Association between differences in body-weight based dose versus actual propofol dosages administered for oocyte retrieval on hemodynamic parameters and reproductive outcomes

Madeline Kroeger, MD,[1] Aditi Katwala, BS,[2] Haley Steffen, MD,[3] Karen Summers, MPH CHEAS,[4] Alexis Ireland, PharmD RPh,[4] Ann Smith, MSN CRNA,[5] Michael Pomeroy, DNP CRNA,[5] Rakesh Sondekoppam, MD,[6] Anita Chazhikattu, MD,[7] Amy ET Sparks, PhD,[4] Jessica Kresowik, MD,[4] Abey Eapen, MBBS PhD[4]

Keywords: Ideal dose, actual dose, propofol, monitored anesthesia care, pregnancy outcomes

Abstract

Objective: *To evaluate the dose-dependent effect of propofol in hemodynamic parameters and reproductive outcomes following In-Vitro Fertilization (IVF) oocyte retrieval (OR)*

Design: *Retrospective cohort study*

Subjects: *1575 women who underwent their first OR under monitored anesthesia care (MAC) and subsequent fresh embryo transfer (ET) between January 2016 through December 2022*

Exposure: *Women in the study were categorized into five cohorts (cohorts A – E) based on increasing dose of total propofol in µg/kg/min.*

Main Outcome Measures: *Primary outcomes were mean differences in ideal dose of propofol based on body weight vs. actual dose administered and the live birth rate (LBR) following a fresh ET. Secondary outcomes included changes in hemodynamic parameters following anesthesia. ANOVA with Tukey post-hoc tests were used to compare means (SD) between the study groups. Paired T-tests assessed the difference between ideal and actual propofol dosing within each group*

Results: *1564 women [mean (SD) age (years), 32.77 (4.25) and mean (SD) weight (Kg), 79.49 (20.70)] were included in the final analysis. The live birth rate (LBR) was 815/1564 (52.1%). There was a statistically significant difference in the ideal total dose of propofol and the actual dose administered, mean [(95% CI, P value)] 196.83 [(190.85 – 202.82), <0.001)]. Although not*

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Corresponding author: *Abey Eapen, REI Division, Department of Obstetrics and Gynecology, University of Iowa Health Care, 200 Hawkins Drive, Iowa City, IA 52242. 1-319-356-4645. abey-eapen@uiowa.edu https://orcid.org/0000-0003-1951-758X*

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statistically significant, the LBR improved with increasing dose of propofol; 50.2% (cohort A) to 55.4% (cohort E). The adjusted Risk Ratio (aRR), (95% CI) of LBR with an additional mg of propofol/kg/min was 1.25 (0.75 – 2.09). Similar, non-significant improvements were observed in clinical pregnancy rate; 60.1% (cohort A) to 65.7% (cohort E); aRR (95% CI) = 1.25 (0.80 – 1.96). Compared to the start of procedure, there was a statistically significant reduction in mean +/- SD in heart rate (bpm), -8.08 ± 13.01 and mean +/- SD (mm/Hg) systolic BP [-17.44 ± 16.28], diastolic BP [-12.76 ± 13.62] and mean arterial pressure [-14.04 ± 13.16] at the end of the procedure.

Conclusion: *Despite the statistically significant higher dose of propofol administered during IVF oocyte retrieval and the associated significant changes in hemodynamic parameters; there was a trend of increasing LBR and clinical pregnancy rate with higher doses of propofol.*

[1]Department of Obstetrics and Gynecology, Carle Foundation Hospital, Urbana, Illinois, USA.
[2]Carver College of Medicine, University of Iowa, Iowa City, Iowa. USA. 52242
[3]Department of Obstetrics and Gynecology, University of Iowa Health Care, Iowa City. Iowa. USA. 52242
[4]Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, University of Iowa Health Care, Iowa City. Iowa. USA. 52242
[5]Department of Anesthesia, University of Iowa Health Care, Iowa City. Iowa. USA. 52242
[6]Department of Anesthesia, Perioperative and Pain Medicine, Stanford University, Palo Alto, California. USA. 94304
[7]Department of Anesthesia, Division of Critical Care, University of Iowa Health Care, Iowa City. Iowa. USA. 52242

Introduction

Oocyte retrieval is a rate limiting step in In-Vitro Fertilization (IVF) treatment.[1] Worldwide, the majority of IVF clinics perform the oocyte retrieval (OR) procedure under monitored anesthesia care (MAC) as it is considered to be an invasive and painful procedure.[2] Multiple IVF studies have investigated various anesthetic techniques and medications for management of pain and anxiety during OR procedure.[2-5] While there is no optimal technique or medication, intravenous propofol is the most commonly used medication for MAC in IVF based on the efficacy and favorable pharmacokinetic profile.[6]

Propofol is an intravenous lipophilic emulsion and has sedative properties. It is used for induction and maintenance of anesthesia.[7] The hemodynamic and biochemical changes following induction of anesthesia are well known and include significant decreases in blood pressure, leading to reduced perfusion of the ovarian follicles and endometrium, decreases in hemoglobin concentration and plasma cortisol level, and increases in blood glucose levels.[8,9] Animal studies have shown that propofol can negatively affect cleavage of mouse oocytes and early embryonic development and also confirmed a reduction in rate of sperm fusion with metaphase II mouse oocytes.[10] Studies in humans suggests conflicting evidence in the effects of propofol on both anesthesia and IVF related outcomes. A prospective study in 30 women undergoing transvaginal OR concluded that a propofol-based anesthesia resulted in significant concentrations of this medication in follicular fluid in a dose and time dependent manner.[11] A total of 245 women undergoing IVF cycles were included in this retrospective cohort study. A retrospective cohort study compared IVF outcomes of 129 women who underwent oocyte retrieval under propofol anesthesia and 116 without anesthesia. Fertilization rate was lower in retrievals under anesthesia compared to without (53.4%± 34.8 vs. 63.7%± 33.6, respectively; $p = 0.02$) and the study concluded that general anesthesia administered during oocyte retrieval may have adverse effects on the fertilization potential of oocytes.[12] Furthermore, a prospective observational cohort study of 349 oocytes suggested that oocytes of embryos that implanted had higher oxygen consumption compared to embryos that did not implant.[13] This demonstrates that the hemodynamic effects of conscious sedation on blood pressure and associated reduced perfusion could lead to alterations in fertilization and implantation rates. However, a Cochrane review of 24 randomized controlled trials involving 3160 women investigated different methods of pain relief including general anesthesia and concluded no evidence to support a particular anesthetic medication or technique to improve IVF outcomes.[14]

There are multiple high-quality studies showing some favorable, dose-dependent, non-anesthetic effects of propofol.[15-19] For example, the use of propofol in reducing cancer recurrence and as a treatment option for endometriosis, cancer tumor therapy, and in breast and endometrial cancer has gathered significant clinical interest in the recent years. Propofol is thought to have anti-inflammatory, anti-oxidant, and also an immunomodulatory role.[20,21] Propofol affects the immune system by suppressing T cell function, decreasing the number of CD8+ T cells and inhibit the production of proinflammatory cytokines.[22] In addition, propofol can also modulate the tumor microenvironment by reducing inflammation and remodeling the extra cellular matrix.[23] If the above biological mechanisms were to be true, these may have substantial clinical implications in women undergoing IVF treatment. Therefore, we decided to analyze a large dataset of treatment cycles conducted in a tertiary academic institution in the United States to address this knowledge gap.

Our aim was to perform a clinically focused study to investigate (a) the dosing trends in anesthesia for monitored anesthesia care (by analyzing the ideal dose of propofol based on body weight vs. actual dose administered) and (b) the pharmacodynamics of propofol infusion (by analyzing the changes in hemodynamic parameters) and (c) the dose-dependent effects of propofol on selected maternal and neonatal outcomes (by analyzing live birth rates, clinical pregnancy rates, miscarriage rates, preterm birth and birth weight in singleton pregnancies) in women undergoing IVF oocyte retrieval and a subsequent fresh embryo transfer.

Materials and methods

<u>*Study design and population*</u>

We conducted a retrospective cohort study to investigate the potential for non-anesthetic effects of propofol on IVF outcomes. Patient demographic characteristics, medical and obstetric history, treatment cycle characteristics and outcomes are tracked in the database for future research. The present study received IRB approval (IRB# 20200328) to abstract additional anesthesia metrics from the electronic medical record of patients enrolled in the database. Intraoperative data such as medications administered, heart rate, blood pressure, and mean arterial pressure at anesthesia induction and emergence were entered into REDCap software[24,25] after eligible patients were identified in the database.

Patients who underwent their first IVF oocyte retrieval under conscious sedation and those who proceeded with a subsequent fresh embryo transfer at a single academic IVF center between January 2016 and December 2022 were eligible for inclusion. We excluded treatment cycles if (a) transfer of any embryos which did not result from the current retrieval cycle (ie. reciprocal IVF), and (b) not having a documented weight on file in the electronic medical record for the window from their pre-operative visit through the date of their retrieval procedure.

We defined ideal dose of propofol as the optimal dose of propofol based on the patient's body weight and the actual dose is what the patient eventually received based on the clinical practice of the anesthesiologist, and patient response to intra-operative stimuli. As there were no practice standards or guidelines available specifically for MAC for IVF procedures, we calculated the ideal bolus dose as 0.015 mg/kg and ideal infusion dose as 0.075 mg/kg/min for full duration of procedure. These doses were the recommended maximum dosing for adult patients to manage patient and clinical needs adequately while maintaining optimal cardiorespiratory function.[26] In addition, as a meaningful categorization for propofol exposure during IVF oocyte retrieval has yet to be established due to the dearth of literature on the topic, we categorized propofol dose by quintiles to analyze the reproductive outcomes.

<u>*Ethics approval*</u>

All patients at our institution have the opportunity to consent to participation in our center's IVF database (University of Iowa; IRB # 201303841 and # 201709794) at their new IVF appointment. In addition, the institutional review board and ethics committee approved this study (IRB# 20200328).

<u>*Anesthesia procedures and monitoring*</u>

Anesthesia for oocyte retrieval began with a pre-anesthetic assessment of the patient. This included an anesthesia-focused physical assessment of each system, focusing on co-morbidities, Mallampati score, neck extension, dentition, anesthetic history, and the patients' weight on the day of the procedure. An American Society of Anesthesiologists physical status score is assigned based on this assessment. (ASA PS guide: https://www.asahq.org/standards-and-practice-parameters/statement-on-asa-physical-status-classification-system).

Upon arrival in the OR suite, patient monitors were placed, including electrocardiogram, non-invasive blood pressure, and pulse oximeter. Oxygen was administered via nasal cannula or simple face mask, with continuous end tidal carbon dioxide monitoring throughout the procedure. An infusion of propofol was administered, titrated between 150-250 mcg/kg/min, along with a bolus of 10-80 mg of propofol and 25-100 mcg of fentanyl. All medications were titrated to effect according to the patient's response to the procedure and anesthesia. After the procedure, the patient was transported to the recovery area, where vital signs and pain level were monitored. Care was transferred to recovery nursing staff with a report of any pertinent information (e.g. medications, intra procedure issues, patient concerns, etc.) to ensure continuity of care. Vital signs, pain score and nausea were reassessed and documented every 15 minutes for a minimum of one hour. Criteria for discharge from the hospital included stable vital signs, adequate pain control, and the ability to micturate.

Outcome variables assessed

Our exposure of interest was total propofol dose. We accounted for variance in exposure to propofol due to length of procedure, and distribution across body mass. Further, we performed the calculation as:

$$\frac{\dfrac{bolus\ dose\ (\mu g)\ +infusion\ dose(\mu g)}{patient\ body\ weight\ (kg)}}{duration\ from\ anesthesia\ induction\ to\ emergence\ (min)}$$

Our primary outcome variable was live birth. Secondary outcomes included clinical pregnancy, miscarriage, biochemical pregnancy loss, and ectopic pregnancy. Among patients with live birth, we examined outcomes of preterm birth, defined as delivery prior to 37 weeks' gestation; early preterm birth, defined as delivery prior to 32 weeks' gestation; and singleton birth weight.

Live birth rate (LBR) was defined as a birth in which at least one fetus is liveborn. All outcomes were defined as per the Society of Assisted Reproductive Technology (SART) data entry regulations. The secondary outcomes included 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), and miscarriage (a pregnancy that fails to develop normally and is spontaneously lost before 18 weeks from the date of transfer). Live birth, biochemical pregnancy, clinical pregnancy and miscarriage rates are rates per transfer cycle. Implantation rate was defined as the rate per embryos transferred.

Covariates

Information on baseline demographic, hormonal assessment, and treatment characteristics (Table 1) was collected from the database. Baseline demographic characteristics included age, BMI, smoking status, race, infertility diagnosis, and previous reproductive history. Treatment characteristics included total FSH dose, type of treatment protocol, type of insemination, the stage and number of embryos transferred. The FSH dose in international unit (IU) was the gonadotrophins used prior to the oocyte retrieval. Embryo stage at transfer was classified based on the difference in days between oocyte retrieval and embryo transfer as cleavage stage (days 2 to 3), or a blastocyst stage (day 5). IVF treatment protocols examined included a long agonist, agonist-flare, and an antagonist protocol. Based on the type of oocyte insemination in the embryology laboratory, each treatment cycle was classified as IVF (standard insemination), or intracytoplasmic sperm injection (ICSI). Fertilization rate was calculated number of 2 pronuclei divided by number fertilized. Number of embryos available was calculated by summing the number embryos resulting from the controlled ovarian stimulation that were either transferred or frozen.

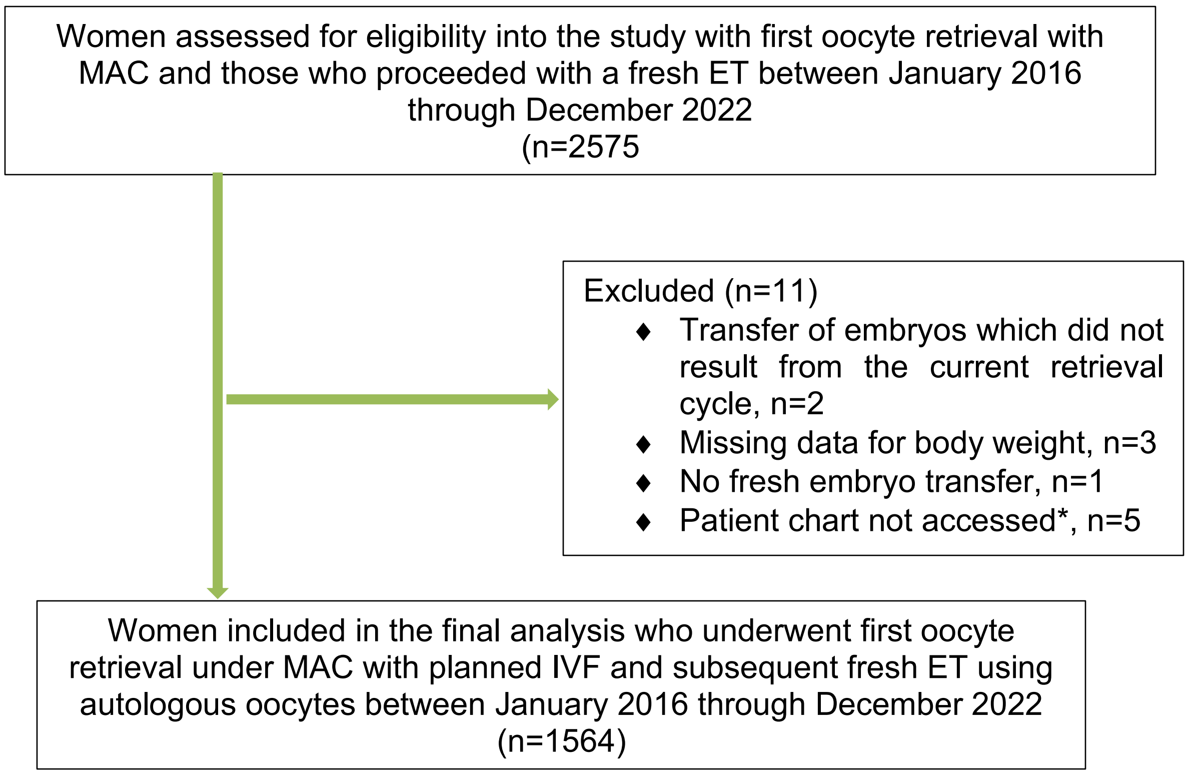
Statistical Analysis

Data collection and data cleaning was performed between 02 Feb 2024 and 20 Oct 2024. Descriptive statistics for baseline and treatment characteristics were calculated for all treatment cycles. We summarized patient and treatment characteristics with mean ± standard deviation or frequency (percentage) and compared across propofol dosage quintiles with ANOVA or Welch with Tukey post hoc test and Chi-square with post hoc z tests with Bonferroni correction as appropriate. Differences in anesthesia parameters from induction to emergence and between ideal and actual propofol dosages were compared within each quintile using paired t tests.

A modified Poisson Regression approach[27,28] was used to estimate adjusted relative risks for binomial outcome data including live birth, clinical pregnancy, and miscarriage. Potential confounders and effect modifiers accounted for as covariates in the regression models included maternal age, maternal history of smoking, length of controlled ovarian stimulation, insemination method, number of mature oocytes retrieved, and number of embryos transferred. Potential confounders were selected a-priori based on the literature and the study teams clinical experience. Adjusting for BMI was not appropriate as it was already included in the model as patients' body weight. Given the known issues of analysis based on arbitrary categorization based on quantiles, we entered propofol dose (µg/kg/min) as a continuous variable in regression modeling.[29] All statistical analyses were performed with SPSS v29.

Results

Between January 2016 and December 2022, there were a total of 1575 treatment cycles performed using monitored anesthesia care in women who had IVF using fresh, autologous oocytes and had a subsequent fresh embryo transfer. Details of flow of patients in this study are shown in flow chart (Figure 1). The baseline demographic, treatment cycle characteristics and anesthesia parameters are presented in Table 1.



*MAC=monitored anesthesia care; ET=embryo transfer; *Patient charts were not accessed for confidentiality reasons*

Figure 1. Flow diagram of patient selection into the study cohort.

In the final analysis, we included 1564 women [mean (SD) age (years) was 32.77 (4.25), BMI (Kg/m^2), was 28.75 (7.28), body weight (Kg) was 79.49 (20.70) and body surface area was 1.9 (0.28)]. The mean (SD) parity was 0.36 (0.73) and mean (SD) prior miscarriages was 0.33 (0.77). There was no difference for self-reported race and no clinically significant difference in infertility diagnosis or history of prior smoking status between the cohorts based on increasing total propofol dose (mcg/min/Kg) received. Controlled ovarian stimulation, n (%) was achieved via a long luteal gonadotropin releasing hormone (GnRH) agonist in 113 (7.3), GnRH agonist with flare in 402 (26.0) and with a GnRH antagonist protocol in 1030 (66.7) patients. The mean (SD) duration in controlled ovarian stimulation in days was 11.78 (1.86) and mean (SD) endometrial thickness in mm was 10.85 (2.48). Standard insemination (IVF technique) was performed in 56.6% and intracytoplasmic sperm injection (ICSI technique) in 43.4% of patients. The mean (SD) number of embryos available was 4.47 (3.31). Elective single embryo transfer was performed in 72.9% of patients.

At the start of the procedure, the mean (SD) patient heart rate (bpm) was 83.37 (13.75), systolic BP (mmHg) was 127.45 (18.16), diastolic BP (mmHg) was 77.99 (12.43), and the mean arterial pressure (mmHg) was 95.24 (13.03). The mean (SD) duration of procedure in minutes was 22.24 (6.95), with the propofol bolus dose administered averaging 63.3 mg (53.34) and a mean total infusion dosage of 327 mg (163.13).

Women in this study also received concomitant medications which included fentanyl (98.0%), lidocaine (81.6%), ondansetron (80.4%), and dexamethasone (25.9%). The relationship between propofol dose and fentanyl dose was investigated using Pearson correlation. There was a weak, negative correlation between total propofol dose and fentanyl dose, r= -.167, p<.001.

The LBR in cohort A-E were 50.2%, 49.8%, 50.5%, 54.6%, 55.4% respectively. The adjusted Risk Ratio, aRR (95% CI) for LBR per additional mg propofol/Kg/min was 1.25 (0.75 – 2.09). The clinical pregnancy rates in cohort A-E were 60.1%, 60.4%, 60.1%, 62.8%, 65.7% respectively. Table 2 presents the association of reproductive outcomes with total propofol dose received in five cohorts (Cohorts A-E) based on total propofol dose range in mcg/Kg/minute.

Table 3 presents the changes in hemodynamic parameters with total propofol dose received in the whole sample and in five difference cohorts (Cohorts A-E) based on total propofol dose range in mcg/Kg/minute. In the whole sample, the mean (SD) difference in heart rate (bpm) was -8.08 (13.01), systolic blood pressure was -17.44 (16.28), diastolic blood pressure was -12.76 (13.62) and mean arterial pressure was -14.04 (13.16). The mean difference (95%CI, p value) in ideal and actual propofol bolus dose was 3.68 (0.98 – 6.38, 0.08). There was a statistically significant difference in the ideal and actual propofol infusion dose [193.15 (186.89 – 199.41, <0.001)] and total dose of propofol [196.83 (190.85 – 202.82, <0.001)]. There was a statistically significant difference in all anesthesia parameters within all cohorts except for mean difference in ideal and actual propofol infusion dose.

Discussion

We report findings from a large cohort study investigating the dosing trends of propofol, hemodynamic changes and reproductive outcomes following monitored anesthesia care for IVF oocyte retrieval. Statistically significant differences were observed between the ideal dose based on body weight versus actual dose of propofol administered with significant changes in hemodynamic parameters. The study also showed statistically non-significant trend of increase in live birth rate and clinical pregnancy rate in cohorts of women receiving higher doses of propofol for IVF oocyte retrieval. The amplitude of increase in live birth rates in this study is more pronounced with increasing dose of propofol administered during monitored anesthesia care. This is a new and interesting finding.

Despite the shift of practice in reproductive medicine towards elective freeze-all of embryos, a majority of women still benefit from a fresh embryo transfer.[30] 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. Therefore, the findings from this study cannot be understated. The study is noteworthy in the context that to the best of our knowledge, there has yet to be a study to investigate the association of reproductive outcomes based on dose-dependent increase in propofol used for monitored anesthesia care for IVF oocyte retrieval. We used data from a tertiary academic IVF unit which is managed as per reporting standards for the Society of Assisted Reproductive Technology Clinical Outcomes Reporting System (SARTCORS) and the Centers for Disease Control and Prevention (CDC). Furthermore, compared to some of the prior cohort studies related to this topic, our study had a large number of treatment cycles. This allowed us to divide data to five different cohorts, each containing more than 300 treatment cycles. The large data set also allowed us to perform statistical adjustments for a number of potential demographic and treatment variable confounders and effect modifiers.

The association of propofol anesthesia and IVF outcomes has been investigated previously in several small, single center studies with conflicting conclusions. Some studies concur with conclusions similar to our study. A retrospective study conducted in a tertiary IVF center investigated the effects of propofol, ketamine, or combination of propofol and ketamine for oocyte retrieval on IVF outcomes.[31] This study included 333 undergoing IVF treatment evaluated in three groups: propofol (n = 217), or ketamine (n = 60), or P + K (n = 56) for anesthesia during OR. The study concluded that women in propofol group had better fertilization rates; however, extended anesthesia duration (>30 min) was associated with low implantation rates (p = 0.04) and clinical pregnancy rates (p = 0.02). A Cochrane review compared the effects of five different methods of conscious sedation and pain relief including general anesthesia from 24 randomized controlled trials, involving 3160 women.[14] Authors concluded that evidence was insufficient to show conclusively whether any of the interventions influenced pregnancy rates.

Propofol has also been shown to result in suboptimal reproductive outcomes. A retrospective study analyzed IVF outcomes of 129 women who underwent oocyte retrievals under anesthesia and 116 without anesthesia. Compared to women with anesthesia, the fertilization rates were higher in women who had oocyte retrieval without anesthesia (53.4% +/- 34.8 vs. 63.7% +/- 33.6; p = 0.02). This study concluded that general anesthesia with propofol may have adverse effects on the fertilization potential of oocytes.[12] The outcomes of clinical pregnancy and live birth are more clinically relevant than fertilization potential, making our study results reassuring to patients. In another retrospective study comparing EMLA cream, propofol, thiopental sodium, sevoflurane for IVF oocyte retrieval, authors found significantly lower fertilization in propofol, and thiopental sodium groups compared to EMLA cream and sevoflurane, $p < 0.001$.[32] The conclusions for the aforementioned studies had limitations based on participant numbers, study design and methodology. Moreover, none of the studies analyzed anesthesia or reproductive outcomes based on increments of propofol dosing.

Our study did not investigate potential biological pathways by which propofol dose could increase live birth rates among women undergoing fresh embryo transfer. However, potential mechanisms may include the following considerations. First, propofol and the EDTA component may offer an anti-inflammatory function by inhibiting neutrophil chemotaxis and decrease production of reactive oxygen species in a dose dependent manner.[33] Second, the phenolic hydroxyl group in propofol may offer an anti-oxidant function by scavenging free radicals and inhibiting lipid peroxidation which in turn increases tissue antioxidant capacity.[34] Third, the lipid component of propofol may offer an immunomodulatory function by decreasing production of TNF-A, IL-1, IL-6, IL-8, IL-10 and iNOS.[35] It may be postulated that these anti-inflammatory, anti-oxidant, and immunomodulatory functions of propofol may exert positive changes in the oocyte and endometrium in a dose-dependent manner.

Propofol is an injectable emulsion and contains soybean oil, glycerol, and egg lecithin.[36] Interestingly, intravenous intralipids (IVIL), another fat-based emulsion of soybean oil, glycerine, phospholipids, egg, and polyunsaturated fatty acids, has been evaluated in several IVF studies as a potential intervention to suppress the maternal immunological response. Systematic review and meta-analysis of studies conducted in 2020[37] and 2021[38] which included five randomized controlled trials concluded that women receiving intravenous intralipids around the time of embryo transfer had a higher chance of clinical pregnancy and live birth. Authors postulate that IVIL modulated immune function by reducing monocyte endothelial adhesion and pro-inflammatory cytokine generation and by downregulation of uNK cell macrophages pro-inflammatory mediators especially T1 helper cells.

Therefore, the potential biological mechanisms mediated by emulsion-based medications need to be investigated further by performing large, well-designed studies.

Several limitations of the dataset must also be considered. First, our study has inherent limitations associated with a single center study and the retrospective nature. Second, the anesthesia protocol at this institution allows variability in dosing for the bolus and infusion propofol dose. Third, we are unable to account for the possible ‘adjuvant’ effect of concomitant medications. Fourth, based on the study design and aims, we only included data from treatment cycles which resulted in a fresh embryo transfer. Therefore, the outcomes based on propofol dose may not be applicable to women undergoing frozen embryo transfers. Fifth, we were unable to distinguish whether the higher dose of medications translated to a higher serum level and also whether the non-anesthetic effects of propofol could be impacting both the oocyte and implantation environment.

Conclusions

In women who underwent their first IVF oocyte retrieval under monitored anesthesia care, we observed a statistically significant difference between the ideal dose versus actual dose of propofol administered and associated significant changes in hemodynamic parameters. Despite the statistically significant higher dose administered, there was a trend of increase in live birth rate and clinical pregnancy rate with increasing dose of propofol as part of monitored anesthesia care for IVF oocyte retrieval. These results are very reassuring for both patients and providers desiring anesthesia for IVF oocyte retrieval.

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Table 1. Baseline demographic and treatment cycle characteristics and anesthesia parameters

			Total Propofol Dosage Range µg/kg/min					
Predictor Variables	**Statistics/Level**	**Full Sample**	**Cohort A <174.75**	**Cohort B 174.75 – 204.59**	**Cohort C 204.60 – 237.34**	**Cohort D 237.35 – 276.99**	**Cohort E ≥277.00**	**p-value**
		N = 1564	n = 313	n = 313	n = 313	n = 314	n = 312	
Female Age, Mean (SD)		32.77 (4.25)	33.00 (4.09)	33.09 (4.11)	32.49 (4.49)	32.66 (4.45)	32.59 (4.11)	.316
Body Weight in Kg, Mean (SD)		79.49 (x.xx)	86.12 (22.12) [B,C,D,E]	81.35 (21.25) [A,E]	79.54 (20.84) [A,E]	77.95 (19.44) [A,E]	72.46 (17.16) [A,B,C,D]	<.001[2]
BMI, Mean (SD)		28.75 (7.28)	30.76 (8.17) [C,D,E]	29.21 (7.24) [E]	28.87 (7.14) [A,E]	28.31 (6.91) [A,E]	26.59 (6.21) [A,B,C,D]	<.001[2]
BSA, Mean (SD)		1.90 (0.28)	2.00 (0.37) [B,C,D,E]	1.93 (0.26) [A,E]	1.90 (0.26) [A,E]	1.88 (0.24) [A,E]	1.81 (0.22)[A,B,C,D]	<.001[2]
Race, n (%)	White	1396 (90.2)	247 (88.4)	279 (90.0)	284 (91.9)	281 (90.9)	278 (90.0)	
	Black	30 (1.9)	7 (2.3)	9 (2.9)	4 (1.3)	7 (2.3)	3 (1.0)	
	Hispanic	35 (2.3)	8 (2.6)	5 (1.6)	4 (1.3)	6 (1.9)	12 (3.9)	
	Asian	74 (4.8)	18 (5.8)	15 (4.8)	13 (4.2)	12 (3.9)	16 (5.2)	
	Other	12 (0.8)	3 (1.0)	2 (0.6)	4 (1.3)	3 (1.0)	0 (0)	
Smoker, n (%)		233 (14.9)	37 (11.8)	43 (13.8)	48 (15.4)	56 (17.9)	49 (15.7)	.273
AFC – mean (SD)		25.84 (13.94)	25.96 (14.49)	27.39 (14.77)	25.89 (13.32)	25.16 (13.32)	24.81 (13.68)	.178
Infertility Diagnosis, n (%)	DOR	175 (11.2)	36 (11.5)	32 (10.2)	39 (12.5)	30 (9.6)	38 (12.2)	.750
	Endometriosis	209 (13.4)	40 (12.8)	35 (11.2)	37 (11.8)	48 (15.4)	49 (15.7)	.333
	Male Infertility	558 (35.7)	102 (32.6)	108 (34.5)	129 (41.2)	101 (32.3)	118 (37.8)	.096
	Ovulation Disorder	266 (17.0)	64 (20.5)	62 (19.8)	47 (15.0)	51 (16.3)	42 (13.5)	.084
	Tubal Factor	280 (17.9)	57 (18.3)	64 (20.4)	52 (16.6)	58 (18.6)	49 (15.7)	.578
	Unexplained	377 (24.1)	63 (20.2)	78 (24.9)	74 (23.6)	79 (25.3)	83 (26.6)	.396

	Uterine Factor	71 (4.5)	13 (4.2)	14 (4.5)	19 (6.1)	15 (4.8)	10 (3.2)	.537
	Other	121 (7.7)	25 (8.0)	25 (8.0)	19 (6.1)	29 (9.3)	23 (7.4)	.664
	Multiple Diagnoses	420 (26.9)	76 (24.4)	86 (27.5)	90 (28.8)	82 (26.3)	86 (27.6)	.781
Parity, Mean (SD)		0.36 (0.73)	0.32 (0.66)	0.41 (0.86)	0.35 (0.71)	0.37 (0.74)	0.32 (0.66)	.562[2]
Prior Miscarriages, Mean (SD)		0.33 (0.77)	0.27 (0.64)	0.33 (0.86)	0.35 (0.73)	0.35 (0.79)	0.34 (0.81)	.642
COS protocol	Agonist	113 (7.3)	81 (26.4)	79 (25.5)	79 (25.6)	78 (25.1)	85 (27.6)	.674
	Agonist-Flare	402 (26.0)	17 (5.5)	20 (6.5)	20 (6.5)	28 (9.0)	28 (9.1)	
	Antagonist	1030 (66.7)	209 (68.1)	211 (68.1)	210 (68.0)	205 (65.9)	195 (63.3)	
Days of COS - Mean (SD)		11.78 (1.86)	12.04 (2.30)	11.67 (1.62)	11.73 (1.56)	11.83 (1.89)	11.64 (1.81)	.053
ET - Mean (SD)		10.85 (2.48)	10.84 (2.56)	10.93 (2.48)	10.92 (2.47)	10.76 (2.41)	10.79 (2.50)	.884
Type of Treatment	ICSI	676 (43.4)	130 (41.7)	153 (48.9)	126 (40.4)	136 (43.7)	131 (42.1)	.232
	IVF	883 (56.6)	182 (58.3)	160 (51.1)	186 (59.6)	175 (56.3)	180 (57.9)	
Oocytes Retrieved		16.20 ± 9.59	15.74 ± 9.41	17.08 ± 10.11	17.17 ± 10.25	15.69 ± 8.85	15.31 ± 9.16	.038
Embryos - Mean (SD)		4.47 (3.31)	4.26 (3.11)	4.77 (3.62)	4.65 (3.48)	4.45 (3.37)	4.23 (2.90)	.168[2]
Embryos transferred	SET	176 (11.3)	40 (12.8)	29 (9.3)	33 (10.5)	42 (13.4)	32 (10.3)	.502
	eSET	1140 (72.9)	222 (70.9)	231 (73.8)	232 (74.1)	216 (69.0)	239 (76.6)	
	DET	248 (15.9)	51 (16.3)	53 (16.9)	48 (15.3)	55 (17.6)	41 (13.1)	
Heart Rate[1] -Mean (SD)		83.37 (13.75)	80.38 (13.23) [C,D,E]	82.75 (13.53)	84.48 (14.35) [A]	84.95 (13.72) [A]	84.29 (13.49) [A]	<.001
Systolic BP [1] Mean (SD)		127.45 (18.16)	126.60 (18.47)	127.78 (17.94)	127.45 (17.65)	128.58 (16.30)	126.85 (20.24)	.672
Diastolic BP [1] - Mean (SD)		77.99 (12.43)	77.03 (12.07)	77.65 (11.98)	77.78 (12.38)	79.29 (12.23)	78.21 (13.42)	.220
MAP [1] - Mean (SD)		95.24 (13.03)	93.96 (13.210	95.08 (12.76)	95.07 (12.61)	96.71 (12.54)	95.38 (13.90)	.129
Duration of procedure, Mean (SD)		22.24 (6.95)	24.60 (6.65) [D,E]	24.58 (7.20)[D,E]	23.26 (6.72) [D,E]	20.60 (6.19) [A,B,C,E]	18.14 (5.56) [A,B,C,D]	<.001[2]

Actual Propofol Bolus Dose in mg, Mean (SD)		63.30 (53.34)	55.64 (45.70)[E]	59.04 (48.90)[E]	63.35 (57.56)[E]	63.37 (54.62)[E]	75.12 (57.17) [A,B,C,D]	<.001[2]
Ideal[3] Propofol Bolos Dose in mg, Mean (SD)		59.62 (15.52)	64.59 (16.59) [B,C,D,E]	61.02 (15.94) [A,E]	59.66 (15.63) [A,E]	58.46 (14.58) [A,E]	54.34 (12.87) [A,B,C,D]	<.001[2]
Actual Propofol Infusion Dose (mg/min), Mean (SD)		327.00 (163.13)	261.69 (132.68) [B,C,D,E]	325.75 (165.26) [A]	344.91 (159.12)[A]	346.53 (163.89) [A]	356.19 (174.57) [A]	<.001[2]
Ideal[3] Propofol Infusion Dose (mg/min), Mean (SD)		97.89 (37.74)	160.38 (66.91) [C,D,E]	151.48 (64.00) [C,D,E]	138.70 (53.55) [A,B,D,E]	120.68 (49.15) [A,B,C,E]	97.89 (37.74) [A,B,C,D]	<.001[2]
Concomitant Medications	Fentanyl	1533 (98.0)	301 (96.2) [B]	312 (99.7) [A]	310 (99.0)	308 (98.4)	302 (96.8)	.006
	Fentanyl, mean dose (SD)	97.32 (36.33)	103.40 (34.43) [D,E]	103.49 (41.84) [D,E]	98.95 (33.55) [E]	91.22 (34.85) [A,B]	89.40 (33.93) [A,B,C]	<.001[2]
	Lidocaine	1276 (81.6)	275 (87.9) [B,E]	245 (78.3) [A]	262 (83.7)	252 (80.5)	242 (77.6) [A]	.005
	Lidocaine, mean dose (SD)	56.38 (14.29)	58.18 (13.22)	54.86 (14.01)	55.34 (16.06)	55.73 (15.13)	57.70 (12.47)	.018[2]
	Ondansetron	1257 (80.4)	240 (76.7) [E]	234 (74.8) [E]	257 (82.1)	259 (82.7)	267 (85.6) [A,B]	.003
	Ondansetron, mean dose (SD)	4.59 (19.64)	4.03 (0.36)	6.97 (45.50)	4.03 (0.35)	4.05 (0.43)	4.06 (0.49)	0.788[2]
	Dexamethasone	405 (25.9)	35 (11.2) [C,D,E]	56 (17.9) [D,E]	77 (24.6) [A,E]	109 (34.8) [A,B]	128 (41.0) [A,B,C]	<.001
	Dexamethasone, mean dose (SD)	5.30 (2.25)	6.40 (2.69) [D,E]	6.05 (2.62) [D]	5.45 (2.40)	4.68 (1.73) [A,B]	5.12 (2.07) [A]	<.001[2]

p-value for ANOVA or Chi square as appropriate unless otherwise noted. All variables missing data for <3% of the sample. Mean dosages presented are for the portion of the sample who received the medication.
[1] Measures taken at start of (anesthesia/procedure)
[2] p value for Welch test
[3]Ideal bolus dose calculated as .015 mg/kg/min IV for 5 min (maximum from Medscape Reference). Ideal infusion dose calculated as .075 mg/kg/min for full duration of procedure (maximum from Medscape Reference).

[A]differs from <174.75 micrograms propofol/kg/min group at .05 significance level in Tukey post hoc testing for ANOVA or post hoc z test for Chi-square.
[B]differs from 174.75-204.59 micrograms propofol/kg/min group at .05 significance level in Tukey post hoc testing for ANOVA or post hoc z test for Chi-square.
[C]differs from 204.60 – 237.34 micrograms propofol/kg/min group at .05 significance level in Tukey post hoc testing for ANOVA or post hoc z test for Chi-square.
[D]differs from 237.35 – 276.99 micrograms propofol/kg/min group at .05 significance level in Tukey post hoc testing for ANOVA or post hoc z test for Chi-square.
[E]differs from >276.99 micrograms propofol/kg/min group at .05 significance level in Tukey post hoc testing for ANOVA or post hoc z test for Chi-square

Table 2. Association of reproductive outcomes with total propofol dose received – full analysis

Outcomes	Total numbers (n=1564)	Total Propofol Dosage Range µg/kg/min					Crude Risk Ratio Propofol (mg)/kg/min	Adjusted Risk Ratio Propofol (mg)/kg/min
		Cohort A (n=313)	Cohort B (n=313)	Cohort C (n=313)	Cohort D (n=313)	Cohort E (n=312)		
Live birth Rate								
Frequency (%)	815 (52.1)	157 (50.2)	156 (49.8)	158 (50.5)	171 (54.6)	173 (55.4)	1.41 (0.82 – 2.44)	1.25 (0.75 – 2.09)
Clinical Pregnancy Rate								
Frequency (%)	966 (61.8)	188 (60.1)	189 (60.4)	188 (60.1)	196 (62.8)	205 (65.7)	1.36 (0.85 – 2.18)	1.25 (0.80 – 1.96)
Miscarriage Rate								
Frequency (%)	138/966 (14.3)	29/188 (15.4)	28/189 (14.8)	29/188 (15.4)	21/196 (10.7)	31/205 (15.1)	0.92 (0.13 – 6.47)	1.28 (0.20 – 8.27)
Biochemical Pregnancy								
Frequency (%)	144 (9.2)	33 (10.5)	32 (10.2)	28 (8.9)	24 (7.7)	27 (8.7)	0.83 (0.04 – 16.99)	0.93 (0.08 – 11.33)
Ectopic Pregnancy Rate								
Frequency (%)	16 (1.0)	6 (1.9)	4 (1.3)	1 (0.3)	5 (1.6)	0 (0)	0.00 (0.00 – 0.29)	0.00 (0.00 – 0.34)
Preterm Birth								
Frequency (%)	107/818 (13.1)	12/157 (7.6)	28/158 (17.7)	22/159 (13.8)	22/171 (12.9)	23/173 (13.3)	3.01 (0.54 – 16.63)	3.93 (0.71 – 21.94)
Early Preterm Birth								
Frequency (%)	19/818 (2.3)	3/157 (1.9)	3/158 (1.9)	4/159 (2.5)	5/171 (2.9)	4/173 (2.3)	1.83 (0.02 – 147.00)	1.17 (0.01 – 140.84)
Singleton Birth Weight								
Kg, Mean ± SD	3.25 ± 5.98	3.33 ± 5.61	3.27 ± 6.27	3.30 ± 5.29	3.19 ± 5.96	3.15 ± 6.50	0.53 (0.29 – 0.95)	0.49 (0.27 – 0.90)

Risk ratios adjusted for patient age, length of COS (days), smoking, type of insemination, number of mature oocytes retrieved, and number of embryos transferred.

Table 3. Relationship between anesthesia parameters and total propofol dose received – full analysis

Anesthesia Parameters	Whole Sample	Propofol Dosage based on μg/kg/min				
		Cohort A (<174.75)	Cohort B (174.75 – 204.59)	Cohort C (204.60 – 237.34)	Cohort D (237.35 – 276.99)	Cohort E (≥277.00)
Change in Heart Rate (bpm) +/- SD	-8.08 ± 13.01	-6.13	-6.36	-9.15	-8.82	-9.96
Mean (95% CI of difference), P value		*(-7.78 - -4.78), <0.001*	*(-7.89 - -4.84), <0.001*	*(-10.48 - -7.82), <0.001*	*(-10.33 - -7.31), <0.001*	*(-11.42 - -8.49), <0.001*
Change in Systolic Blood Pressure	-17.44 ± 16.28	-15.26	-17.18	-17.92	-19.03	-17.80
Mean (95% CI of difference), P value		(-17.08 - -13.43), <0.001	(-18.92 - -15.44), <0.001	(-19.58 - -16.27), <0.001	(-20.73 - -17.33), <0.001	(-19.88 - -15.71), <0.001
Change in Diastolic Blood Pressure	-12.76 ± 13.62	-10.78	-12.20	-13.22	-13.97	-13.61
Mean (95% CI of difference), P value		*(-12.27 – -9.30), <0.001*	*(-13.72 - -10.68), <0.001*	*(-14.68 - -11.75), <0.001*	*(-15.48 - -12.45), <0.001*	*(-15.19 - -12.04), <0.001*
Change in Mean arterial pressure	-14.04 ± 13.16	-11.77	-13.66	-14.28	-15.66	-14.85
Mean (95% CI of difference), P value		*(-13.24 - - 10.31), <0.001*	*(-15.08 - -12.24), <0.001*	*(-15.65 - - 12.90), <0.001*	*(-17.18 - -14.13), <0.001*	*(-16.36 - -13.33), <0.001*
Difference in Ideal[3] & Actual Propofol Bolus	3.68	-8.95	-1.97	3.70	4.91	20.78
Mean (95% CI of difference), P value	(0.98 – 6.38), 0.008	*(-13.95 - -3.95), <0.001*	*(-7.53 – 3.58), 0.485*	*(-2.78 – 10.18), 0.262*	*(-1.27 – 11.09), 0.119*	*(14.31 – 27.24), <0.001*
Difference in Ideal[3] & Actual Propofol Infusion	193.15	101.32	174.28	206.21	225.85	258.30
Mean (95% CI of difference), P value	(186.89 – 199.41), <0.001	*(92.18 – 110.45), <0.001*	*(162.42 – 186.14), <0.001*	*(193.84 – 218.59), <0.001*	*(212.59 -239.12) <0.001*	*(242.18 – 274.18), <0.001*
Difference in Total dose of Propofol	196.83	92.36	172.30	209.91	230.76	279.08
Mean (95% CI of difference), P value	(190.85 - 202.82), <0.001	(83.95 – 100.78), <0.001	(162.27 – 182.34), <0.001	(199.23 – 220.60), <0.001	(218.93 – 242.60), <0.001	(263.76 – 294.40), <0.001

p-values for two-sided paired t tests

[3] Ideal bolus dose calculated as .015 mg/kg/min IV for 5 min (maximum from Medscape Reference). Ideal infusion dose calculated as .075 mg/kg/min for full duration of procedure (maximum from Medscape Reference).