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Gonadotropin dose is negatively correlated with live birth rate: analysis of over 650,000 ART cycles

Valerie L. Baker, M.D.[1,*], **Morton B. Brown, Ph.D**[2], **Barbara Luke, Sc.D, M.P.H.**[3], **George W. Smith, Ph.D**[4], and **James J. Ireland, Ph.D**[5]

[1]Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Stanford University School of Medicine, Stanford, CA 94304

[2]Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, MI 48109

[3]Department of Obstetrics, Gynecology, and Reproductive Biology, Michigan State University, East Lansing, MI 48823

[4]Laboratory of Mammalian Reproductive Biology and Genomics, Department of Animal Science, Michigan State University, East Lansing, MI 48824

[5]Molecular Reproductive Endocrinology Laboratory, Department of Animal Science, Michigan State University, East Lansing, MI 48824

Abstract

Objective—To evaluate the correlation between total gonadotropin dose and live birth rate

Design—Retrospective analysis

Setting—Clinic-based data

Patients—658,519 fresh autologous cycles of in vitro fertilization (IVF) reported to the Society for Assisted Reproductive Technology from 2004 to 2012

Interventions—None

Main outcome measures—Logistic regression models were fitted to live birth rates using categorized values for total follicle stimulating hormone (FSH) dose and number of oocytes retrieved as the primary predictor variables. To reduce the effect of the most significant confounders which may lead physicians to prescribe higher doses of FSH, additional analyses were performed limited to good prognosis patients (<35 years of age, BMI<30, no diagnosis of

[*]Corresponding author and reprint requests: Valerie L Baker, M.D., Phone: 650-723-3861, Fax: 650-736-7036, 300 Pasteur Drive, Room HH333, Stanford, CA 94305, ; Email: vlbaker@stanford.edu

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diminished ovarian reserve, endometriosis, or ovulatory disorder) and including duration of gonadotropin treatment.

Results—Live birth rate significantly decreased with increasing FSH dose, regardless of the number of oocytes retrieved.. The statistically significant decrease in live birth rate with increasing FSH dose remained in patients with good prognosis, and regardless of female age, except for women aged ≥35 with 1–5 oocytes retrieved.

Conclusion—This analysis suggests that physicians may wish to avoid prescribing a high dose of FSH.. However, the results of this study do not justify the use of minimal stimulation or natural cycle IVF.

Capsule—Live birth rate decreased with increasing FSH dose, regardless of number of oocytes retrieved.

Keywords

in vitro fertilization; gonadotropin dose; live birth rate

INTRODUCTION

Gonadotropin is commonly administered during IVF cycles at doses which allow retrieval of multiple oocytes, with the goal of improving the chance of live birth above what would have been possible with retrieval of a single oocyte (1). The number of oocytes retrieved is positively correlated with live birth rate (2–5). While it is generally agreed there is benefit to the retrieval of multiple oocytes, it is now recognized that the abnormal hormonal mileu generated by ovarian stimulation may have adverse effects on the endometrium during fresh autologous cycles of IVF (6–11). Furthermore, there is evidence that superovulation may adversely affect embryo quality, possibly through interference with natural selection of the best quality oocytes or other repercussions of ovarian stimulation on oocyte, aneuploidy, or embryo quality (8, 12–15). Given the potential for adverse consequences of ovarian stimulation on the endometrium, oocyte, or embryo, there is increasing interest in mild ovarian stimulation for IVF with the goal of retrieving a limited number of oocytes (15, 16).

Less attention has been given to the possibility that the dosage of gonadotropin may influence chance of live birth. Several small studies suggest that high gonadotropin dose is associated with a reduction in live birth rate (17, 18). A meta-analysis of 11 randomized trials which examined FSH dose (including a total of 1967 women) found no benefit of a daily gonadotropin dose of >200 IU in normal responders <39 years of age (19), a dose which is modest compared with doses commonly used in the United States. Two small studies found no benefit of increasing the starting dose of recombinant FSH from 150 IU to 300 IU in women with low anti-Mullerian hormone (AMH) concentrations (20) or in women with an antral follicle count of less than 5 (21). A recent randomized trial of a novel recombinant human FSH found a positive dose-response relationship among the 265 women included with respect to number of oocytes retrieved (the endpoint for which the study was powered), but no difference in the number of good quality blastocysts with increasing dose (22).

Although FSH dose-response studies during ART in women are limited, results of dose-response studies in cattle show that maximal response to superovulation (SOV_{MAX}) plateaus, and FSH doses exceeding the SOV_{MAX} decrease ovulatory follicle number, estradiol production, number of retrieved, number of fertilized ova, and number of transferable embryos (23–32), and increase the number of degenerated embryos (27) per retrieval. Taken together, these findings in cattle along with findings in women imply that high FSH doses during IVF may impair ovulatory follicle number/function, oocyte and embryo quality, and embryo survival.. Greater study of the potential effect of gonadotropin dose on live birth rate in IVF is therefore warranted.

The objective of this study was to examine the correlation between total gonadotropin dosage and live birth rate for fresh autologous cycles of IVF. By utilizing a large database, it was possible to examine the relationship between gonadotropin dose and live birth rate while stratifying for number of oocytes retrieved. The large database also allowed us to perform subgroup analysis to account for factors such as age, BMI, and diminished ovarian reserve that could simultaneously have a negative effect on live birth rate and lead physicians to prescribe a higher dose of gonadotropin.

MATERIALS AND METHODS

The study population included fresh IVF cycles with at least one autologous oocyte which were reported to the Society for Assisted Reproductive Technology Clinic Outcomes Reporting System (SART CORS) from 2004–2012 (N=658,519). SART CORS contains data from more than 90% of all clinics providing IVF in the United States. Data are collected and verified by SART, then reported to the Centers for Disease Control and Prevention (CDC) in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102–493). Cycles were excluded if they were used for research, embryo banking, used a gestational carrier, or used oral medication for ovulation induction.

Cycles were categorized by number of oocytes retrieved (1–5, 6–10, 11–15, 16–20, 20–25, >25), follicle stimulating hormone (FSH) dose (<1000 IU, 1001–2000 IU, 2001–3000 IU, 3001–4000 IU, 4001–5000 IU, and ≥5000 IU), and female age (≤34 years, 35–39 years, and ≥40 years). The total gonadotropin dose as reported to SART CORS reflects the total dose of FSH from both FSH-only and human menopausal gonadotropin (HMG) preparations, and does not include the dose of luteinizing hormone (LH) activity, if any was administered. To characterize the study population, oocyte number was compared across categories of gonadotropin dose and female age using χ^2 for categorical variables of gonadotropin dose and oocyte number.

Logistic regression models were fitted to the data using categorical values for total gonadotropin dose as the primary predictor variable and live birth rate as the primary outcome variable. Live birth rate was calculated per cycle. A live birth was defined as one reported by the fertility clinic as a live birth and if it was confirmed that the length of gestation was ≥22 weeks and birth weight was ≥300 grams. Tests for trends in live birth rates as a function of gonadotropin dose or number of oocytes retrieved were analyzed by

fitting logistic regression to the live birth rate where the six categories of gonadotropin dose and the six categories of oocyte number retrieved were each recoded as 1 through 6.

To account for the most significant confounders which may lead physicians to prescribe higher doses of FSH, a subgroup analysis was limited to good prognosis patients (<35 years of age, BMI<30, no diagnosis of diminished ovarian reserve, endometriosis, or ovulatory disorder). Subgroup analysis was also performed for cycles for each of the three most common protocols (GnRH agonist long, GnRH agonist flare, GnRH antagonist).

A second analysis was performed taking into account the number of days of gonadotropin stimulation and average daily dose. Information to allow calculation of these parameters was available for about half of the cycles (N=369,501). This analysis was limited to cycles with 5–19 days of ovarian stimulation, with the assumption that outliers beyond this range could represent data entry errors, a restriction that eliminated <1% of the observations. Daily gonadotropin dose was calculated by dividing the total dose of gonadotropin by the number of days of ovarian stimulation. Analysis was limited to cycles with 25 IU-1200 IU calculated daily dose also to prevent inclusion of cycles with data entered in error, a restriction that eliminated <1% of the observed data.

Logistic regression models were fitted to live birth rate that initially included all diagnoses, age, number of oocytes retrieved, and gonadotropin dose as predictor variables. Of the diagnoses, diminished ovarian reserve, tubal disease, uterine abnormality, and “other” were all found to have a negative effect on live birth rate, and thus were retained in the model, while the other diagnoses were dropped. The interactions between age, number of oocytes retrieved, and gonadotropin dose were small and were also dropped from the model. Odds ratios with 95% Wald confidence limits were calculated to estimate the effect of either total gonadotropin dose or average daily gonadotropin dose on live birth rate.

Data were analyzed by SAS software, version 9.3 (SAS Institute) and Excel (Microsoft). The study was approved by the Institutional Review Boards at Stanford University, Michigan State University, and the University of Michigan.

RESULTS

A description of the study population is provided in Table 1. Approximately 82% of cycles utilized a total FSH dose between 1000 IU and 5000 IU, with a median total gonadotropin dose of approximately 3000 IU. For women aged ≤34, one third were treated with a dose of 2001–3000 IU FSH, whereas for women ≥40, about one third were treated with a total FSH dose of >5000 IU. Nearly one third of cycles which utilized the highest dose (≥ 5000 IU) were associated with retrieval of only 1–5 oocytes, suggesting that physicians anticipated the poor response and chose a high starting dose, or a lengthy ovarian stimulation was required in these poor responders. However, relatively high doses of gonadotropin were also used in many women with a high number of oocytes retrieved. For example, nearly 18% of cycles which used 4000–5000 IU had retrieval of over 15 oocytes.

This study excluded cycles where zero oocytes were retrieved, which comprised approximately 0.5% of all cycles (data not shown). The highest rates of no oocytes retrieved

were at the two extremes of gonadotropin dose (0.9% of cycles with dose of <1000 IU and 1.0% of cycles with dose of >5000 IU). As expected, the distribution of oocyte number retrieved varied depending on infertility diagnoses (shown in Supplemental Table 1). For example, 34.5% of cycles with a diagnosis of diminished ovarian reserve were associated with retrieval of 1–5 oocytes, compared with 8.7% of cycles with a diagnosis of ovulation disorder. Differences were significant at $p<0.0001$ across oocyte groups within infertility diagnosis and FSH dose categories for all ages, and within oocyte groups across FSH dose categories for all ages, and within each age group.

Live birth rate decreased with increasing gonadotropin dose, regardless of the number of oocytes retrieved ($p<0.0001$) across nearly all oocyte and dose categories (Table 2). Differences were significant at $p<0.0001$ across nearly all oocyte groups within FSH dose categories, and within oocyte groups across FSH dose categories for nearly all ages, and within each age group. The exception to this trend of decreasing live birth with increasing gonadotropin dose occurred for women aged 35 and over with 1–5 eggs retrieved, where there was no statistically significant change in live birth rate with increasing gonadotropin dose. Live birth rate also increased with increasing number of oocytes retrieved for any category of gonadotropin dose ($p<0.0001$). The same observation of decreasing live birth rate with increasing gonadotropin dose also generally held for each of the three most common protocols utilized (Supplemental Tables 2, 3, and 4).

We examined the relationship between gonadotropin dose and live birth rate limited to cycles performed for women expected to have a good prognosis. These women were <35 years of age, with BMI<30, and without a diagnosis of diminished ovarian reserve, endometriosis, or ovulatory disorder. Over 90% of these good prognosis patients received a total gonadotropin dose of 1000–5000 IU (Supplemental Table 5). Among these good prognosis patients, the live birth rate decreased with increasing dose of gonadotropin, regardless of the number of oocytes retrieved ($p<0.0001$ for all oocyte number categories) (Table 3).

Table 4 demonstrates the relationship between average daily dose of gonadotropin and live birth. This analysis was performed to address the possibility that total gonadotropin dose may be high because of a slow response to gonadotropin and a need for a prolonged ovarian stimulation rather than due to a high starting daily dose. The live birth rate decreased as the daily dose of gonadotropin increased, regardless of the number of oocytes retrieved ($p<0.0001$) for all age groups.

Logistic regression models which included diagnosis as predictors along with gonadotropin dose also showed a decrease in live birth rate with high gonadotropin dose. Using total gonadotropin dose of <1000 IU as the reference group, the odds ratio of live birth was 0.64 (95% CI 0.61–0.67) for total gonadotropin dose 5000 IU and greater, 0.79 (CI 0.76–0.83) for 4000–4999 IU, 0.89 (CI 0.85–0.93) for 3000–3999 IU, 1.02 (CI 0.97–1.06) for 2000–2999 IU, and 1.11 (1.06–1.16) for 1000–1999. Thus, a total gonadotropin dose over 3000 IU was associated with a statistically significant decrease in live birth rate, but a total dose of 1000–1999 was associated with a higher live birth rate than <1000 IU. A similar trend was seen using average daily dose along with infertility diagnoses as predictors. Using a daily dose of

150 IU or lower as a reference group, the odds ratio for live birth was 0.68 (95% CI 0.66–0.70) with a total daily dose of over 450 IU, 0.84 (0.82–0.86) for 301–450 IU, but not significantly lower with an odds ratio of 0.98 (0.96–1.01) for 151–300 IU.

DISCUSSION

Live birth rate decreased with increasing total FSH dose, regardless of the number of oocytes retrieved and patient age, except for women aged 35 and older with 1–5 oocytes retrieved. The absolute percentage drop in live birth with increasing gonadotropin dose was clinically significant, with an absolute decline in live birth rate of more than 20% when comparing the highest gonadotropin dose with the lowest gonadotropin dose in women of all ages. The average daily dose of gonadotropin was also inversely correlated with live birth rate, suggesting that the inverse relationship between total gonadotropin dose and live birth rate was due to a higher starting or daily dose and not simply due to longer duration of gonadotropin treatment. In models which adjusted for diagnosis in the prediction of live birth, a total dose of 3000 IU or greater and an average daily dose of over 300 IU were associated with a statistically significant decrease in live birth rate. Although we are reporting an inverse relationship between gonadotropin dose and live birth rate, it is important to note that our data do not provide justification for the use of natural cycle or minimal stimulation protocols for IVF. There are three protocols most commonly used during ART with different effects on endogenous gonadotropin production. With a long agonist protocol, endogenous production of FSH and LH is suppressed. In contrast, the endogenous production of FSH and LH is increased during the first few days of an agonist flare protocol. During an antagonist protocol, there will be baseline endogenous production of FSH and LH until the antagonist is initiated. In addition, the choice of protocol may differ depending on the expected ovarian response. Despite these expected differences in endogenous gonadotropin production and reason for protocol choice, the same general trend of decreasing live birth rate with increasing FSH dose was seen for all three protocols.

One potential explanation for the negative correlation between gonadotropin dose and live birth rate seen in non-randomized studies could be due to patient characteristics such as reduced sensitivity to FSH (33) which may influence both live birth rate and the FSH dose prescribed. We could not determine if the dosing decision was driven by prior response to gonadotropin. Although we did examine a subset of cycles that did not include the designated diagnosis of diminished ovarian reserve, it is possible that some of these cycles included women who had diminished ovarian reserve even though this diagnosis was not reported by the IVF program. SART CORS does not contain information about antral follicle count. Furthermore, SART CORS did not include a field for serum AMH until 2012, which was the final year of the 9 years included in our dataset, and too few AMH values were entered in this first year that the field was introduced to provide meaningful analysis. Thus these predictors of ovarian sensitivity which may be utilized by physicians to determine dose (34, 35) could not be included in our analysis.

We acknowledge that our findings could be explained in part by the tendency of physicians to prescribe a higher dose of gonadotropin when they expect a low ovarian response or have other reasons to expect a poor prognosis. However, there are several reasons why our results

provide reason for concern regarding high gonadotropin dose. The inverse correlation between FSH dose and live birth rate was generally independent of patient age and number of oocytes retrieved, the largest and most important potential confounders in the analysis. In addition, the inverse correlation between FSH and live birth rate held in the models which adjusted for diagnosis as a predictor of live birth. Subgroup analysis limited to patients with expected good prognosis yielded the same results. Furthermore, the inverse relationship between gonadotropin dose and live birth rate held when average daily dose was used as the predictor, implying that the findings were not simply due to a longer duration of treatment. A randomized trial utilizing gonadotropin doses in the ranges typically prescribed in the United States would be the most definitive way of accounting for potential confounders. However, a randomized study with sufficient sample size across age groups and range of ovarian reserve would be expensive and likely impractical. At this time, our observational data are probably the best available for the doses currently used in the United States, and suggest that there may be a negative effect of high gonadotropin dose.

Our study has several other limitations. It was not possible to determine the dose of LH activity (LH or hCG) received in addition to FSH because the total gonadotropin dose reported to SART CORS includes the FSH activity from both FSH-only and HMG preparations combined. The dose of hCG to stimulate oocyte maturation was unknown. Our analysis did not include potential pregnancies from frozen embryo transfers. It is not possible to definitively know why there was no discernable effect of gonadotropin dose for cycles in women ≥35 who had 1–5 oocytes retrieved, although it is plausible that no effect for this subgroup was noted given the overall low pregnancy rates in these cycles. In these older patients with a low number of eggs retrieved, only a limited number of follicles could respond regardless of the gonadotropin dose, and these few remaining FSH-responsive follicles may contain poor quality oocytes.

Because our study was retrospective, our findings are correlative and do not provide mechanistic insight into FSH action nor do they provide insight into how to determine when an FSH dose is excessive and detrimental to live birth rate. Observations in cattle suggest that the adverse effect of high doses of gonadotropin on outcome may be at least in part due to a direct on the oocyte as high FSH doses in cattle are associated with a decrease in the number of transferable embryos (23–32) and increase in the number of degenerated embryos (27) per retrieval. High FSH/LH doses, similar to those used during IVF cycles to stimulate growth of multiple ovulatory follicles, uncouple gonadotropin receptors from their respective signaling systems in granulosa, thecal and luteal cells in animal models (36, 37), and in antral follicles in rodents (38). High FSH causes granulosa cells in rats to undergo luteinization (39). In dose response studies, high yet physiological FSH doses trigger luteinization of granulosa cells isolated from small antral follicles of cattle with low or a high AFC (40). Moreover, premature luteinization (as determined by high circulating progesterone concentrations) (41) may be caused by excessive FSH doses during IVF cycles (42). Although it is unknown if premature luteinization per se negatively impacts oocytes, high IVF doses or high circulating FSH diminish blastocyst development (43) and cause infertility in rodents (44). Superovulation diminishes developmental competence of bovine oocytes (45, 46) and alters epigenetic marks on expressed genes in mice (47–49) and humans (50). Furthermore, high FSH doses increase aneuploidy in mice (51) and are

suspected to increase aneuploidy in human embryos compared with milder FSH protocols during ART (14, 15). Further studies to unravel mechanisms by which FSH may impair oocyte development, embryo survival or otherwise affect the probability of pregnancy are warranted, preferably both in humans and in cattle which are a single-ovulating species with multiple waves of antral follicle growth during a long reproductive cycle (52, 53).

Although ovarian stimulation has been documented to have effects on the endometrium via supraphysiologic estradiol levels or premature rise in progesterone secretion (54, 55), it is less clear that there is a direct effect of exogenous gonadotropin on the endometrium. A theoretical effect of gonadotropin stimulation on the endometrium is possible from hCG contained in human menopausal gonadotropin which could be present in low concentration at the time of implantation. However, any such effect of exogenous gonadotropin is purely speculative and a recent randomized trial found no effect of hCG infusion into the uterine cavity at the time of embryo transfer (56).

Strengths of this study include the large sample size with an unselected population which allows results to be extrapolated to a normal population undergoing IVF, the large range of total gonadotropin dose examined, the stratification based on number of oocytes retrieved, and the subgroup analysis of good prognosis patients. The group of investigators offered diverse perspectives when designing the study and interpreting the data, including a clinical reproductive endocrinologist, an epidemiologist, a statistician and two investigators with extensive experience studying superovulation in cattle.

Conclusions

Although there are limitations of a retrospective study, it is notable that the strong inverse relationship between gonadotropin dose and live birth rate was significant regardless of age of patient or number of oocytes retrieved, except for patients 35 and older with retrieval of 1–5 oocytes. Our analysis suggests that physicians may wish to avoid prescribing a high dose of FSH, particularly for women predicted to have a normal response or high number of oocytes retrieved.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Description of study population showing the percentage of cycles as a function of the number of oocytes retrieved at each FSH dose. Each row totals 100%. N=number of cycles.

		Number of Oocytes Retrieved					
FSH Dose (IU)	**N**	**1–5**	**6–10**	**11–15**	**16–20**	**21–25**	**>25**
All female ages							
<1000	10,916	12.1	21.2	25.5	18.8	11.1	11.4
1000–2000	132,976	6.7	20.0	26.5	21.3	12.9	12.7
2001–3000	184,182	9.7	26.3	27.4	18.5	9.8	8.3
3001–4000	116,419	16.4	32.4	25.6	14.1	6.5	5.0
4001–5000	105,635	22.7	36.7	23.0	10.5	4.4	2.8
≥5001	108,391	33.7	38.4	17.7	6.7	2.2	1.3
Total	658,519	16.3	29.7	24.6	15.1	7.8	6.6
Age≤34 years							
<1000	7,793	7.6	20.6	26.7	20.3	12.0	12.8
1000–2000	91,534	4.8	18.9	26.6	22.2	13.7	13.8
2001–3000	97,444	6.3	23.8	28.4	20.4	11.2	9.8
3001–4000	43,255	10.6	29.6	28.1	16.9	8.3	6.5
4001–5000	28,195	15.8	34.9	26.2	13.2	5.8	4.0
≥5001	22,086	25.2	38.1	21.8	9.2	3.4	2.3
Total	290,307	8.9	25.2	27.0	18.9	10.5	9.5
Age 35–39 years							
<1000	2,309	15.3	24.4	24.4	17.3	9.7	9.0
1000–2000	33,676	8.4	21.8	26.8	20.2	11.7	11.0
2001–3000	64,877	11.0	28.3	27.2	17.4	8.8	7.2
3001–4000	47,865	16.5	33.9	25.6	13.6	6.0	4.4
4001–5000	45,556	21.7	37.6	23.3	10.6	4.4	2.5
≥5001	45,584	32.2	39.3	18.3	6.8	2.2	1.2
Total	239,867	17.8	32.3	24.4	13.7	6.6	5.2
Age ≥40 years							

FSH Dose (IU)	N	Number of Oocytes Retrieved					
		1–5	6–10	11–15	16–20	21–25	>25
<1000	814	47.1	17.8	16.6	8.4	5.7	4.5
1000–2000	7,766	21.5	24.7	23.9	14.9	8.3	6.8
2001–3000	21,861	20.5	31.1	23.2	13.5	6.5	5.3
3001–4000	25,299	26.0	34.5	21.2	10.3	4.6	3.3
4001–5000	31,884	30.2	37.2	19.7	8.0	3.1	1.9
≥5001	40,721	39.9	37.6	14.8	5.2	1.6	0.8
Total	128,345	30.4	34.9	19.3	8.9	3.8	2.7

Table 2

Live birth rate (%) per cycle as a function of gonadotropin dose and number of oocytes retrieved. Differences were significant at p<0.0001 across oocyte groups within FSH dose categories, and within oocyte groups across FSH dose categories for all ages, and within each age group. The symbol --- indicates that the total cell count was <100.

	Number of Oocytes Retrieved						
FSH Dose (IU)	**All**	**1–5**	**6–10**	**11–15**	**16–20**	**21–25**	**>25**
All ages							
<1000	42.9	21.7	42.3	46.5	49.8	47.4	42.5
1000–2000	43.9	25.6	41.1	45.9	47.9	47.0	43.7
2001–3000	38.6	22.2	36.3	41.5	43.4	42.8	40.1
3001–4000	31.7	19.0	30.8	35.7	37.0	37.7	35.4
4001–5000	26.4	16.1	27.1	30.9	32.6	32.0	30.9
≥5001	19.9	12.5	21.8	26.2	26.2	25.5	26.5
Age ≤34 years							
<1000	47.2	33.4	46.3	49.4	51.5	49.5	43.3
1000–2000	47.4	33.6	45.0	49.5	50.2	49.5	44.9
2001–3000	44.5	31.3	42.5	47.0	47.4	46.3	42.7
3001–4000	40.2	28.3	39.7	43.1	42.4	42.7	40.1
4001–5000	36.0	25.7	37.0	38.9	39.3	38.7	34.4
≥5001	29.9	21.9	31.8	34.6	32.9	29.6	30.6
Age 35–39 years							
<1000	38.5	20.4	38.2	40.9	45.4	43.9	44.7
1000–2000	39.6	23.5	37.6	40.6	44.6	42.3	41.5
2001–3000	36.3	22.4	35.1	38.3	41.0	40.2	37.9
3001–4000	32.2	21.9	31.9	35.1	37.0	37.0	34.3
4001–5000	28.9	19.5	29.8	32.8	33.9	32.2	33.1
≥5001	23.3	16.2	25.3	28.9	28.6	27.4	29.4
Age ≥40 years							
<1000	13.6	5.0	13.8	25.9	---	---	---
1000–2000	20.7	8.3	19.1	24.6	26.0	29.1	30.2

FSH Dose (IU)	Number of Oocytes Retrieved						
	All	1–5	6–10	11–15	16–20	21–25	>25
2001–3000	19.2	9.1	18.2	22.0	25.4	26.6	26.7
3001–4000	16.1	9.0	15.5	20.4	22.0	23.7	22.5
4001–5000	14.3	8.1	15.0	18.3	20.3	20.5	20.0
≥5001	10.6	6.0	12.3	15.7	16.2	17.8	15.1

Table 3

Live birth rate per cycle as a function of gonadotropin dose and number of oocytes retrieved with analysis limited to cycles with good prognosis (<35 years of age, BMI<30, no diagnosis of diminished ovarian reserve, endometriosis, or ovulatory disorder).

	Number of Oocytes Retrieved						
FSH dose (IU)	**All**	**1–5**	**6–10**	**11–15**	**16–20**	**21–25**	**>25**
<1000	35.1	48.3	50.4	51.4	48.1	42.9	48.1
1000–2000	34.8	45.6	50.4	51.2	50.6	46.8	48.6
2001–3000	32.9	43.5	47.9	48.0	47.2	44.3	45.7
3001–4000	29.2	41.3	43.8	44.1	42.9	41.0	41.6
4001–5000	27.0	37.6	39.3	40.7	40.4	35.9	37.3
≥5001	23.7	32.3	34.8	33.3	27.0	30.7	31.1

Table 4

Live birth rate (%) as a function of average daily gonadotropin dose, stratified by number of oocytes retrieved and age. Differences were significant at $p<0.0001$ across oocyte groups within FSH dose categories, and within oocyte groups across FSH dose categories for all ages and within each age group.

	Number of Oocytes Retrieved				
FSH Daily Dose (IU)	**All**	**1–5**	**6–10**	**11–15**	**16+**
All ages					
025–150	42.3	22.7	40.8	45.3	45.2
151–300	40.6	23.2	37.8	43.2	43.8
301–450	30.3	17.0	29.7	35.0	36.8
451+	20.7	12.2	22.8	27.5	28.0
Age ≤34 years					
025–150	45.5	30.0	44.5	47.9	46.8
151–300	45.0	30.9	42.5	47.6	46.4
301–450	39.4	26.5	39.0	42.2	42.4
451+	31.4	21.7	33.7	36.5	34.4
Age 35–39 years					
025–150	37.1	19.8	35.7	39.4	41.4
151–300	36.6	21.7	35.1	38.4	40.5
301–450	30.6	19.5	30.3	35.0	35.8
451+	24.0	15.6	26.2	29.9	30.7
Age ≥40 years					
025–150	17.4	6.8	16.2	27.9	25.8
151–300	19.3	8.0	18.3	23.0	25.4
301–450	15.1	7.8	15.1	19.1	23.2
451+	11.0	6.1	12.5	17.0	17.2