation syndrome; ICSI = intracytoplasmic sperm injection; OHSS = ovarian hyperstimulation syndrome; P4 = progesterone; PGS = preimplantation genetic screening.

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embryos. In addition, these patients had lower clinical pregnancy rates and live-birth rates in the index (fresh) cycle. The highest clinical pregnancy rates and live-birth rates were achieved in group 3 (31.4% and 23.2%, respectively). In total 298 (23.1%) of 1,292 patients who used all embryos from the index cycle achieved at least one live birth across all cycles, while just 54 (4.2%) of 1,292 achieved ≥2 live births across all cycles.

## Modeling Success in Relation to Oocyte Number

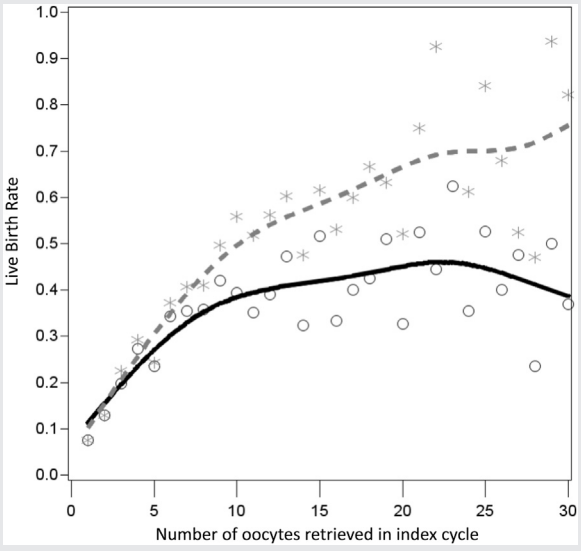
In our unadjusted univariate model for the outcome of ≥1 live births in the index cycle we investigated for multiple factors including reason for infertility, maternal age at cycle start, BMI, day of embryo transfer, whether preimplantation genetic screening (PGS) was performed, progesterone on the day of trigger, peak $E_2$ concentration, whether intracytoplasmic sperm injection (ICSI) was performed, and the fertilization rate. Unsurprisingly we found that younger age was a strong predictor of cycle success. Age was investigated as a linear variable, dichotomized at 35 years, and as a linear variable with ages under 35 years analyzed as 35 years. This truncated version of age fit best and was used in the multivariable model.

Body mass index, blastocyst transfer, oocyte number, and fertilization rate were also statistically significant in our univariate model ($P<.001$) as was the use of PGS ($P=.003$), and these were all included in our multivariate model. Similarly, peak $E_2$, divided into five groups of (pg/mL) 0–1,000, 1,000–2,000, 2,000–3,000, 3,000–4,000, and 4,000–5,000 and progesterone on day of trigger were included ($P=.001$ and $P=.026$, respectively). There were few patients with peak $E_2$ >5,000 pg/mL, and these were truncated into the last group.

Unfortunately, the infertility diagnosis was not universally available, so we did not use it in our model. Supplemental Table 2 (available online) summarizes the results of our multivariable model for the outcome of ≥1 live births in the index (fresh) cycle, with and without adjustments. The area under the curve for our receiver operating characteristic curve (ROC) model was 0.69. Age, BMI, fertilization rate, and progesterone on the day of trigger were all independent, statistically significant variables for the outcome. In addition, there was a trend toward statistical significance for blastocyst transfer ($P=.056$). Controlling for age, $E_2$ level, BMI, ICSI, PGS, fertilization rate, and progesterone level on the day of trigger, as the number of oocytes retrieved increases the chance of at least one live birth in cycle 1 increases ($P=.07$), with an OR 1.02 (2% live birth increase) per additional oocyte (95% CI, 1.00–1.04).

We then applied the independent variables used to model the outcome of ≥1 live births in the fresh cycle to create a

## FIGURE 1




The relationship of live-birth rate in the index cycle (○) and the cumulative live-birth rate (*) across all (fresh and frozen) cycles per oocyte retrieved. The superimposed smoothed lines show the live-birth rate in the index cycle (*solid line*) and live-birth rate across all cycles (*broken line*) in relation to the number of oocytes retrieved.

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new model to the outcome of ≥1 live births across all cycles (fresh and frozen). We also ran the univariate models for this outcome and again noted that age, BMI, day of transfer, peak $E_2$, and fertilization rate all appeared to be statistically significant variables. In our multivariate model (Table 2), when controlling for risk factors, age, BMI, blastocyst transfer, PGS, and fertilization rate were all statistically significant, independent variables. In addition, the number of oocytes was a strong, independent variable for the outcome of ≥1 live births across all cycles. From our multivariable model, we concluded that the chance of at least one live birth (cumulative, over all cycles) statistically significantly increased ($P$=.0001), with OR 1.05 (5% live birth increase per additional oocyte: 95% CI, 1.02–1.07). The area under the ROC curve for this model was 0.74.

Finally, we investigated the outcome of ≥2 live births across all cycles. To estimate the maximum number of live births from one, complete IVF cycle, we assumed that all remaining frozen embryos were used. Among our cohort, 201 (9%) patients achieved this outcome. We estimated that a further 336 patients would achieve ≥2 cumulative live births if all remaining frozen embryos were transferred. In total, 498 (22.4%) of 2,226 patients would achieve ≥2 live births. We performed the multivariate analysis again, and the area under the ROC curve for the model was 0.80. We found that age, ICSI, blastocyst culture, PGS, and fertilization rate were all statistically significant independent variables for our outcome. Therefore, controlling for age, $E_2$, BMI, ICSI, PGS, fertilization rate, and P4 on day of trigger, as the number of oocytes retrieved increased, the chance of at least two live births (cumulative, over all cycles) increased ($P$=.0001), with OR 1.08 (8% live birth increase per additional oocyte: 95% CI, 1.06–1.11). These results are shown in Table 3. Of note our results reflect oocyte retrieval numbers up to and including 30 oocytes retrieved as we had few patients with more than 30 oocytes retrieved.

## DISCUSSION

We have demonstrated that a single, complete IVF cycle with high oocyte yield (>15 oocytes) can satisfy the average couple's overall reproductive goal of ≥2 live births, in 22.4% of cases. In this respect, this particular subset of patients would need only one stimulation cycle without any added inconveniences of COH, such as venipuncture, stress of subsequent oocyte retrievals involving monitoring, anesthesia, surgical risks, OHSS, or potential to drop out of treatment. In addition, we have completed a separate analysis for the outcome of ≥1 live births, as this is usually patients' primary goal on presentation to a fertility clinic.

## TABLE 2

**A multivariable logistic regression model for the cumulative outcome of ≥1 live births across all cycles (fresh and frozen) (ROC area = 0.74).**

| Term in model | Unadjusted OR | Adjusted OR | 95% CI for adjusted OR | *P* value |
|---|---|---|---|---|
| Age (OR per 5-y increase)[a] | 0.26 | 0.32 | (0.25–0.40) | <.0001 |
| Peak $E_2$ per 1,000 pg/mL increase[b] | 1.40 | 1.09 | (0.98–1.23) | .1273 |
| BMI (>35 kg/m$^2$) | 0.44 | 0.97 | (0.95–0.99) | .0037 |
| ICSI | 0.95 | 0.83 | (0.66–1.05) | .1227 |
| Blastocyst transfer | 3.32 | 1.58 | (1.22–2.05) | .0006 |
| PGS yes (vs. no) | 1.47 | 1.82 | (1.18–2.86) | .0074 |
| No. of fertilized/oocyte (OR per change of 0.1)[c] | 1.43 | 1.31 | (1.19–1.45) | <.0001 |
| P4 on day of trigger (ng/mL) | | | | .2005 |
| Unknown P4 on day of trigger (versus P4 ≥1) | 0.83 | 1.06 | (0.80–1.39) | .6858 |
| P4 on day of trigger <1 (vs. P4 ≥1) | 0.88 | 1.27 | (0.96–1.67) | .0961 |
| No. of oocytes retrieved (values >30 counted as 30) | 1.08 | 1.05 | (1.02–1.07) | <.0001 |

*Note:* The adjusted OR is the adjusted odds ratio estimated from the logistic regression model. BMI = body mass index; CI = confidence interval; $E_2$ = estradiol; PGS = preimplantation genetic screening; P4 = progesterone; ROC = receiver operating characteristic.

[a] Age <35 years counted as 35 years.

[b] Values >5,000 counted as 5,000.

[c] Values >0.6 counted as 0.6.

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**TABLE 3**

**A multivariable logistic regression model for the estimated cumulative outcome of ≥2 live births across all cycles (fresh and frozen) (ROC area = 0.80).**

| Term in model | Beta (SE) | Adjusted OR | 95% CI for adjusted OR | *P* value |
|---|---|---|---|---|
| Intercept | 3.626 (1.357) | | | |
| Age (OR per 5-y increase)[a] | −1.241 (0.173) | 0.29 | (0.21–0.41) | <.0001 |
| Peak $E_2$ per 1,000 pg/mL increase[b] | 0.082 (0.067) | 1.09 | (0.95–1.24) | .2205 |
| BMI (>35 kg/m$^2$) | −0.002 (0.012) | 1.00 | (0.98–1.02) | .8511 |
| ICSI | −0.453 (0.146) | 0.64 | (0.48–0.85) | .0018 |
| Blastocyst transfer | 0.747 (0.163) | 2.11 | (1.53–2.91) | <.0001 |
| PGS yes (vs. no) | −1.028 (0.284) | 0.36 | (0.21–0.62) | .0003 |
| Number fertilized/oocyte (OR per change of 0.1)[c] | 0.469 (0.080) | 1.60 | (1.37–1.87) | <.0001 |
| P4 on day of trigger (ng/mL) | | | | .0754 |
| Unknown P4 on day of trigger (versus P4 ≥1) | 0.293 (0.171) | 1.34 | (0.96–1.87) | .0859 |
| P4 on day of trigger <1 (versus P4 ≥1) | 0.380 (0.172) | 1.46 | (1.04–2.05) | .0272 |
| No. of oocytes retrieved[d] | 0.081 (0.012) | 1.08 | (1.06–1.11) | <.0001 |

*Note:* The adjusted OR is the adjusted odds ratio estimated from the logistic regression model. BMI = body mass index; CI = confidence interval; $E_2$ = estradiol; PGS = preimplantation genetic screening; P4 = progesterone; ROC = receiver operating characteristic; SE = standard error.

[a] Age <35 years counted as 35 years.
[b] Values >5,000 counted as 5,000.
[c] Values >0.6 counted as 0.6.
[d] Values >30 counted as 30.

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## Optimum Number of Oocytes

Clinicians have long voiced concerns regarding the effect of high oocyte yield on IVF outcome; however, the available evidence in the literature is reassuring in this regard. Data are conflicting regarding the effect of gonadotropin dose/high oocyte yield on aneuploidy rates, with some studies noting a dose related effect (28), and others refuting this association (29). In addition, high oocyte yield has not been shown to increase miscarriage rates (5, 6).

It is interesting that, when we investigated both the clinical pregnancy rate and the live-birth rate in the index cycle only, we noted that both peaked in the 15 to 25 oocyte group (42.8% and 37.1%, respectively) before tapering in the >25 oocyte group (36.2% and 30.9%). We hypothesized that this is related to the aforementioned effects of extremely high peak $E_2$ levels affecting endometrial receptivity as well as increasing progesterone levels. As these were both statistically significant in our univariate analysis ($P$=.001 and 0.026, respectively), we sought to further investigate this in our multivariate analysis.

For the outcome of ≥1 live births in the index cycle, progesterone remained a statistically significant variable ($P$=.013) although $E_2$ level was not ($P$=.610). Previous studies have supported our findings regarding progesterone (10, 30), and it is likely a result of embryo/uterine dyssynchrony (31). The literature (6, 26, 32, 33) also supports our findings that live-birth rates in the fresh cycle peak when about 15 oocytes are retrieved. However, these data pertain to the index fresh cycle only, and there are far fewer data regarding the effects of high oocyte yield on cumulative live-birth rate (fresh plus frozen embryos) (33).

As has been previously demonstrated (34), we found a decrease in fertilization rates among the groups with higher oocyte yield. Ultimately this did not have a detrimental effect on the net overall embryo number or quality. Of note, groups 4 and 5 had the highest likelihood of having a blastocyst transferred in the index (fresh) cycle (73 % and 87% respectively). Consistent with previous studies (35, 36) we found that high oocyte yield results in increased numbers of usable blastocysts.

Although many of our patients had embryos still cryopreserved at the conclusion of this study period, patients in group 5 still achieved the highest live single birth rate overall as well as the highest likelihood of achieving ≥2 live births (57.9% and 15.1%, respectively). In our multivariate analysis for our primary outcome of ≥2 live births, there was a linear increase in likelihood with each additional oocyte retrieved (OR 1.08).

Regarding our subset of patients who used all their embryos, we felt that because we chose a relatively narrow study period we would inherently bias our results using data from only those patients. We hypothesized that these patients typically would have lower fertilization rates, fewer blastocysts, and ultimately worse outcomes. We were able to substantiate this hypothesis to be true (see Supplemental Table 1).

Historically, the fear of OHSS has been the primary deterrent for physicians when choosing aggressive controlled ovarian hyperstimulation. Society of Assisted Reproductive Technologies (SART) data have shown that there is a fourfold increase in OHSS rates in fresh cycles where 16 to 20 oocytes are retrieved compared with cycles where 6 to 10 oocytes are retrieved (32). One needs to weigh the potential risks of OHSS against the risks of performing another stimulation cycle, also taking into account the strategies that have now been demonstrated to markedly lower severe OHSS rates. A retrospective study by Verwoerd et al. (37) identified a threshold of ≥24 retrieved oocytes to recommend a freeze all cycle. In addition, alternative/adjunctive strategies to prevent OHSS include using a GnRH agonist to trigger oocyte maturation, using lower doses of hCG, withholding gonadotropin use ("coasting"), using cabergoline, using paracentesis aggressively, and considering not using a trigger (38–40). Indeed, in our study, although we had 38 (1.7%) of 2,226 patients who developed any form of OHSS, with the management strategies mentioned here, a

distinct minority of 3 (0.14%) of 2,226 needed hospitalization for further supportive care (see Table 1).

## Changing Practice with Freeze-all and PGS Circumvents OHSS and the Endometrial Effect

In vitro fertilization practice is evolving so as to limit the risks of aggressive ovarian stimulation on the endometrium and OHSS. Currently many clinics are considering the strategy of stimulating and cryopreserving all embryos to minimize both (41). In our multivariate models, $E_2$ was not a statistically significant variable; although while there was a trend toward statistical significance with progesterone ($P=.075$), it was clearly less of a factor than in fresh cycles alone. The percentage of cycles for which PGS was performed in our study was too low to show a statistically significant difference in outcome. However, our practice had an increased use of PGS over the course of the study period, with a corresponding increase in elective single-embryo transfer, consistent with national trends.

## Benefits of Fewer Stimulation Cycles

The main risks of IVF stem from the stimulated cycle, and they include the risk of OHSS, anesthesia, oocyte retrieval, and a possible cancer risk. Also, most of the costs of IVF (including drug costs) result from the costs incurred during a fresh IVF cycle (42, 43). Studies have reported that the average costs were $15,715 per fresh cycle and $3,812 per frozen cycle, after converting the costs to 2012 U S. dollars (42, 43). It stands to reason that patients who achieve their desired goal for a family (which we define as two children) with the fewest fresh stimulated cycles could benefit from reduced costs and risks from IVF. In a prospective study, our group has previously demonstrated that the most common reason for insured patients (insured for up to six cycles) to drop out of treatment before a third cycle was stress (39%). In addition, it is well established that the greatest risk of patients dropping out is after the first cycle (44, 45).

## Study Limitations

To our knowledge, ours is the first study to investigate the rates of family completion as defined by two or more live births resulting from one ovarian stimulation cycle. A strength of this study was the ability to link all treatments for an individual patient. As well, we tracked each individual embryo, allowing us to identify from which ovarian stimulation cycle each replaced frozen-thawed embryo came.

A limitation of this study is that, although the majority of our cryopreservation was performed using vitrification methods, not all were. A further limitation was that clinical IVF practices have shifted in their methodologies; even since 2012, our own clinic has changed to screening more for aneuploidy, transferring a single blastocyst when possible, and to deferring fresh transfers and performing more frozen transfers.

## The One-and-Done Concept

Predicting reproductive outcome with IVF has great utility both for patients and providers. The former have the opportunity to build realistic expectations, and the latter can provide better patient counseling according to measured clinical parameters. We have demonstrated that high oocyte yield can lead to excellent total reproductive outcomes. The concept of attempting to use one stimulation cycle to complete the family, "one-and-done," would allow almost one quarter of our patients to safely achieve $\geq 2$ live births (and thereby potentially complete an average-sized family) with just one stimulation cycle. Most importantly, we showed that as the number of oocytes retrieved increases, the chance of at least two live births (cumulative, over all cycles) increases by 8% per each additional oocyte.

The one-and-done concept will not be a realistic option for all cases. This study has shown that there is a subset of patients who can achieve $\geq 2$ live births from just one stimulation; unfortunately we are unable to investigate whether the same patients could be successful with fewer oocytes. Of the patient cohort studied only 31.4% achieved >15 oocytes.

The ability to achieve a high oocyte yield is obviously mitigated by a number of factors. For example, increasing maternal age has a strong negative correlation with oocyte yield. Studies have also demonstrated the negative effect of increasing BMI on a variety of assisted reproduction outcomes, including absolute oocyte yield and number of oocytes reaching metaphase II (46). Our data also showed a trend of increasing mean BMI among our patients with lower oocyte yield. In addition, as expected, the assessment of ovarian reserve, such as day-3 follicle-stimulating hormone values, correlated with oocyte yield in the index cycle, data for which there is enormous support for in the literature (47, 48).

# CONCLUSION

In this study we propose the concept of one-and-done, where a single cycle of COH to retrieve a maximal number of oocytes could better serve couples. This approach, however, depends on each individual patient's response to stimulation. In this study, approximately one in four couples could achieve two live births and complete their theoretical nuclear family. The cohort of patients who do achieve two live births are ultimately better-responding patients. Although many stimulation strategies aim to produce modest follicle pools, it may now be time to rethink this strategy as implementation of freeze-all strategies and vitrification have removed some of the risks associated with COH, while possibly improving IVF success.

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## SUPPLEMENTAL TABLE 1

**In vitro fertilization outcome data including live birth data for all cycles that used all embryos after retrieval by either a fresh or frozen transfer.**

| | Oocyte yield | | | | | |
|---|---|---|---|---|---|---|
| **Variable** | **1–3** | **4–9** | **10–14** | **15–25** | **> 25** | **All** |
| No. of retrievals with no embryos remaining | 182 | 599 | 271 | 207 | 33 | 1,292 |
| % retrievals with no embryos remaining | 92.9% (182/196) | 75.1% (599/798) | 50.8% (271/533) | 37.8% (207/547) | 21.7% (33/152) | 58.0% (1,292/2,226) |
| Mean fertilization rate (%) | 58.5% | 57.0% | 55.5% | 52.6% | 42.6% | 53.2% |
| Clinical pregnancy (1st cycle) (%) | 29 (15.9%) | 161 (26.9%) | 72 (26.6%) | 65 (31.4%) | 7 (21.2%) | 334 (25.9%) |
| Clinical pregnancy (frozen) | 2 | 14 | 30 | 29 | 7 | 82 |
| ≥1 live birth 1st cycle (%) | 24 (13.2%) | 123 (20.5%) | 53 (19.6%) | 48 (23.2%) | 4 (12.1%) | 252 (19.5%) |
| ≥1 live birth across all cycles (%) | 25 (13.7%) | 129 (21.5%) | 72 (26.6%) | 65 (31.4%) | 7 (21.2%) | 298 (23.1%) |
| ≥2 live births across all cycles (%) | 4 (2.2%) | 31 (5.2%) | 6 (2.2%) | 12 (5.8%) | 1 (3.0%) | 54 (4.2%) |

*Vaughan. The more oocytes the better. Fertil Steril 2016.*

## SUPPLEMENTAL TABLE 2

**A multivariable logistic regression model for outcome of ≥1 live birth in the intended first cycle (ROC area = 0.687).**

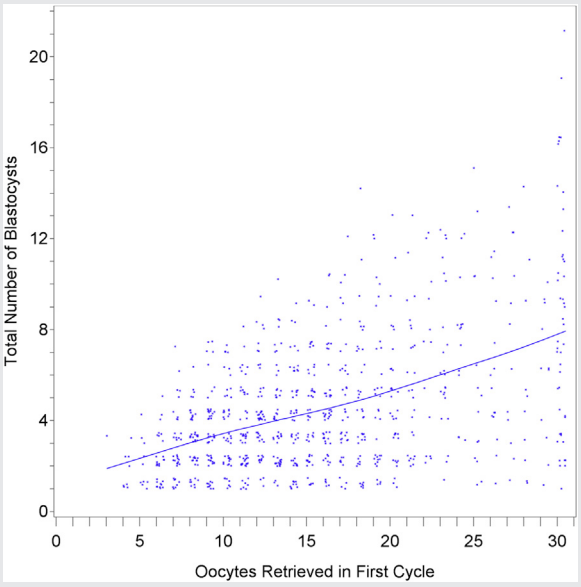
| Term in model | Unadjusted OR | Adjusted OR | 95% CI for adjusted OR | *P* value |
|---|---|---|---|---|
| Age (OR per 5-y increase)[a] | 0.32 | 0.36 | (0.28–0.46) | <.0001 |
| Peak $E_2$ per 1,000 pg/mL increase[b] | 1.14 | 1.03 | (0.92–1.15) | .6103 |
| BMI (>35 kg/m$^2$) | 0.39 | 0.97 | (0.95–0.98) | .0004 |
| ICSI | 0.96 | 0.91 | (0.72–1.14) | .4173 |
| Blastocyst transfer | 2.31 | 1.30 | (0.99–1.69) | .0563 |
| PGS yes (vs. no) | 1.67 | 0.92 | (0.59–1.42) | .6997 |
| Number fertilized/oocyte (OR per change of 0.1)[c] | 1.31 | 1.22 | (1.10–1.35) | .0002 |
| P4 on day of trigger (ng/mL) | 1.39 | | | .0134 |
| Unknown P4 on day of trigger (versus P4 ≥1) | | 1.15 | (0.87–1.51) | .3354 |
| P4 on day of trigger <1 (versus P4 ≥1) | | 1.49 | (1.13–1.96) | .0048 |
| No. of oocytes retrieved[d] | 1.03 | 1.02 | (1.00–1.04) | .0731 |

*Note:* The adjusted OR is the adjusted odds ratio estimated from the logistic regression model. BMI = body mass index; CI = confidence interval; $E_2$ = estradiol; PGS = preimplantation genetic screening; P4 = progesterone; ROC = receiver operating characteristic; SE = standard error.

[a] Age <35 years counted as 35 years.
[b] Values >5,000 counted as 5,000.
[c] Values >0.6 counted as 0.6.
[d] Values >30 counted as 30.

*Vaughan. The more oocytes the better. Fertil Steril 2016.*

## SUPPLEMENTAL FIGURE 1




The number of useable blastocysts on days 5 and 6 in relation to the number of oocytes retrieved. Useable blastocysts are defined as those blastocysts either transferred in the fresh cycle or deemed of such quality that they were frozen on days 5 and 6 of treatment. The curved line shows the mean number of useable blastocysts in relation to oocytes retrieved, and each dot represents the number of useable blastocysts for each patient.

*Vaughan. The more oocytes the better. Fertil Steril 2016.*