EVALUATING THE IMPACT OF TOTAL GONADOTROPIN DOSE ON LIVE BIRTH RATE BETWEEN FRESH EMBRYO TRANSFER VS. FROZEN EMBRYO TRANSFER FROM THE SAME IVF CYCLE

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INTRODUCTION

Munch et al. (1) found a 38% reduction in live birth rates amongst patients that received a high gonadotropin (Gn) dose (>2500 IU) during fresh embryo transfer cycles compared to frozen embryo transfer cycles from the same in vitro fertilization (IVF) cycle. However, once adjusted for important covariates like age and BMI, this difference was no longer significant. Compared to Europe, North American practice involves using significantly higher Gn doses. This is the first study to examine the impact of total Gn dose on live birth rate using North American Gn levels.

HYPOTHESIS

We hypothesized that a high Gn dose has a deleterious effect on embryo implantation during fresh embryo transfers, independent of age and ovarian reserve. An elevated Gn dose may be an indication to freeze all embryos during IVF.

OBJECTIVE

The primary objective was to compare the live birth rate by Gn dose, among patients who underwent fresh and frozen embryo transfers from the same IVF cycle.

The secondary objectives included comparing other pregnancy outcomes such as implantation rate and ongoing pregnancy rate.

METHODS

We established a retrospective cohort of patients who underwent IVF treatment with ovarian stimulation, followed by a fresh embryo transfer and then a subsequent frozen embryo transfer, using embryos from the same IVF cycle. The study period was January 2010 to December 2019.

Inclusion criteria: Female, aged 18-42 years; first IVF cycle; Autologous IVF stimulation; IVF with fresh embryo transfer, followed by at least one frozen embryo transfer; and single embryo transfers (both fresh and frozen).

For patients with multiple IVF cycles within the study period, only the first IVF cycle was included. For patients with multiple frozen embryo transfers, only the first frozen embryo transfer was included.

Patients were grouped based on the total Gn dose received during the IVF stimulation as follows: less than 1800 IU, 1800-3600 IU, 3601-5400 IU, more than 5400 IU.

STATISTICS

For comparisons between groups, ANOVA or Chi-square tests were used depending on the variable. To evaluate the association between high Gn doses and live birth rate, a binomial multivariate logistic regression model was constructed, adjusting for age, BMI, smoking status, antral follicular count (AFC), infertility diagnosis, length of ovarian stimulation, number of mature oocytes, and embryonic stage. Data were analyzed using R, version 4.0.2.

Table 1. Sociodemographic characteristics

Characteristic		Total Gonadotropin Dose (IU) < 1800 n = 200	1801-3600 n = 698	3601-5400 n = 430	> 5400 n = 179	P-value
Age (years)		30.3 ± 3.7	31.7 ± 3.7	33.9 ± 3.8	35.5 ± 3.3	<0.001
BMI (kg/m^2)		24.5 ± 4.6	25.0 ± 4.8	25.8 ± 5.2	26.2 ± 5.5	0.002
Active smoking		13%	9%	10%	7%	0.23
Gravida	0	69.5%	66.6%	61.6%	58.1%	0.04
	1	20.0%	18.2%	18.8%	22.3%	0.63
	≥ 2	10.5%	15.0%	19.5%	19.6%	0.01
Para	0	89.1%	86.8%	79.5%	79.3%	<0.001
	1	8.6%	10.6%	14.9%	14.5%	0.04
	≥ 2	2.3%	2.4%	5.6%	6.1%	0.01
Spon. Abortion	0	87.7%	85.8%	82.6%	79.9%	0.08
	1	8.6%	9.2%	10.7%	13.4%	0.32
	≥ 2	3.6%	4.9%	6.7%	6.7%	0.28
D&C	0	96.8%	94.8%	91.6%	89.4%	0.003
	1	2.7%	3.2%	4.9%	5.6%	0.23
	≥ 2	0.5%	1.0%	2.8%	2.2%	<0.05
Ectopic preg.	0	97.3%	95.4%	95.3%	95.5%	0.66
	1	2.3%	3.2%	2.8%	3.9%	0.80
	≥ 2	0.0%	1.3%	1.9%	0.6%	0.17
Infertility diagnosis						
None		1.8%	0.7%	0.9%	0.6%	0.47
Tubular or endometriosis 3-4		6.4%	13.2%	13.3%	11.7%	0.04
Male factor		37.3%	41.4%	37.9%	26.3%	0.003
Ovulatory dys.		17.7%	9.9%	2.8%	2.8%	<0.001
Unexplained or diminished OR		30.0%	29.5%	38.8%	49.2%	<0.001
Multiple		6.8%	5.3%	6.3%	9.5%	0.22
Length of infertility (years)		2.6 ± 1.7	3.2 ± 2.5	3.1 ± 2.2	3.1 ± 2.4	0.02
AFC		29.0 ± 13.2	22.8 ±10.7	15.3 ± 8.0	11.6 ± 6.0	<0.001
AMH (ng/mL)		5.0 ± 4.1	3.7 ± 2.9	2.0 ± 2.0	1.3 ± 1.6	<0.001
FSH (IU/mL)		5.9 ± 1.6	6.0 ± 1.9	7.1 ± 4.2	7.5 ± 3.4	<0.001

Spon.: spontaneous; D&C: dilation and curettage; preg.: pregnancy.

Table 2. IVF Characteristics

	Total Gonadotropin Dose (IU) < 1800 n = 200	1801-3600 n = 698	3601-5400 n = 430	> 5400 n = 179	P-value
Protocol type					
Antagonist	89.1%	88.1%	83.3%	61.5%	<0.001
Short	1.4%	2.3%	11.4%	37.4%	<0.001
Long	9.5%	9.6%	5.3%	1.1%	<0.001
Stimulation time (days)	10.2 ц 1.7	10.8ц 1.6	11.5ц 1.5	13.5ц 1.9	<0.001
Number of mature oocytes	12.1ц 5.8	11.2ц 4.7	8.5ц 4.0	7.5ц 3.8	<0.001
Embryonic stage					
Cleavage	49.1%	44.6%	50.0%	55.3%	<0.05
Blastocyte	50.9%	55.4%	50.0%	44.7%	<0.05
Number of frozen embryos	2.7ц1.6	2.6ц1.7	2.2ц1.4	1.9ц1.3	<0.001
Frozen embryo transfer protocol					
Substituted	93.6%	90.4%	88.1%	90.5%	0.17
Natural	6.4%	9.3%	11.9%	9.5%	0.15

Table 3. Pregnancy Outcomes - Adjusted

	Total Gonadotropin Dose (IU) < 1800 n = 200	1801-3600 n = 698	3601-5400 n = 430	> 5400 n = 179
Fresh Embryo Transfer				
Implantation rate	Reference	0.92 (0.67-1.27)	0.73 (0.49-1.08)	0.99 (0.58-1.69)
Pregnancy	Reference	0.91 (0.66-1.25)	0.72 (0.49-1.08)	0.99 (0.58-1.69)
Live birth	Reference	0.98 (0.70-1.37)	0.73 (0.48-1.11)	0.87 (0.49-1.57)
Frozen Embryo Transfer				
Implantation rate	Reference	1.52 (1.08-2.16)	1.45 (0.95-2.20)	1.21 (0.68-2.14)
Pregnancy	Reference	1.48 (1.04-2.11)	1.44 (0.94-2.21)	1.30 (0.72-2.33)
Live birth	Reference	1.52 (1.06-2.21)	1.38 (0.88-2.16)	1.39 (0.75-2.56)

Adjusted for: age, BMI, smoking status, antral follicular count (AFC), infertility diagnosis, length of ovarian stimulation, number of mature oocytes, and embryonic stage.
Odds ratio (95% confidence interval).

RESULTS

A total of 1527 patients were included in the cohort. As expected, there were significant differences in patient age, BMI, infertility diagnosis, length of infertility, ovarian reserve (AFC, AMH, FSH), IVF protocol type, duration of ovarian stimulation, number of mature oocytes, embryonic stage and number of frozen embryos between Gn dose groups (tables 1 & 2). Unadjusted regression analysis showed a significant negative association between total Gn dose and live birth rate in fresh embryo transfers, however once adjusted for relevant covariates, no significant association was detected (table 3).

DISCUSSION

Diminished ovarian reserve is associated with decreased IVF success, independently of age. This patient group typically needs higher Gn doses during ovarian stimulation, therefore, it is crucial to determine the impact of higher Gn doses on IVF outcomes, independently of age and ovarian reserve. To date, no RCTs have examined this relationships, however some retrospective studies have. Malizia et al. (2) found no association between the total Gn dose and live birth rate, consistent with our results.

Strengths: our study used live birth rate as the primary outcome, which is the ultimate goal of fertility treatments; we included many important covariates in our analysis, which is, to our knowledge, the most complete retrospective analysis to date; we have a large study sample (1527 patients); and fresh and frozen embryo transfers from the same IVF cycle were compared.

Limitations: our study is retrospective in nature and thus can only determine an association, high-quality RCTs are needed to fully understand this relationship.

CONCLUSION

Contrary to our starting hypothesis, a high total Gn dose in IVF is not associated with significant differences in live birth rate following fresh embryo transfer, independently of age and ovarian reserve. Therefore, a high total Gn dose in IVF is not an indication to freeze all embryos. Further prospective study is warranted in order to solidify this conclusion.

REFERENCES

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