Association between duration of controlled ovarian stimulation and live birth rate in women undergoing In Vitro Fertilization: a SART CORS analysis

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Keywords: In Vitro Fertilization, embryo transfer, duration of controlled ovarian stimulation, SART CORS

Abstract

Background: *In-Vitro Fertilization (IVF) treatment involves synchronization of multiple time-sensitive events, most of which are rate-limiting too. Controlled ovarian stimulation (COS) is one such event. The reproductive outcomes based on the duration of COS (d-COS) in a fresh, IVF embryo transfer (ET) are not well established and therefore, remains largely uncertain.*

Objective*: To evaluate the association between d-COS and live birth rate (LBR) in women undergoing a fresh IVF-ET using autologous oocytes.*

Methods: *A retrospective cohort study was conducted using a US nationwide IVF register – SARTCORS (Society for Assisted Reproductive Technology Clinic Outcomes Reporting System). From a total of 93,889 cycles, we included 56,666 fresh, autologous, IVF - ET treatment cycles from January 2014 through December 2015, with follow-up until October 2016. Adjusted odds and risk ratio with 95% confidence intervals were estimated while controlling for multiple demographic factors and other potential confounders.*

Variables and outcomes: *The primary exposure variable was d-COS defined as the difference in days between gonadotrophin administration and oocyte retrieval. The primary outcome measure was live birth following a fresh IVF-ET. Secondary outcome measures included biochemical pregnancy rate, miscarriage rate, implantation rate and clinical pregnancy rate.*

Results*: A total of 56,666 treatment cycles (mean [SD] age of 33.9 [4.47], BMI of 26.1 [6.02], AMH value of 2.19 [3.37]), and a baseline FSH value of 7.62 [3.49]) underwent a fresh IVF-ET. The LBR after a combined analysis for all ages and all protocols was 44.2 % (n = 25043). In the combined analysis, there was a statistically significant decrease in the live birth rate with LBR with d-COS beyond 10 days. The adjusted OR (95% CI) of LBR for a woman who had 11, 12, 13 and ≥14 days of COS, compared to optimal duration of 10 days was 0.97 (0.87-*

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0.99), 0.94 (0.8-1), 0.83 (0.77-0.89) and 0.73 (0.68-0.79) respectively. The AOR (95% CI) of miscarriage rates for a woman who had 11, 12, 13 and ≥14 days of COS, compared to referent was 1.12 (1-1.26), 0.99 (0.87-1.12), 1.03 (0.90 - 1.17) and 1.04 (0.90 - 1.2) respectively. With increasing d-COS, the implantation rate (IR) and clinical pregnancy rate (CPR) also showed a decreasing trend, as with other reproductive outcomes. The RR (95% CI) for implantation rate in a woman who had 11, 12, 13 and ≥14 days of COS, compared to referent was 0.97 (0.93-1), 0.97 (0.93-1.01), 0.91 (0.87-0.95) and 0.86 (0.82-0.9). The adjusted OR (95% CI) of CPR for a woman who had 11, 12, 13 and ≥14 days of COS, compared to referent was 0.95 (0.89-1.01), 0.93 (0.87-0.99), 0.8 (0.75-0.86) and 0.7 (0.65-0.75) respectively.

***Conclusions and Relevance**: In this nationwide cohort study of women undergoing fresh IVF-ET using autologous oocytes, controlled ovarian stimulation lasting approximately 10-days was associated with an optimal live birth rate.*

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Introduction

Optimizing clinical outcomes in In-Vitro Fertilization (IVF) treatment remains a clinical challenge.[1] The number of people undergoing assisted reproductive technology (ART) treatment continues to rise worldwide.[2,3] There are several modifiable and non-modifiable factors which influence the outcome of ART treatment.[4] Several recent studies have reported improved live birth rates based on modifiable factors such as achieving an ideal oocyte number,[5] optimizing endometrial thickness,[6] endometrial receptivity,[7] and extending the embryo culture.[8]

Controlled ovarian stimulation (COS) is a modifiable but rate-limiting step in IVF treatment. Studies have evaluated reproductive outcomes associated with the duration of controlled ovarian stimulation (d-COS), although with varying conclusions. A study analysing 6,749 women undergoing a day three embryo transfer concluded that ovarian stimulation ≤13 days was associated with increased odds of clinical pregnancy and live birth (LBR).[9] An analysis on data from our Academic IVF program on 1,314 treatment cycles in women who underwent a fresh IVF-ET suggested a significant association of reduction in LBR with increasing d-COS (OR 0.83; 95% CI [0.78-0.89], P<0.001).[10] However, several other studies with similar designs did not show any relationship with final reproductive outcomes.[11-13] The conclusions of the above studies are limited as they are mostly single center studies with small numbers of participants, with drawbacks with the study design, performing univariate analysis, or the d-COS being treated as categorical variables (rather than a continuous variable) and limiting the analysis for d-COS to a pre-specified duration in the total cohort sample (rather than based on the individual treatment type). We were unable to identify any study evaluating the clinical outcomes based on d-COS and by the type of individual treatment protocol and adjusted by maternal age and body mass index, number of oocytes retrieved, type of insemination, number and the stage of the embryos transferred. Therefore, there was a need for evaluating the reproductive outcomes associated with d-COS in a larger cohort.

We, therefore, performed a multivariate analysis using data from a US nationwide IVF register (SARTCORS) that contained demographic and treatment variable information needed to evaluate the association of duration of controlled ovarian stimulation with live birth rates following a fresh IVF-ET using autologous oocytes.

Materials and Methods

Ethical Statement

The study was determined to be exempt from review by the University of Iowa Institution Review Board (IRB ID 201608711), as data were de-identified by SART CORS prior to provision to the study team.

Data Sources

The data used for this study were obtained from the SART Clinic Outcome Reporting System (SART CORS). Data were collected through voluntary submission, verified by SART, and 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). SART maintains HIPAA-compliant business associates agreements with reporting clinics. In 2004, following a contract change with the CDC, SART gained access to the SART CORS data system for the purposes of conducting research. In 2017, 82% of all assisted reproductive technology (ART) clinics in the United States were SART members.[3]

The data in the SART CORS are validated annually with 7-10% of clinics receiving on-site visits for chart review based on an algorithm for clinic selection. During each visit, data reported by the clinic were compared with information recorded in patients' charts. In 2019, records for 2,014 cycles at 34 clinics were randomly selected for full validation, along with 213 fertility preservation cycles selected for partial validation. The full validation included review of 1,300 cycles for which a pregnancy was reported. Nine out of eleven data fields selected for validation were found to have discrepancy rates of ≤5% . The exceptions were the diagnosis field, which, depending on the diagnosis, had a discrepancy rate between 2.5% and 17.8%, and the start date, which had a 8.4% discrepancy rate. Obstetrical outcomes from Massachusetts ART records during 2004-2008 have been validated to have >95% agreement with vital records.[14]

Study Population and Design

A total of 93,889 women (aged 21 to 45 years) who underwent their first autologous IVF oocyte retrieval between January 2014 and December 2015 were identified. We excluded (a) natural cycle IVF, (b) treatments using oral ovulation induction medications, (c) treatment cycles which did not result in a fresh embryo transfer, (d) treatment cycles which utilized pre-implantation genetic testing (PGT), as the final reproductive outcomes may be confounded by this technique, and (e) any treatment cycles with missing data on a variable of interest. A treatment cycle with d-COS less than six days or longer than 20 days were also excluded as these are outliers in standard clinical practice. The remaining dataset included 56,666 women, of which 18,485 (33%) had cleavage stage transfer and 38,181(67%) had blastocyst stage

transfer, which was selected as the study cohort (Figure 1).

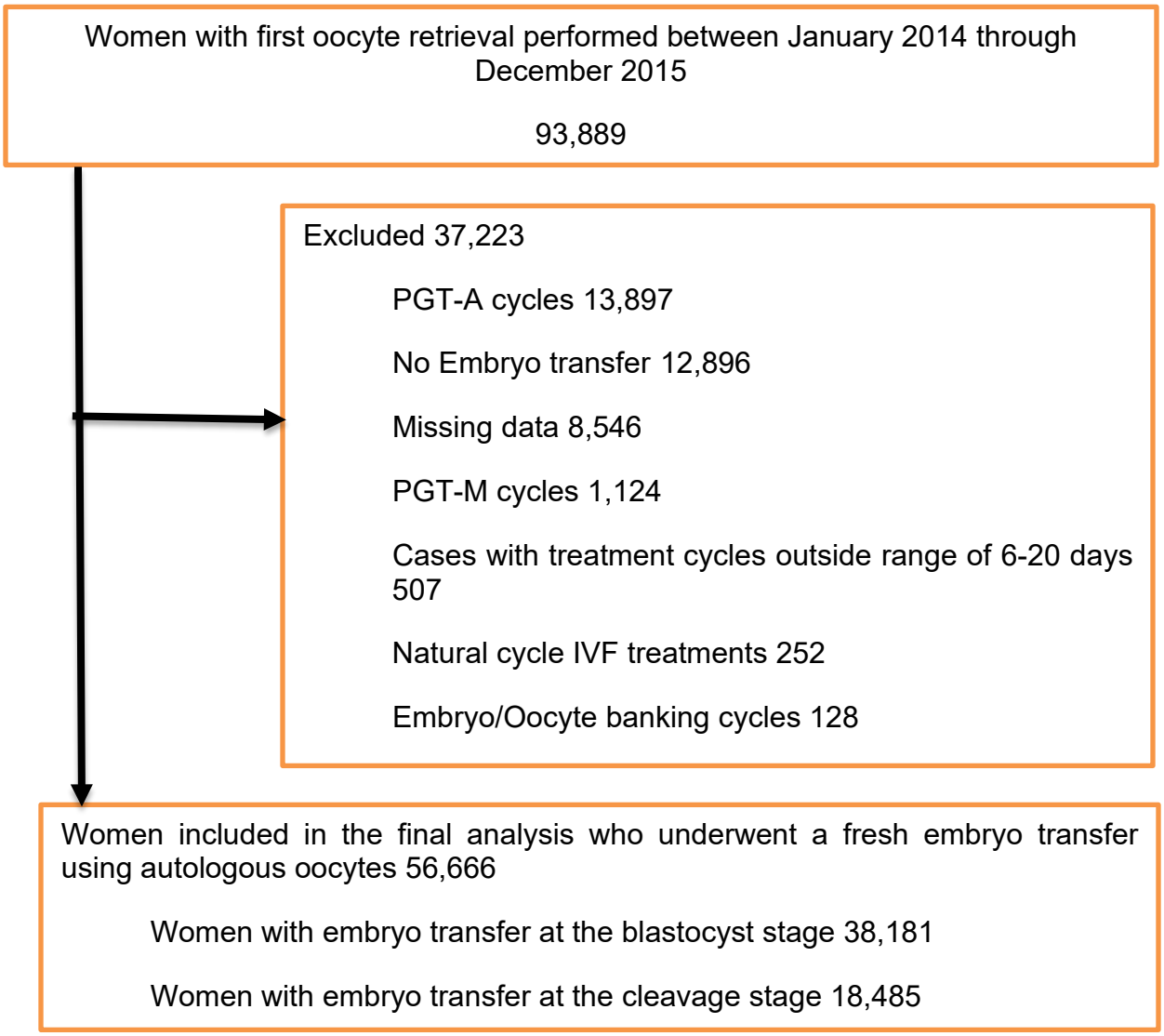

Figure 1. Study Cohort Creation: Selection of women undergoing a fresh embryo transfer using autologous oocyte following controlled ovarian stimulation between January 2014 and December 2015, is presented. The final cohort had 56,666 unique treatment cycles. PGT-A indicates preimplantation genetic testing for aneuploidy. PGT-M, preimplantation genetics testing for monosomic single gene disorders.

Main exposure

The primary exposure variable was duration of ovarian stimulation, defined as the difference in days between starting gonadotrophins in the individual IVF protocol and the oocyte retrieval.

Outcome measures

Live birth rate, defined as a birth in which at least one fetus is liveborn, was the primary outcome of interest in this study. All outcomes were defined as per SART data entry regulations for participating clinics. The secondary outcomes included *implantation rate* (the number of beating fetal hearts on ultrasound or the number of infants born (whichever was greater) divided by the number of embryos transferred), *biochemical pregnancy* (positive serum beta-hCG without confirmation of a viable gestational sac within the uterus by ultrasound), *clinical pregnancy* (a pregnancy where at least one gestational sac is confirmed on ultrasound, or if missing ultrasound data, which resulted in documentation of a birth, spontaneous abortion, or therapeutic abortion), *miscarriage* (a pregnancy that fails to develop normally and is spontaneously lost before 18 weeks from the date of transfer), and *multiple pregnancy* (a pregnancy in which more than one beating fetal heart was confirmed on ultrasound or more than one infant was born). Live birth, biochemical pregnancy, clinical pregnancy, miscarriage, and multiple pregnancy rates are rates per transfer cycle. Implantation rate is rate per embryos transferred.

Statistical analyses

Data cleaning, defining the study population and statistical analysis was performed from October 1, 2020, through September 15, 2021. Association between duration of ovarian stimulation (as a continuous variable) and primary and secondary outcomes was established using multivariate poisson and logistic regression. Descriptive statistics for baseline and treatment characteristics were calculated for all treatment cycles. Based on d-COS in days (≤8, 9, 10, 11, 12, 13, and ≥14), where appropriate, the mean, median and the proportion of events were calculated and tested with one-way ANOVA, Kruskal-Wallis, and chi-square tests. Initially, analysis was performed on all protocols, all ages, and all type of embryos. Further, analysis was done on subsets of cleavage stage embryo and blastocyst embryo, based on the three different IVF protocols. Further, we performed analysis of live birth in subgroups (Table 3) based on the type of insemination, stage of embryos, maternal age (<35, 35-37, 38-40 and >40 years), maternal BMI (<18.5, 18.5-24.9, 25-29.9, 30-34.9, 35-39.9, 40-44.9, >45), number of oocytes (1-5, 6-10, 11-15, 16-20, 21-25 and >25), individual treatment protocol (agonist, antagonist and agonist-flare) and the number of embryos transferred (SET, e-SET, DET and MET). We modelled adjustments on maternal smoking status, previous reproductive history, and duration of infertility. The strength of association between d-COS and reproductive outcomes is presented as odds ratio (OR) and rate ratio (RR) with 95% confidence interval (CI). A 2-sided p value <0.05 was considered as

statistically significant.

Results

Study population

Between January 2014 and December 2015, there was a total of 56,666 fresh, autologous, treatment cycles in which women had a fresh IVF-ET following controlled ovarian stimulation. Among these, (14,788/56,666, 26.1%) were on agonist protocol, (3,805/56,666, 6.7%) were on agonist with flare protocol, and (38,073/56,666, 67.2%) were on an antagonist protocol. The overall LBR was 44.1 % (25,043/56,666) and LBR in agonist, agonist with flare and antagonist protocols were (7,302/14,788, 49.4%), (1,216/3,805, 32.0%), and (16,525/38,073, 43.4%) respectively. Women, prior to treatment start had a mean [SD] age of 33.9 [4.47], BMI of 26.1 [6.02], AMH value of 2.19 [3.37]), and a baseline FSH value of 7.62 [3.49].

The baseline and treatment characteristics are presented in Table 1. The demographic variables for maternal age, maternal BMI, self-reported race, ovarian reserve testing and infertility diagnosis were similar among the different groups based on the durations of controlled ovarian stimulation. Controlled ovarian stimulation was achieved via a long luteal gonadotropin releasing hormone (GnRH) agonist (14,788/56,666, 26.1 %), GnRH agonist with flare (3805/56,666, 6.7 %) or with a GnRH antagonist protocol (38,073/56,666, 67.1 %). The treatment characteristics were also similar between different groups based on the durations of controlled ovarian stimulation except the need for a significantly higher FSH dose during treatment with increasing duration of treatment. Livebirth rates based on number of oocytes, type of treatment protocol, stage of embryos and maternal BMI are shown in Figures 2A-2D.

Table 1. Baseline Characteristics and Treatment Cycle Characteristics

			Duration of Controlled Ovarian Stimulation						
Predictor	Statistics/Level	Whole Sample (n=56,666)	≤8 (n=586)	9 (n=3,308)	10 (n=9,486)	11 (n=14,357)	12 (n=12,253)	13 (n=8,466)	≥14 (n=8,210)
Age, Mean (SD)		33.99 (4.47)	34.45 (4.92)	33.64 (4.55)	33.48 (4.46)	33.66 (4.38)	34.01 (4.39)	34.36 (4.41)	34.87 (4.54)
BMI, Mean (SD)		26.15 (6.02)	25.39 (5.54)	25.31 (5.22)	25.74 (5.69)	25.95 (5.80)	26.27 (6.02)	26.51 (6.45)	26.83 (6.54)
Smoking status, n (%)	No	48,724 (95.4%)	509 (95.9%)	2,840 (95.7%)	8,090 (95.1%)	12,521 (95.6%)	10,587 (95.5%)	7,229 (95.8%)	6,948 (95.4%)
	Yes	2,305 (4.5%)	22 (4.1%)	129 (4.3%)	420 (4.9%)	578 (4.4%)	501 (4.5%)	319 (4.2%)	336 (4.6%)
AMH, Mean (SD)		2.19 (3.37)	1.65 (2.64)	2.14 (2.90)	2.3 (3.12)	2.33 (3.12)	2.21 (3.53)	2.05 (3.18)	1.95 (4.15)
Infertility diagnosis, n (%)	Diminished Ovarian Reserve	5,688 (10.0%)	78 (13.3%)	278 (8.4%)	734 (7.7%)	1,123 (7.8%)	1,192 (9.7%)	1,027 (12.1%)	1,256 (15.3%)
	Endometriosis	2,320 (4.1%)	28 (4.8%)	133 (4.0%)	362 (3.8%)	633 (4.4%)	485 (4.0%)	361 (4.3%)	318 (3.9%)
	Male Factor	12,381 (21.8%)	129 (22.0%)	814 (24.6%)	2,269 (23.9%)	3,357 (23.4%)	2,765 (22.6%)	1,670 (19.7%)	1,377 (16.8%)
	Multiple	13,083 (23.1%)	134 (22.9%)	771 (23.3%)	2,087 (22.0%)	3,162 (22.0%)	2,785 (22.7%)	1,988 (23.5%)	2,156 (26.3%)
	Other	3,394 (6.0%)	33 (5.6%)	171 (5.2%)	560 (5.9%)	895 (6.2%)	739 (6.0%)	496 (5.9%)	500 (6.1%)
	Anovulation	4,994 (8.8%)	38 (6.5%)	251 (7.6%)	798 (8.4%)	1,288 (9.0%)	1,047 (8.5%)	775 (9.2%)	797 (9.7%)

	Tubal Factor	4,624 (8.2%)	43 (7.3%)	268 (8.1%)	801 (8.4%)	1,208 (8.4%)	1,003 (8.2%)	671 (7.9%)	630 (7.7%)
	Unexplained	10,182 (18.0%)	103 (17.6%)	622 (18.8%)	1,875 (19.8%)	2,691 (18.7%)	2,237 (18.3%)	1,478 (17.5%)	1,176 (14.3%)
Race, n (%)	Asian	4,482 (12.7%)	40 (11.0%)	231 (11.6%)	774 (13.4%)	1165 (13.1%)	946 (12.4%)	652 (12.1%)	674 (12.9%)
	Black	2,919 (8.3%)	33 (9.1%)	130 (6.5%)	380 (6.6%)	642 (7.2%)	627 (8.2%)	482 (9.0%)	625 (12.0%)
	Hispanic	2,968 (8.8%)	32 (9.2%)	183 (8.2%)	471 (8.2%)	742 (8.3%)	632 (8.3%)	444 (8.9%)	464 (8.9%)
	Other	720 (2.0%)	6 (1.7%)	23 (1.2%)	91 (1.6%)	169 (1.9%)	166 (2.2%)	130 (2.4%)	135 (2.6%)
	White	24,176 (68.6%)	252 (69.4%)	1,426 (71.6%)	4,044 (70.2%)	6,191 (69.5%)	5,282 (69.0%)	3,660 (68.2%)	3,321 (63.6%)
Parity, Mean (SD)		0.28 (0.69)	0.27 (0.59)	0.26 (0.65)	0.27 (0.68)	0.28 (0.68)	0.28 (0.67)	0.28 (0.7)	0.3 (0.72)
Prior Spontaneous Abortions, Mean (SD)		0.78 (0.99)	0.84 (0.93)	0.81 (1.10)	0.79 (0.99)	0.77 (0.99)	0.78 (0.97)	0.77 (0.99)	0.77 (0.99)
Maximum FSH Level, Mean (SD)		7.62 (3.49)	7.76 (3.29)	7.18 (3.36)	7.31 (2.88)	7.46 (3.58)	7.58 (3.01)	7.82 (3.36)	8.25 (4.53)
Total FSH Dosage, Median (IQR)		2,850 (2,025 - 4,050)	1,800 (1,275 - 2,475)	2,025 (1,500 - 2,625)	2,250 (1,688 – 3,000)	2,625 (1,950 – 3,375)	3,000 (2,250 – 4,050)	3,575 (2,625 - 4,850)	4,500 (3,125 - 5,850)
Ovarian stimulation protocol, n (%)	Agonist	14,788 (26.1%)	137 (23.4%)	702 (21.2%)	2,341 (24.7%)	3,954 (27.5%)	3,436 (28.0%)	2,328 (27.5%)	1,890 (23.0%)
	Agonist + Flare	3,805 (6.7%)	58 (9.9%)	203 (6.1%)	414 (4.4%)	645 (4.5%)	718 (5.9%)	681 (8.0%)	1,086 (13.2%)
	Antagonist	38,073 (67.2%)	391 (66.7%)	2,403 (72.6%)	6,731 (71.0%)	9,758 (68.0%)	8,099 (66.1%)	5,457 (64.5%)	5,234 (63.8%)
Type of Treatment, n (%)	ICSI	38,686 (68.3%)	409 (69.8%)	2,332 (70.5%)	6,567 (69.2%)	9,811 (68.3%)	8,271 (67.5%)	5,700 (67.3%)	5,596 (68.2%)
	IVF	14,600 (25.8%)	160 (27.3%)	820 (24.8%)	2,364 (24.9%)	3,629 (25.3%)	3,164 (25.8%)	2,248 (26.6%)	2,215 (27.0%)
	Mixed IVF and ICSI	3,380 (6.0%)	17 (2.9%)	156 (4.7%)	555 (5.9%)	917 (6.4%)	818 (6.7%)	518 (6.1%)	399 (4.9%)
Embryo stage, n (%)	Blastocyst	38,181 (67.4%)	305 (52.0%)	2,131 (64.4%)	6,652 (70.1%)	10,366 (72.2%)	8,416 (68.7%)	5,521 (65.2%)	4,790 (58.3%)

	Cleavage	18,485 (32.6%)	281 (48.0%)	1,177 (35.6%)	2,834 (29.9%)	3,991 (27.8%)	3,837 (31.3%)	2,945 (34.8%)	3,420 (41.7%)
Embryos Available, Mean (SD)		4 (2.86)	3.04 (2.14)	3.79 (2.62)	4.16 (2.93)	4.27 (2.99)	4.12 (2.94)	3.85 (2.74)	3.44 (2.56)
Number of Embryos transferred	SET	5,828 (10.3%)	116 (19.8%)	362 (10.9%)	859 (9.1%)	1,193 (8.3%)	1,211 (9.9%)	862 (10.2%)	1,225 (14.9%)
	eSET	14,180 (25.0%)	101 (17.2%)	812 (24.5%)	2,514 (26.5%)	3,815 (26.6%)	3,148 (25.7%)	2,044 (24.1%)	1,746 (21.3%)
	DET	31,139 (55.0%)	311 (53.1%)	1,826 (55.2%)	5,346 (56.4%)	8,089 (56.3%)	6,655 (54.3%)	4,644 (54.9%)	4,268 (52.0%)
	MET	5,519 (9.7%)	58 (9.9%)	308 (9.3%)	767 (8.1%)	1,260 (8.8%)	1,239 (10.1%)	916 (10.8%)	971 (11.8%)

Missing BMI for 9,340 cases (16.5%), smoking status for 5,637 cases (9.9%), race for 21,401 (37.8%), parity for 260 (0.5%), maximum FSH level for 16,623 (29.3%), and total FSH dosage for 1,017 (1.8%).

AMH = anti-Mullerian hormone, FSH = follicle stimulating hormone, ICSI = intracytoplasmic sperm injection; IVF = in-vitro fertilization; SET = single embryo transfer of only embryo available for transfer; eSET = elective single embryo transfer; DET = double embryo transfer; MET = multiple (≥3) embryo transfer

Figure 2. Live Birth Rates

Figure 2A. Trend of Live Birth Rates based on Duration of Controlled Ovarian Stimulation and Number of Oocytes

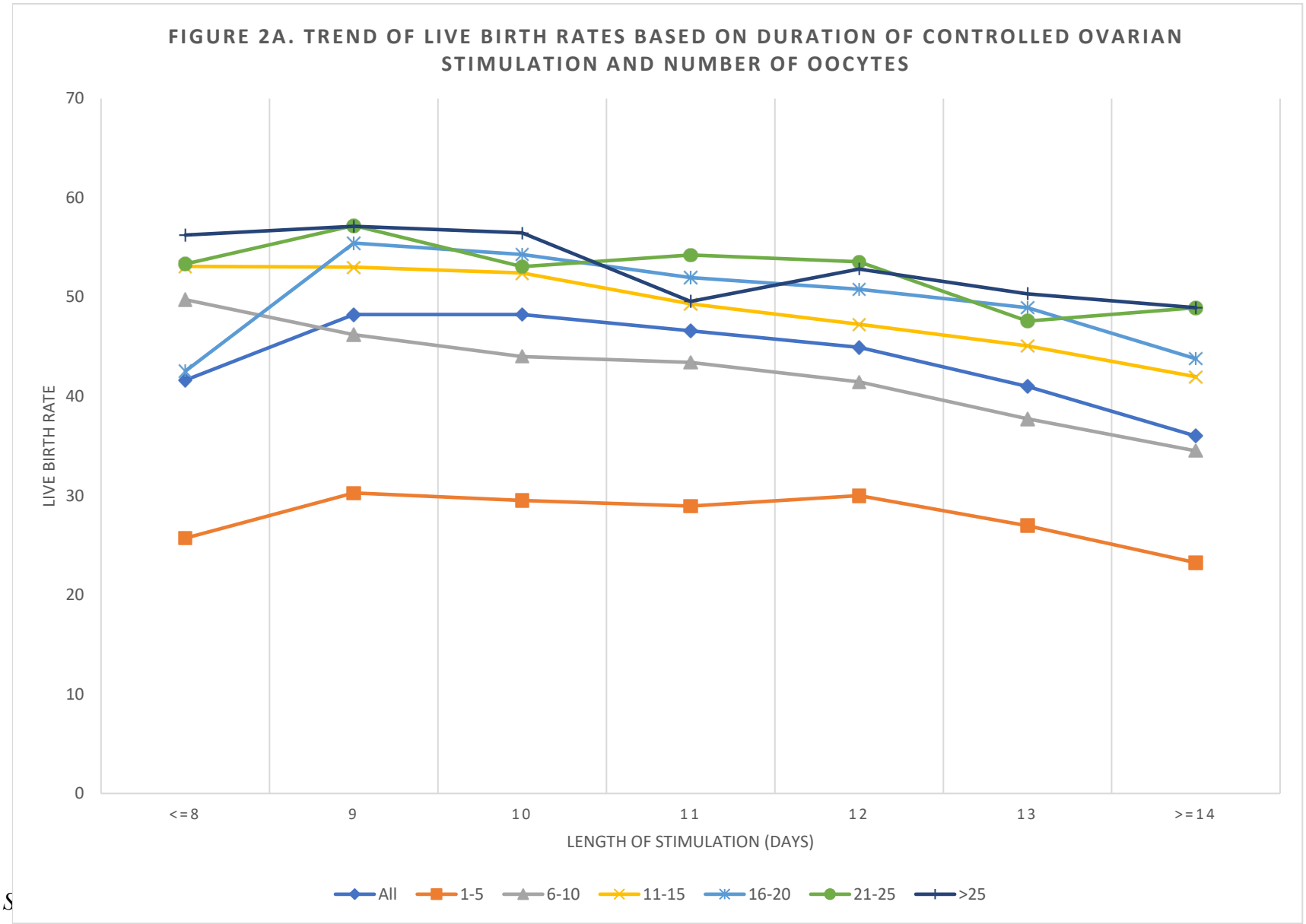

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Figure 2B. Trend of Live Birth Rates based on Duration of Controlled Ovarian Stimulation and Type of Treatment Protocol

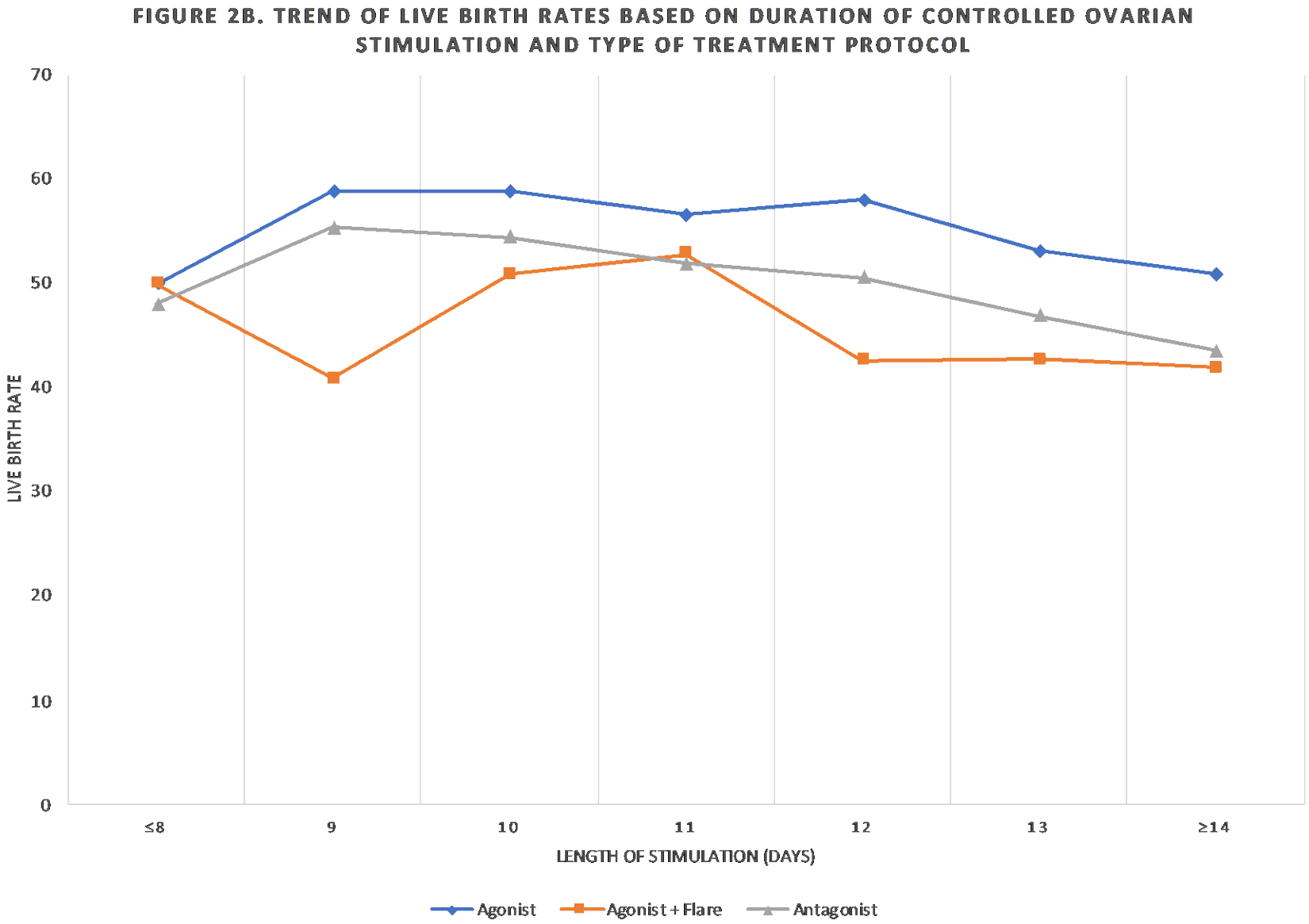


Figure 2C. Trend of Live Birth Rates based on Duration of Controlled Ovarian Stimulation and Embryos Stage

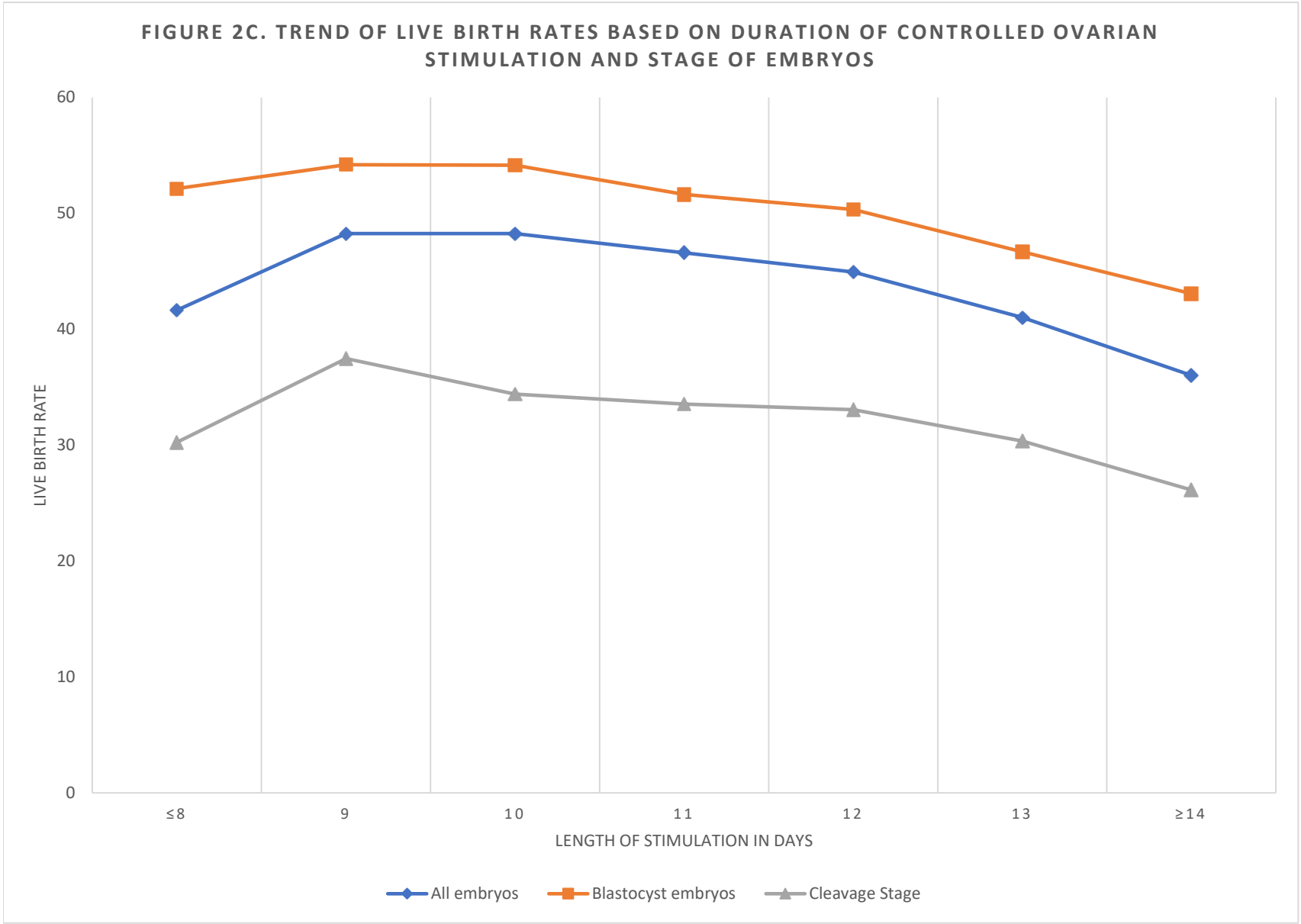
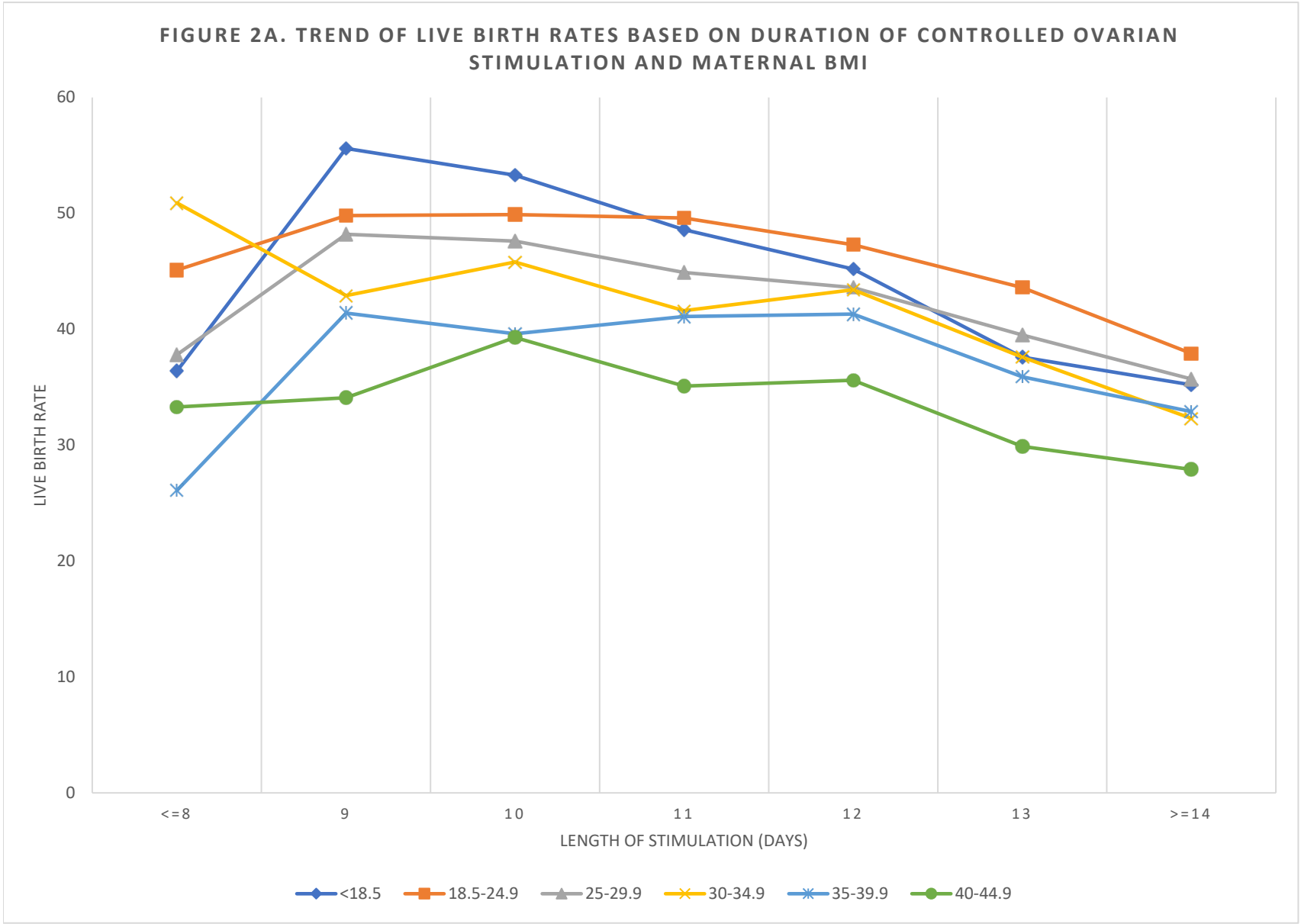


Figure 2D. Trend of Live Birth Rates based on Duration of Controlled Ovarian Stimulation and Maternal BMI



Association of Reproductive Outcomes with d-COS in the Full Analysis Set

The analysis of reproductive outcomes based on duration of ovarian stimulation in the whole sample are shown in Table 2. There was a statistically significant decrease in the *live birth rate* with d-COS beyond 10 days. The adjusted OR (95% CI) of LBR for a woman who had 11, 12, 13 and ≥14 days of COS, compared to optimal duration of 10 days was 0.97 (0.87-0.99), 0.94 (0.80-1.00), 0.83 (0.77-0.89) and 0.73 (0.68-0.79) respectively. The AOR (95% CI) of *miscarriage rates* for a woman who had 11, 12, 13 and ≥14 days of COS, compared to referent was 1.12 (1.00-1.26), 0.99 (0.87-1.12), 1.03 (0.90 -1.17) and 1.04 (0.90 - 1.20) respectively. With increasing d-COS, the *implantation rate* (IR) and *clinical pregnancy rate* (CPR) also showed a decreasing trend, as with other reproductive outcomes. The RR (95% CI) for implantation rate in a woman who had 11, 12, 13 and ≥14 days of COS, compared to referent was 0.97 (0.93-1.00), 0.97 (0.93-1.01), 0.91 (0.87-0.95) and 0.86 (0.82-0.90). The adjusted OR (95% CI) of CPR for a woman who had 11, 12, 13 and ≥14 days of COS, compared to referent was 0.95 (0.89-1.01), 0.93 (0.87-0.99), 0.8 (0.75-0.86) and 0.7 (0.65-0.75) respectively. The negative association for the reproductive outcomes with increasing d-COS for both crude and adjusted OR followed the same pattern when embryos were analysed separately at the cleavage and blastocyst stage. There seems to be a threshold around 12-13 days for d-COS, above which the trends become statistically significant associations.

The suboptimal reproductive outcomes, although not significant in all categories were also observed with decreasing d-COS. The RR (95% CI) for *implantation rate* in a woman who had ≤8 days, compared to referent was 0.74 (0.64-0.86). The crude OR (95% CI) of *clinical pregnancy rate* in a woman who had ≤8 days, compared to referent was 0.72 (0.61-0.85). The crude OR (95% CI) of *live birth rate* in a woman who had ≤8 days, compared to referent was 0.77 (0.65-0.91). When adjusted for multiple covariates, these associations were no longer statistically significant.

Table 2. Association of Reproductive Outcomes based on Duration of Treatment for Controlled Ovarian Stimulation in Fresh IVF-ET – Full Analysis

			Duration of Controlled Ovarian Stimulation						
Reproductive Outcome	Categories	Total Numbers	≤8 days	9 days	10 days	11 days	12 days	13 days	≥14 days
Biochemical Pregnancy Rate	Cleavage stage embryo/s	1,473/18,485	1.1 (0.7 - 1.72)	0.95 (0.73 - 1.23)	Ref	1.07 (0.89 - 1.28)	1.06 (0.89 - 1.27)	1.09 (0.90 - 1.32)	1.14 (0.94 - 1.37)
	Blastocyst stage embryo/s	3,391/38,181	0.87 (0.56 - 1.36)	1.03 (0.86 - 1.23)	Ref	1.09 (0.98 - 1.22)	1.06 (0.94 - 1.19)	1.19 (1.05 - 1.35)	1.22 (1.08 - 1.39)
	All stages - Crude	4,864/56,666	0.96 (0.70 - 1.31)	1 (0.86 - 1.15)	Ref	1.09 (0.99 - 1.20)	1.06 (0.96 - 1.17)	1.15 (1.04 - 1.28)	1.18 (1.06 - 1.31)
	All stages - Adjusted	4,864/56,666	0.93 (0.63 - 1.38)	1.04 (0.87 - 1.24)	Ref	1.06 (0.94 - 1.19)	1.08 (0.96, 1.21)	1.13 (1.00 - 1.29)	1.18 (1.04 - 1.35)
Clinical Pregnancy Rate	Cleavage stage embryo/s	7,319/18,485	0.81 (0.63 - 1.04)	1.04 (0.91 - 1.2)	Ref	0.96 (0.87 - 1.06)	0.91 (0.83, 1.01)	0.83 (0.74 - 0.92)	0.65 (0.59 - 0.72)
	Blastocyst stage embryo/s	22,348/38,181	0.83 (0.66 - 1.05)	1 (0.90 - 1.10)	Ref	0.92 (0.86 - 0.98)	0.86 (0.80 - 0.92)	0.72 (0.67 - 0.78)	0.63 (0.58 - 0.67)
	All stages - Crude	29,667/56,666	0.72 (0.61 - 0.85)	0.97 (0.89 - 1.05)	Ref	0.95 (0.90 – 1.00)	0.87 (0.82 - 0.92)	0.73 (0.69 - 0.78)	0.59 (0.55 - 0.62)
	All stages - Adjusted	29,667/56,666	0.91 (0.74 - 1.11)	1.03 (0.93 - 1.13)	Ref	0.95 (0.89 - 1.01)	0.93 (0.87 - 0.99)	0.8 (0.75 - 0.86)	0.7 (0.65 - 0.75)

Implantation Rate[1]	Cleavage stage embryo/s	2,186/18,485	0.73 (0.50 - 1.06)	1.09 (0.92 - 1.29)	Ref	0.96 (0.85 - 1.09)	0.95 (0.83 - 1.07)	0.83 (0.72 - 0.96)	0.7 (0.61 - 0.81)
	Blastocyst stage embryo/s	13,953/38,181	0.92 (0.79 - 1.06)	0.99 (0.93 - 1.05)	Ref	0.93 (0.89 - 0.97)	0.91 (0.88 - 0.95)	0.83 (0.79 - 0.87)	0.81 (0.77 - 0.85)
	All stages - Crude	16,139/56,666	0.74 (0.64 - 0.86)	0.96 (0.90 - 1.01)	Ref	0.95 (0.91 - 0.99)	0.91 (0.87 - 0.94)	0.8 (0.76 - 0.84)	0.71 (0.68 - 0.75)
	All stages - Adjusted	16,139/56,666	0.91 (0.78 - 1.05)	0.98 (0.93 - 1.04)	Ref	0.97 (0.93 – 1.00)	0.97 (0.93 - 1.01)	0.91 (0.87 - 0.95)	0.86 (0.82 - 0.90)
Miscarriage Rate	Cleavage stage embryo/s	1,385/18,485	1.06 (0.64 - 1.74)	0.72 (0.54 - 0.95)	Ref	1.02 (0.85 - 1.24)	0.96 (0.80 - 1.17)	1.09 (0.89 - 1.34)	1.06 (0.86 - 1.30)
	Blastocyst stage embryo/s	3,044/38,181	0.79 (0.48 - 1.29)	0.99 (0.82 - 1.19)	Ref	1.14 (1.02 - 1.28)	1.11 (0.98 - 1.26)	1.12 (0.98 - 1.29)	1.19 (1.03 - 1.37)
	All stages - Crude	4,429/56,666	0.98 (0.69 - 1.39)	0.91 (0.78 - 1.07)	Ref	1.10 (1.00 - 1.21)	1.07 (0.97 - 1.19)	1.14 (1.01 - 1.27)	1.19 (1.06 - 1.34)
	All stages - Adjusted	4,429/56,666	0.93 (0.62 - 1.40)	0.88 (0.73 - 1.06)	Ref	1.12 (1.00 - 1.26)	0.99 (0.87 - 1.12)	1.03 (0.90 - 1.17)	1.04 (0.90 - 1.20)
Multiple Pregnancy Rate	Cleavage stage embryo/s	1,672/18,485	0.59 (0.34 - 1.01)	1.23 (0.97 - 1.56)	Ref	1.06 (0.89 - 1.26)	0.98 (0.82 - 1.17)	0.87 (0.72 - 1.07)	0.79 (0.64 - 0.96)
	Blastocyst stage embryo/s	5,612/38,181	1.01 (0.72 - 1.42)	0.99 (0.86 - 1.14)	Ref	0.93 (0.85 - 1.01)	0.91 (0.83 – 1.00)	0.86 (0.77 - 0.96)	0.75 (0.66 - 0.84)
	All stages - Crude	7,284/56,666	0.83 (0.63 - 1.11)	1.04 (0.92 - 1.18)	Ref	0.95 (0.88 - 1.03)	0.92 (0.85 – 1.00)	0.86 (0.78 - 0.94)	0.75 (0.67 - 0.83)
	All stages - Adjusted	7,284/56,666	0.86 (0.61 - 1.21)	0.99 (0.85 - 1.15)	Ref	0.95 (0.86 - 1.05)	0.98 (0.88 - 1.09)	0.92 (0.82 - 1.04)	0.89 (0.78 - 1.01)
Live Birth Rate	Cleavage stage embryo/s	5,897/18,485	0.83 (0.63 - 1.08)	1.14 (0.99 - 1.32)	Ref	0.96 (0.87 - 1.07)	0.94 (0.85 - 1.04)	0.83 (0.74 - 0.93)	0.67 (0.61 - 0.75)

	Blastocyst stage embryo/s	19,146/38,181	0.92 (0.73 - 1.16)	1.00 (0.91 - 1.11)	Ref	0.9 (0.85 - 0.96)	0.86 (0.80 - 0.92)	0.74 (0.69 - 0.80)	0.64 (0.59 - 0.69)
	All stages - Crude	25,043/56,666	0.77 (0.65 - 0.91)	1.00 (0.92 - 1.08)	Ref	0.94 (0.89 - 0.99)	0.88 (0.83 - 0.92)	0.75 (0.70 - 0.79)	0.60 (0.57 - 0.64)
	All stages - Adjusted	25,043/56,666	0.96 (0.78 - 1.18)	1.06 (0.97 - 1.17)	Ref	0.93 (0.87 - 0.99)	0.94 (0.88 – 1.00)	0.83 (0.77 - 0.89)	0.73 (0.68 - 0.79)

Statistics presented as odds ratios (95% Confidence Interval) adjusted for maternal age, maternal BMI, smoking status, stage of embryos, type of insemination, number of embryos transferred, and number of oocytes where applicable. Statistically significant at p<.05 level indicated in bold font.
[1]Statistics presented as rate ratios (95% Confidence Interval) adjusted for maternal age, maternal BMI, smoking status, stage of embryos, type of insemination, number of embryos transferred, and number of oocytes where applicable.

Table 3. Subgroup Analysis - Analysis of live births (the primary outcome)

			Duration of Controlled Ovarian Stimulation						
Variables	Categories	Total Numbers	≤8 days	9 days	10 days	11 days	12 days	13 days	≥14 days
Treatment Type	IVF	6,447/ 14,600	0.83 (0.60 - 1.15)	0.99 (0.84 - 1.16)	Ref	0.97 (0.88 - 1.08)	0.92 (0.83 - 1.03)	0.8 (0.71 - 0.89)	0.60 (0.53 - 0.67)
	ICSI	16,967/ 38,686	0.78 (0.64, 0.95)	0.99 (0.9, 1.09)	Ref	0.91 (0.86 - 0.97)	0.85 (0.80 - 0.91)	0.73 (0.68 - 0.78)	0.60 (0.56 - 0.65)
	Mixed IVF and ICSI	1,629/ 3,380	0.21 (0.06 - 0.74)	1.27 (0.89 - 1.82)	Ref	1 (0.81 - 1.24)	0.93 (0.75 - 1.15)	0.76 (0.60 - 0.97)	0.67 (0.51 - 0.87)
Embryo Stage	Cleavage	5,897/ 18,485	0.83 (0.64 - 1.08)	1.14 (0.99 - 1.32)	Ref	0.96 (0.87 - 1.07)	0.94 (0.85 - 1.05)	0.83 (0.75 - 0.93)	0.68 (0.61 - 0.75)
	Blastocyst	19,146/ 38,181	0.92 (0.73 - 1.16)	1 (0.91 - 1.10)	Ref	0.9 (0.85 - 0.96)	0.86 (0.80 - 0.91)	0.74 (0.69 - 0.80)	0.64 (0.59 - 0.69)
Maternal Age	<35	16,385/ 31,490	0.76 (0.60 - 0.95)	1 (0.90 - 1.11)	Ref	0.91 (0.85 - 0.97)	0.89 (0.83 - 0.95)	0.75 (0.70 - 0.81)	0.66 (0.61 - 0.71)

	35-37	5,262/ 11,984	1.33 (0.90 - 1.97)	1.06 (0.89 - 1.27)	Ref	1.02 (0.90 - 1.14)	0.96 (0.85 - 1.08)	0.95 (0.84 - 1.08)	0.73 (0.64 - 0.83)
	38-40	2,732/ 8,474	0.86 (0.53 - 1.38)	1.02 (0.82 - 1.28)	Ref	0.97 (0.84 - 1.13)	0.89 (0.77 - 1.04)	0.75 (0.64 - 0.88)	0.65 (0.55 - 0.77)
	>40	664/ 4,718	0.69 (0.33 - 1.42)	1.2 (0.82 - 1.77)	Ref	1.01 (0.77 - 1.34)	1.02 (0.77 - 1.35)	0.77 (0.56 - 1.05)	0.78 (0.58 - 1.04)
Maternal BMI	<18.5	513/ 1,119	0.45 (0.13 - 1.62)	1.1 (0.63 - 1.91)	Ref	0.84 (0.58 - 1.21)	0.74 (0.49 - 1.09)	0.51 (0.33 - 0.79)	0.47 (0.30 - 0.73)
	18.5-24.9	11,279/ 23,979	0.81 (0.63 - 1.05)	1 (0.89 - 1.12)	Ref	0.99 (0.91 - 1.07)	0.9 (0.83 - 0.98)	0.78 (0.71 - 0.85)	0.61 (0.56 - 0.67)
	25-29.9	5,175/ 11,896	0.67 (0.45 - 0.97)	1.03 (0.87 - 1.22)	Ref	0.9 (0.80 – 1.00)	0.85 (0.75 - 0.95)	0.72 (0.63 - 0.82)	0.61 (0.53 - 0.70)
	30-34.9	2,408/ 5,892	1.23 (0.71 - 2.15)	0.9 (0.69 - 1.16)	Ref	0.84 (0.71 – 1.00)	0.91 (0.77 - 1.08)	0.72 (0.60 - 0.87)	0.56 (0.47 - 0.68)
	35-39.9	1,144/ 2,960	0.57 (0.22 - 1.48)	1.07 (0.70 - 1.63)	Ref	1.07 (0.83 - 1.37)	1.07 (0.83 - 1.37)	0.86 (0.66 - 1.12)	0.74 (0.57 - 0.97)
	40-44.9	362/ 1,048	0.75 (0.13 - 4.22)	0.92 (0.43 - 1.97)	Ref	0.74 (0.48 - 1.14)	0.95 (0.62 - 1.45)	0.57 (0.35 - 0.91)	0.6 (0.38 - 0.95)
Number of Oocytes	1-5	2,237/ 8,110	0.83 (0.59 - 1.16)	1.04 (0.83 - 1.31)	Ref	0.97 (0.82 - 1.16)	1.03 (0.87 - 1.22)	0.88 (0.74 - 1.06)	0.73 (0.61 - 0.86)
	6-10	6,709/ 16,391	1.26 (0.94 - 1.69)	1.09 (0.95 - 1.27)	Ref	0.98 (0.88 - 1.08)	0.9 (0.81 – 1.00)	0.77 (0.69 - 0.86)	0.67 (0.60 - 0.75)
	11-15	7,056/ 14,662	1.02 (0.70 - 1.49)	1.02 (0.88 - 1.19)	Ref	0.88 (0.80 - 0.97)	0.81 (0.73 - 0.90)	0.74 (0.66 - 0.84)	0.66 (0.58 - 0.74)
	16-20	4,671/ 9,158	0.62 (0.35 - 1.12)	1.05 (0.85 - 1.29)	Ref	0.91 (0.80 - 1.03)	0.87 (0.76 - 0.99)	0.81 (0.70 - 0.93)	0.66 (0.56 - 0.77)
	21-25	2,411/ 4,586	1.04 (0.37 - 2.90)	1.19 (0.89 - 1.60)	Ref	1.05 (0.88 - 1.25)	1.02 (0.85 - 1.22)	0.81 (0.65 - 0.99)	0.85 (0.67 - 1.06)
	>25	1,959/ 3,759	0.96 (0.35 - 2.61)	1.03 (0.74 - 1.42)	Ref	0.76 (0.63 - 0.91)	0.86 (0.70 - 1.05)	0.78 (0.62 - 0.99)	0.74 (0.57 - 0.96)
Treatment Protocol	Agonist	7,302/ 14,788	0.66 (0.47 - 0.93)	1 (0.84 - 1.18)	Ref	0.94 (0.85 - 1.04)	0.91 (0.82 - 1.01)	0.73 (0.65 - 0.82)	0.59 (0.52 - 0.67)
	Agonist + Flare	1,216/ 3,805	1.12 (0.63 – 2.00)	1.03 (0.72 - 1.47)	Ref	1.21 (0.93 - 1.58)	1.09 (0.84 - 1.41)	0.98 (0.75 - 1.27)	0.84 (0.66 - 1.07)

	Antagonist	16,525/ 38,073	0.81 (0.66 - 0.99)	1.03 (0.94 - 1.13)	Ref	0.91 (0.86 - 0.97)	0.85 (0.80 - 0.91)	0.75 (0.70 - 0.80)	0.63 (0.58 - 0.67)
Number of Embryos Transferred	SET	1,389/ 5,828	0.51 (0.30 - 0.85)	0.85 (0.64 - 1.12)	Ref	0.95 (0.78 - 1.16)	0.92 (0.76 - 1.12)	0.62 (0.50 - 0.78)	0.62 (0.51 - 0.77)
	eSET	7,179/ 14,180	0.86 (0.58 - 1.29)	1 (0.85 - 1.17)	Ref	0.92 (0.83 - 1.02)	0.89 (0.80 - 0.98)	0.86 (0.77 - 0.97)	0.81 (0.72 - 0.92)
	DET	1,505/ 5,519	1.11 (0.61 - 1.99)	1.37 (1.03 - 1.82)	Ref	0.98 (0.80 - 1.2)	1.13 (0.92 - 1.38)	0.99 (0.80 - 1.23)	0.82 (0.66 - 1.02)
	MET	1,4970/ 31,139	0.94 (0.75 - 1.19)	1.04 (0.94 - 1.16)	Ref	0.93 (0.87 - 0.99)	0.87 (0.81 - 0.93)	0.72 (0.67 - 0.78)	0.58 (0.53 - 0.63)

Subgroup analysis

Table 3 displays the association of LBR with d-COS based on type of treatment, stage of embryos, maternal age, maternal BMI, number of oocytes, treatment protocol and number of embryos transferred.

Type of treatments included standard IVF insemination, ICSI and mixed insemination. There was a decline in live birth rate with d-COS beyond 10 days and statistically significant for all these three groups in women who had 12, 13 or ≥14 days for d-COS. The OR (95% CI) of live birth rate for a woman with IVF, ICSI and mixed IVF and ICSI, who had ≥14 days of COS was 0.66 (0.53-0.77), 0.60 (0.56-0.65), and 0.67 (0.61-0.75) respectively. With less than 10 days d-COS, there was a negative association of LBR, the relation being statistically significant in ICSI in women who had and mixed IVF and ICSI group, in women who had ≤8 days of COS.

Based on the *stage of development*, embryos were classified into cleavage and blastocyst embryos. There was a statistically significant decrease in the live birth rate with d-COS beyond 10 days, in both groups. The OR (95% CI) of live birth rate in cleavage and blastocyst embryos, for a woman who had ≥14 days of COS (compared to referent) was 0.68 (0.61-0.75) and 0.64 (0.59-0.69) respectively. With less than 10 days d-COS, there was a negative association of LBR in women who had ≤8 days of COS, although not statistically significant.

Maternal age was categorized to <35, 35-37, 38-40 and >40 years. There was a general decline in the live birth rate with d-COS beyond 10 days based on advancing maternal age, and statistically significant in women who were <35 years and 38-40 years. For example, the OR (95% CI) of live birth rate for a woman <35, 35-37, 38-40, and >40 years, who had ≥14 days of COS was 0.66 (0.61, 0.71), p<0.01, 0.73 (0.64), p<0.01, 0.65 (0.55-0.77), p<0.01 and 0.78 (0.58-1.04) p=0.09, respectively. With less than 10 days d-COS, the negative association of LBR was significant only in women <35 who had ≤8 days of COS. The OR (95% CI for a woman <35 was 0.76(0.60-0.95), p=0.02.

The *pre-treatment maternal BMI* was categorized into <18.5, 18.5-24.9, 25-29.9, 30-34.9, 35-39.9, 40-44.9, and >45. There was a general decline in the live birth rate with d-COS beyond 10 days in all BMI groups, the relation being statistically significant in women who had 12, 13 or ≥14 days for d-COS. For example, the OR (95% CI) of live birth rate for a woman with BMI <18.5, 18.5-24.9, 25-29.9, 30-34.9, 35-39.9, and 40-44.9 was 0.47 (0.30 – 0.73), 0.61 (0.56 – 0.67), 0.61 (0.53– 0.70), 0.56 (0.47 - 0.68), 0.74 (0.57 – 0.97) and 0.60 (0.38 – 0.95).

With less than 10 days d-COS, the negative association of LBR was significant only in overweight women who had ≤8 days of COS. The OR (95% CI) for a woman with BMI 25-29.9 was 0.67 (0.45 - 0.97).

The *number of oocytes* was categorized in groups of 1-5, 6-10, 11-15, 16-20, 21-25 and >25. There was a statistically significant decrease in the live birth rate

with d-COS beyond 10 days, all groups except in those women who had between 21 and 25 oocytes. The OR (95% CI) of live birth rate for a woman with 11-15 oocytes and 21-25 oocytes, who had ≥14 days of COS was 0.66 (0.56-0.77), p<0.01 and 0.85 (0.67-1.06), p=0.15. With less than 10 days d-COS, the association of LBR remained variable and non-significant in all the groups.

Most women in the study (55% [31,139/56,666]) had a double embryo transfer (DET). An elective single embryo transfer (e-SET) was performed in 25% (14,180/56,666) and 9.7% (5,519/56,666) had more than two embryos transferred (MET). There was a decrease in the live birth rate with d-COS beyond 10 days, in all groups, the association being statistically significant in the e-SET and MET groups. The OR (95% CI) of live birth rate for a woman with e-SET and MET, who had ≥14 days of COS (compared to referent) was 0.81 (0.72-0.92) and 0.58 (0.53- 0.63) respectively. With less than 10 days d-COS, the association of LBR remained variable and non-significant in all the groups, except for women who had ≤8 days of COS, in the SET group.

Discussion

We report findings from a large cohort study investigating the association between the d-COS and live birth rates in women undergoing IVF treatment. We observed a decrease in live birth with extremes of duration of controlled ovarian stimulation. There was a statistically significant, 12.2% decline in the live birth rate in a woman with d-COS of ≥14 days, compared to what seems to be the optimum d-COS of 10 days in this study. The suboptimal reproductive outcomes, although not statistically significant, were also observed with shorter d-COS. There was a 6.6% reduction in live birth rates in a woman with d-COS of ≤8 days compared to the optimal duration for d-COS.

In our study, we observed an increasing gonadotrophin dose requirement for ovarian stimulation in women with an increase in d-COS. Previous studies and clinical practice have established this relationship to be more pronounced in women of advanced maternal age, elevated BMI, or those women with reduced ovarian reserve. However, we did not observe this relationship in our study. The decrease in LBR with deviation from the optimal day (10 days) in the study held true when analysis was performed based on the total number of cycles and based on individual COS treatment protocols. The large sample size in our study allowed to associate the primary outcome in seven subgroups. The subgroup analysis based on categories of maternal age and BMI, number of oocytes, insemination type, stage and the number of embryos transferred demonstrated a reduction in LBR with deviation of d-COS from the optimal standard. The reduction in LBR with these other wise, ‘good prognostic factors’ is a new and important finding. Another important finding from our study is the statistically significant reduction in LBR both in women who had only a single embryo available for transfer (vs. those with multiple available) and in women who had a cleavage stage embryo transfer (vs. those with blastocyst transfer). This was not at all a surprising finding as these two groups are considered as ‘poor prognostic

indicators' in clinical practice. However, it was indeed surprising to note that the same relation of declining LBR was observed when the analysis was performed on blastocyst embryos, ruling out a decline in LBR due to an embryo factor.

A previous large cohort study analysed increasing FSH dose requirements associated with increased d-COS as a possible explanation for decreasing live birth rate.[15] In our study, the decline in LBR was observed independent of gonadotrophin dosing, i.e., the trend of LBR decreasing even in women who had lesser days of stimulation (and therefore lesser total FSH dose), ruling out the possibility of higher gonadotrophin dosing as the reason for the suboptimal outcomes.

The suboptimal reproductive outcomes based on deviation from the typical d-COS may be explained by early follicle recruiters or late follicle recruiters resulting in suboptimal oocyte or embryo quality. Another possible mechanism may be endometrial 'under maturation' or 'over maturation' resulting in changes at an endometrial level.[16] Also, the imbalance in exposure to sex steroids results in premature decidualization and altered endometrial receptivity and eventually an 'endometrial – embryo asynchrony'.[17,18] Elective freezing of embryos following a fresh IVF cycle and assessing IVF success using cumulative pregnancy rates is increasingly recommended and considered as the new standard.[19,20] As not all embryos are suitable for freezing, only a minority of women achieve surplus embryos following a fresh IVF cycle. Therefore, rather than recommending a universal 'freeze all approach' for all, it is crucial not to disregard the concept of optimizing reproductive outcomes following a fresh IVF-ET.

The association of duration of treatment during controlled ovarian stimulation and livebirth rates has been investigated previously in small, single center studies. Our results contrast with those of several relevant studies. A retrospective analysis of 555 fresh IVF-ET cycles in 460 women from an academic institution in the USA reported that d-COS had minimal influence on pregnancy outcomes.[13] The validity of findings may have some limitations for clinical translation as the study analysed only a single type of treatment protocol, grouped d-COS as a categorical variables and limited analysis to those with up to a maximum of 16 days of treatment. Another retrospective study performed in Europe using 10,478 fresh IVF-ET cycles analysed d-COS as a continuous variable in three different IVF protocols and concluded that the duration of ovarian stimulation did not alter the clinical pregnancy rates.[21] The conclusions of this study may also be biased as the authors only included treatment protocols for women aged ≤40 years, and limited analysis to those who underwent between 7 and 16 days of ovarian stimulation.

Our results concur partly with a few studies that analysed reproductive outcomes in increasing d-COS. A retrospective analysis of 663 fresh IVF-ET cycles in women from an academic institution in the USA reported that prolonged d-COS was associated with decreased ART success for all except in women with a diagnosis of polycystic ovarian syndrome.[22] This study concluded that women with 13 or more days of COS had a 34% lower chance of clinical pregnancy as compared to

those who had a shorter cycle (OR 0.66, 95% CI:0.46 – 0.95). Another retrospective study analysing 794 fresh IVF-ET cycles in 545 women from another academic institution in the USA reported that prolonged d-COS was an independent negative predictor of ART success. This study analysed d-COS as a continuous and categorical variable and multivariable analysis suggested that 13 days or longer of stimulation decreased the likelihood of a live birth by 53% as compared to cycles that were 10–12 days long (odds ratio [OR]; 95% [CI]: 0.47; 0.30–0.75).[23] The conclusions for both these studies had limitations as the primary outcome was clinical pregnancy rate, analysis performed on the overall sample and that only the association of increased d-COS was analysed.

The amplitude of difference in the IVF outcome based on d-COS reported in our study, particularly in the decreasing d-COS may be relatively small, which makes it harder to detect in studies with small sample size. However, the trends are visible, and they are statistically significant especially when d-COS extends 3 or more days longer than what seems to be the optimum duration of 10 days. This study has several strengths. First, the use of the SART database provided increased generalizability, as over 95% of IVF cycles in the United States are included in the SART database.[24] Second, the use of this database provided a significant treatment number for analysis, for e.g., even within the least common treatment protocol (an agonist flare protocol), a total of 3,805 cycles were included in our analysis. Third, the multiple subgroup analysis yielded results like those from the primary analysis, supporting the robustness of the study findings.

Several limitations of the dataset must also be considered. Limitations of the SART CORS database include missing data for select variables; race being one of the most notable; and an 8.4% error rate in cycle start date. To protect patient confidentiality, clinic-level data was not included in our dataset. It is possible that clinic-level factors may impact protocol selection and outcomes such as live birth rate. For our study, it was essential to analyse treatment cycles resulting in a fresh embryo transfer, and therefore, we relied on slightly older data from SART CORS (*more recently, fewer fresh embryo transfers have been performed based on evidence suggesting an improvement in LBR after a frozen ET*). Moreover, there have been no significant changes in ovarian stimulation protocols in the last decade, making this cohort an ideal sample for our analysis

In conclusion, we found that among women undergoing fresh IVF-ET using autologous oocytes, a d-COS beyond ten days was associated with a significant reduction in LBR and a non-significant reduction in live birth rate with a duration of controlled ovarian stimulation less than ten days. The findings from this study are useful for reproductive endocrinologists to counsel women undergoing fresh IVF-ET cycles. While other approaches to understanding the potential mechanisms should be pursued, interventions for example, a '*selective freeze all strategy*' in those women having significant deviation from typical d-COS should be investigated further.

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