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An Evaluation of the Effect of Anesthetic Technique on Reproductive Success after Laparoscopic Pronuclear Stage Transfer

Propofol/Nitrous Oxide Versus *Isoflurane/Nitrous Oxide*

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Background: **Laparoscopic pronuclear stage transfer (PROST) is the preferred method of embryo transfer after *in vitro* fertilization in many infertility programs. There are scant data to recommend the use or avoidance of any particular anesthetic agent for use in women undergoing this procedure. The authors hypothesized that propofol would be an ideal anesthetic for laparoscopic PROST because of its characteristic favorable recovery profile that includes minimal sedation and a low incidence of postoperative nausea and vomiting. The purpose of the study was to compare propofol and isoflurane with respect to postanesthetic recovery and pregnancy outcomes after laparoscopic PROST.**

Methods: **One hundred twelve women scheduled for laparoscopic PROST were randomized to receive either propofol/nitrous oxide or isoflurane/nitrous oxide for maintenance of anesthesia.**

Results: **Visual analog scale scores for sedation were lower in the propofol group than in the isoflurane group at all measurements between 30 min and 3 h after surgery. More women experienced emesis and were given an antiemetic during recovery in the isoflurane group than in the propofol group. However, the percentage of pregnancies with evidence of fetal cardiac activity was 54% in the isoflurane group compared with only 30% in the propofol group ($P = 0.023$). Also, the ongoing pregnancy rate was greater in the isoflurane group than in the propofol group (54% *vs.* 29%, $P = 0.014$).**

Conclusions: **Propofol/nitrous oxide anesthesia was associated with lower clinical and ongoing pregnancy rates compared with isoflurane/nitrous oxide anesthesia. (Key words: Anesthetics, inhalational: isoflurane; nitrous oxide. Anesthetics, intravenous: propofol. Assisted reproductive techniques: pronuclear stage transfer.)**

IN 1986, Blackledge *et al.*[1] introduced pronuclear stage transfer (PROST) as a method to enhance the incidence of successful pregnancies in couples with male factor infertility. Subsequently, indications for PROST have expanded, and many reproductive endocrinologists favor this technique for the transfer of preimplantation embryos after *in vitro* fertilization. Pronuclear stage transfer involves the placement of several one-cell embryos into the distal segment of a fallopian tube during laparoscopic surgery. Several authors have reported that each embryo transferred in this manner has about twice the chance of eventually implanting into the uterine wall compared with those transferred directly into the uterine cavity.[2–4] Indeed, some studies have found that the incidence of reproductive success after PROST was greater than after transcervical intrauterine embryo transfer.[2–5] For example, Hammitt *et al.*[2] reported a clinical pregnancy rate of 52% after PROST procedures compared with only 20% after intrauterine embryo transfers.

Despite the increased popularity of PROST, there are no human data to unequivocally promote the use or avoidance of any specific anesthetic agent or technique

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for the purpose of anesthetizing women for this procedure. Others have noted an adverse effect of isoflurane on preimplantation mouse embryos *in vitro*.[6–8] However, the applicability of their findings to human embryo development is questionable because our infertility program has reported high PROST pregnancy rates despite the routine use of isoflurane anesthesia for laparoscopic tubal transfers.[2]

Propofol is an excellent anesthetic for outpatient laparoscopic surgical procedures because patients tend to recover quickly with little sedation and nausea.[9] Preliminary laboratory data suggest that it does not harm preimplantation mouse embryos *in vitro*,[10] but we are not aware of any published clinical data to confirm its safety in humans when administered during *embryo* transfer procedures. The purpose of the current study was (1) to evaluate measures of reproductive success after administration of either propofol or isoflurane anesthesia for PROST and (2) to confirm whether propofol anesthesia resulted in a more rapid recovery with fewer postoperative side effects compared with isoflurane anesthesia when given for laparoscopic PROST.

Methods

The protocol was approved by the University of Iowa Human Subjects Review Committee. After hormonal stimulation, preovulatory oocytes were harvested transvaginally followed by insemination with spermatozoa *in vitro*.[2] Autologous PROST cycles were defined as those transfers in which the oocyte donor and the embryo recipient were the same individual. Donor-recipient PROST cycles were defined as transfers in which oocytes were anonymously donated by a woman other than the one receiving the pronuclear stage embryos. If evidence of successful fertilization (*i.e.*, the presence of two intracellular pronuclei) was present 16–18 h after insemination, the patient was prepared for laparoscopic PROST. Before surgery, written informed consent was obtained from all women participating in the study protocol. At that time, each participant was randomized to receive either propofol/nitrous oxide or isoflurane/nitrous oxide anesthesia for laparoscopic transfer. Randomization was performed by opening one of a series of sequentially numbered opaque envelopes that contained the group assignment. The patient, but not the anesthesiologist, was blinded to the group assignment. Individuals who failed to conceive after participating in the study were eligible for a second randomization during a subsequent PROST procedure.

Anesthetic Technique

General anesthesia was induced with an intravenous bolus of 50–100 μg fentanyl followed by either 2–2.5 mg/kg propofol (propofol group) or 3–6 mg/kg sodium thiopental (isoflurane group). Before laryngoscopy and tracheal intubation, 0.4–0.5 mg/kg atracurium was administered intravenously. A continuous infusion of propofol ($\leq$200 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was used for maintenance of anesthesia in the propofol group. Isoflurane ($\leq$2% inspired) was used for maintenance of anesthesia in the isoflurane group. Nitrous oxide (50%) in oxygen was administered to all patients throughout surgery. In both groups, an additional 50–100 μg fentanyl was given during surgery as determined by the attending anesthesiologist. Incremental doses of atracurium were given to maintain adequate neuromuscular relaxation intraoperatively. At the end of surgery, residual neuromuscular blockade was reversed with intravenous glycopyrrolate and neostigmine. Nitrous oxide administration was discontinued at the time of skin closure. (This was defined as time zero for all postoperative measurements.)

Surgical Technique

After establishing pneumoperitoneum with carbon dioxide, the proximal end of one fallopian tube was identified during laparoscopy and was cannulated with an introducer sleeve. Subsequently, a transfer catheter was advanced through the sleeve, and two or more pronuclear stage embryos were injected into the ampullary portion of the fallopian tube. After verifying that all embryos had been expelled from the transfer catheter, pneumoperitoneum was released and the puncture wounds were closed. All surgeries were performed by one of two faculty reproductive endocrinologists (C.H.S. or B.J.V.).

Postoperative Management

The first 84 patients were instructed to remain recumbent during the initial 4 h after surgery. (Patients were instructed to refrain from ambulating for several hours after surgery with the hope that this practice would limit any migration of the conceptus within the fallopian tube. Later, this period of strict immobilization was reduced from 4 to 3 h after all other gamete or embryo transfer procedures. At that time, we decided to incorporate this change into our methodology so that the study protocol would be more relevant to current clinical practice at The University of Iowa Hospitals and Clinics. Hence the final 28 women were re-

quired to remain recumbent for only 3 h after surgery.) In the recovery room, ice chips and clear liquids were given orally as tolerated. Intravenous morphine (2–3 mg) or oral acetaminophen with codeine was given as needed to treat postoperative pain. Metoclopramide (10 mg) was administered intravenously for the treatment of persistent nausea. Patients who continued to experience nausea and vomiting after an initial dose of metoclopramide were given either a second intravenous dose of 10 mg metoclopramide or 0.625 mg droperidol at the discretion of the attending anesthesiologist. Patients were discharged from the hospital when they had voided and were able to ambulate, unless they were experiencing significant somnolence, nausea, or pain. Intramuscular progesterone (25–50 mg) was given daily until results of the chemical pregnancy test(s) were known. If a chemical pregnancy was detected, progesterone administration was continued for at least 2 weeks more.

Measurements

Patient visual analog scale (VAS) scores for nausea (0 = no nausea and 100 = worst possible nausea) and sedation (0 = wide awake and 100 = almost asleep) were obtained at 15, 30, 60, 120, 180, and 240 min after surgery. (VAS scores at 240 min were not obtained in the final 28 study patients.) At discharge, patients were asked to describe their overall satisfaction with the anesthetic technique as very satisfied (0), somewhat satisfied (1), somewhat dissatisfied (2), or very dissatisfied (3). Patients were unaware of their group assignment until after completion of the discharge questionnaire.

Fifteen days after surgery, maternal plasma β-human chorionic gonadotropin concentrations were determined from samples of maternal venous blood to establish whether PROST had resulted in a chemical pregnancy. Positive results were verified with an additional plasma β-human chorionic gonadotropin measurement 48 h later. If a chemical pregnancy was still evident at this time, a vaginal ultrasound examination was performed 24 days after surgery to note the presence and number of gestational sacs within the uterine cavity. If present, an additional ultrasound examination was performed 10 days later to determine whether viable fetal cardiac activity ($\geq$100 beats/min) was present. Clinical pregnancies were defined as evidence of viable fetal cardiac activity at that time. Ongoing pregnancies were defined as clinical pregnancies in which spontaneous abortion (of all fetuses) had not occurred. Each gestational sac with fetal cardiac activity was defined as a successful implantation. Implantation rate was calculated as follows: number of successful implantations divided by total number of embryos transferred. Reproductive data were not included in the analysis of pregnancy results if the patient received gamete intrafallopian transfer simultaneous with PROST.

Statistical Analysis

Comparisons of continuous data between the two groups were made using unpaired t tests. Nonparametric comparisons between groups were made using the chi-square test (2×2) with contingency correction or the Mann-Whitney U test. Bonferroni adjustments were used in comparing nausea and sedation measurements at specific times. $P < 0.05$ was considered statistically significant.

Results

One hundred twelve PROST cycles were studied between June 1992 and May 1994. Ninety-four women were enrolled once in the study, and nine agreed to participate during two laparoscopic PROST procedures. Among the nine patients who consented to randomization on two instances, three received propofol twice, two received isoflurane twice, and four were given each anesthetic once. There were no significant differences in patient demographic data or infertility factors between the two groups (tables 1 and 2). Also, the number of embryos transferred during PROST was similar in the two groups (median 4, range 2–6; for each group).

VAS scores for nausea did not differ significantly between the two groups at any time (fig. 1). However, the incidences of vomiting and antiemetic administration were smaller ($P < 0.05$) in the propofol group than in the isoflurane group (table 3). The intervals elapsed from the end of surgery until patients could tolerate ice chips or ambulate were each shorter ($P < 0.05$) in the propofol group than in the isoflurane group. Patient VAS sedation scores were significantly lower ($P < 0.05$) in the propofol group than in the isoflurane group at all measurements between 30 min and 3 h after surgery (fig. 2). Also, the interval between the end of surgery and hospital discharge was shorter ($P < 0.05$) after propofol anesthesia than after isoflurane anesthesia. Overall patient satisfaction was high in both groups but was slightly higher ($P < 0.05$) in the propofol group (fig. 3).

Table 1. Patient Demographic Data

	Propofol (n = 57)	Isoflurane (n = 55)
Age (yr)	35 ± 5	35 ± 5
Weight (kg)	71 ± 16	69 ± 16
Plasma follicular stimulating hormone (mIU/ml)*†‡	8.3 ± 3.2	9.4 ± 4.5
Plasma estradiol (pg/ml)*†§	2047 ± 1185	1711 ± 1028
No. of previous PROST procedures†		
0	47	42
1	7	5
2	1	1
≥3	1	2
No. of previous live births after PROST†	3	3
Autologous cycles†	46/56 (82%)	41/50 (82%)
Donor–recipient cycles†	10/56 (18%)	9/50 (18%)

PROST = pronuclear stage transfer; GIFT = gamete intrafallopian transfer; HCG = human chorionic gonadotropin.

Continuous data are expressed as mean ± SD.

* Includes only autologous PROST cycles.

† Excludes laparoscopies in which simultaneous GIFT was performed or in which tubal transfer was abandoned.

‡ Sample drawn on third day of menstrual cycle.

§ Sample drawn on day of HCG administration.

Four women were not included in the analysis of pregnancy data because extensive tubal disease discovered during laparoscopy precluded successful tubal transfer. Also, two women (isoflurane group) were excluded because they received a gamete intrafallopian transfer procedure in addition to PROST. One of these two patients achieved a singleton ongoing pregnancy.

Table 2. Sources of Infertility Data*

	Propofol (n = 56)	Isoflurane (n = 50)
Endometriosis	14	21
Ovulatory dysfunction	16	17
Male factor	18	13
Unexplained	8	8
Maternal age	8	8
Tubal	5	3
Cervical	3	5
Uterine	2	4
Genetic	2	1
Immunologic	0	3
Hormonal	1	1
Other	0	1

* Excludes laparoscopies in which simultaneous GIFT was performed or in which tubal transfer was abandoned.

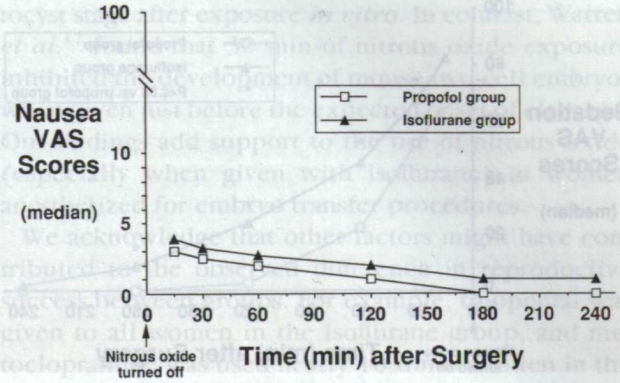

Fig. 1. Nausea visual analog scale (VAS) scores during recovery from anesthesia. Median VAS scores for nausea were low at all measurements and did not differ significantly between the two groups at any time.

The incidence of chemical pregnancies did not differ significantly between the two groups (table 4). However, the percentage of gestations with evidence of fetal cardiac activity was greater ($P = 0.023$) in the isoflurane group than in the propofol group. Also, the ongoing pregnancy rate was greater ($P = 0.014$) in the isoflurane group than in the propofol group (54% *vs.* 29%). The difference in implantation rate after PROST did not differ significantly between the two groups (table 5). If the statistical analysis is repeated without reproductive data from all rerandomized transfers, both the incidence of PROSTs resulting in fetal cardiac activity and the implantation rates differed significantly between the two groups (59% *vs.* 29% and 21% *vs.* 11%, respectively, in the isoflurane and propofol groups; tables 4 and 5).

Table 3. Postoperative Data

	Propofol (n = 57)	Isoflurane (n = 55)	*P*
Metoclopramide use (%)	4	36	<0.05
Morphine use (%)	39	36	NS
Incidence of vomiting (%)	9	25	<0.05
Time to ice chips or oral fluids (min)	95 ± 41	129 ± 80	<0.05
Time to ambulation (min)*	252 ± 42	281 ± 67	<0.05
Time to hospital discharge (min)*	270 ± 49	313 ± 89	<0.05

Continuous data are expressed as mean ± SD.

* Does not include data for four women who were not instructed to remain immobile after surgery because tubal transfer was abandoned.

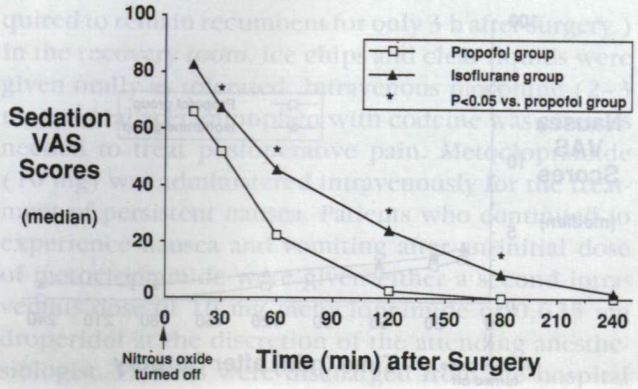

Fig. 2. Sedation visual analog scale (VAS) scores during recovery from anesthesia. Patient VAS sedation scores were lower ($P < 0.05$) in the propofol group than in the isoflurane group at all measurements between 30 min and 3 h after surgery.

Discussion

Results of laboratory studies could cause one to question the use of isoflurane anesthesia for women undergoing laparoscopic PROST.[6–8] For example, Chetkowski *et al.*[6] observed that 30 min of exposure to 1.5% isoflurane reduced the percentage of two-cell mouse embryos developing to the blastocyst stage from 79% to 44%. Despite the accumulation of laboratory data demonstrating potential embryo toxicity from isoflurane, many anesthesiologists continue to administer isoflurane to women undergoing laparoscopic PROST. (Perhaps many, like ourselves, are reluctant to abandon the use of an established anesthetic when pregnancy rates after PROST are already high in their own infertility programs.) The current findings strongly support our earlier clinical impression that isoflurane probably

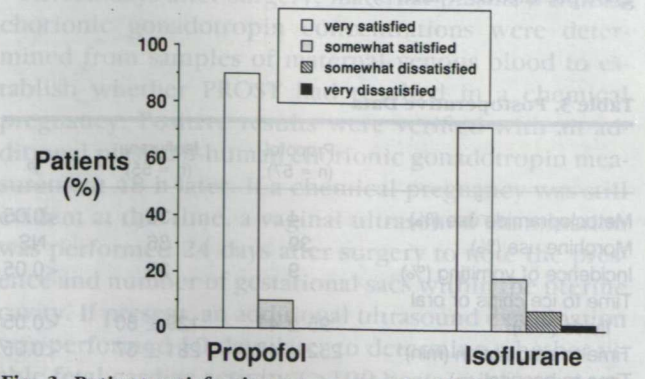

Fig. 3. Patient satisfaction responses. At discharge, patients were asked to describe their overall satisfaction with the anesthetic technique as very satisfied, somewhat satisfied, somewhat dissatisfied, or very dissatisfied. Patient satisfaction was high in both groups but was slightly higher ($P < 0.05$) in the propofol group than in the isoflurane group.

Table 4. Chemical and Ultrasound Pregnancy Data

	Propofol (n = 56)	Isoflurane (n = 50)	*P*
Chemical pregnancy data*			
Autologous cycles			
Age ≤ 39 yr	20/38 (53)	24/37 (65)	
Age ≥ 40 yr	1/8 (13)	3/4 (75)	
All	21/46 (46)	27/41 (66)	
Donor–recipient cycles	7/10 (70)	8/9 (89)	
All cycles	28/56 (50)	35/50 (70)	0.058, NS
Ultrasound-confirmed pregnancy data†‡§			
Autologous cycles			
Age ≤ 39 yr	14/38 (37)	21/37 (57)	
Age ≥ 40 yr	0/8 (0)	2/4 (50)	
All ages	14/46 (30)	23/41 (57)	
Donor–recipient cycles	3/10 (30)	4/9 (44)	
All cycles	17/56 (30)	27/50 (54)	0.023

Values in parentheses are percentages. NS = not significant.

* Determined by the presence of detectable levels of β-HCG in a sample of maternal venous blood 15 days after PROST.

† Determined by the presence of viable fetal cardiac activity (≥100 beats/min) on a vaginal ultrasound 34 days after PROST.

‡ The ongoing pregnancy rate was 27/50 (54%) in the isoflurane group *versus* 16/56 (29%) in the propofol group as of September 27, 1994 ($P = 0.014$).

§ If the analysis is restricted to one randomization per patient, the incidence of PROSTs resulting in viable fetal cardiac activity was 15/52 (29%) in the propofol group and 27/46 (59%) in the isoflurane group ($P = 0.006$). Also, the ongoing pregnancy rate was 14/52 (27%) and 27/46 (59%) in the propofol and isoflurane groups, respectively ($P = 0.003$).

Table 5. Implantation Data*

	Propofol	Isoflurane	*P*
Autologous cycles			
Age ≤ 39 yr	22/145 (15)	27/141 (19)	
Age ≥ 40 yr	0/28 (0)	3/16 (19)	
All	22/173 (13)	30/157 (19)	
Donor–recipient cycles	4/45 (9)	7/37 (19)	
All cycles†‡	26/218 (12)	37/194 (19)	0.061, NS

Values in parentheses are percentages.

* Successful implantation was defined as the presence of viable fetal cardiac activity (≥100 beats/min) 34 days after PROST.

† If the analysis is restricted to one randomization per patient, the implantation rate was 22/202 (11%) in the propofol group and 37/178 (21%) in the isoflurane group ($P = 0.012$).

‡ There were ten singleton implantations, five twin implantations, and two triplet implantations in the propofol group. In the isoflurane group, there were 19 singleton implantations, six twin implantations, and two triplet implantations.

does not exert a substantial detrimental effect on subsequent embryo development and implantation when given during PROST procedures.

There are at least two possible reasons why our results appear to contradict earlier studies of mouse embryo development after exposure to isoflurane *in vitro*. First, because embryos are transferred into the fallopian tube near the conclusion of surgery, concentrations and durations of isoflurane exposure used in laboratory studies may have substantially exceeded the exposure that occurs during PROST. Second, others have challenged the accuracy of the two-cell mouse embryo assay with regard to its ability to predict human reproductive toxicity.[11–13] However, most of these criticisms have been directed at the assay's low sensitivity not its specificity. Nevertheless, the current results suggest that the two-cell mouse embryo assay has limited clinical application with regard to anesthetic choice for laparoscopic embryo transfer procedures.

Others have reported that propofol administration to women undergoing ultrasound-guided transvaginal oocyte retrieval or gamete intrafallopian transfer does not impair reproductive success.[14–16] Although these studies involve exposure to human *oocytes* and not *embryos,* we hypothesized that pregnancy outcomes after PROST would not be adversely effected by propofol anesthesia. Unexpectedly, pregnancy rates were significantly lower in the propofol group than in the isoflurane group. A random selection bias did not appear to have produced this difference because the number of embryos transferred and the etiologies of infertility were similar in both groups. Ideally, one would prefer to randomize participants based upon the number of embryos transferred and each couple's specific source of infertility (*e.g.,* male factor, ovarian failure, age, immunologic, endometriosis). For pragmatic reasons, we did not stratify the randomization procedure for source(s) of infertility since this is often not apparent until the time of surgery (*i.e.,* endometriosis). Regardless of the reasons responsible for the differences in pregnancy outcomes observed in the present study, our results suggest the need for careful review of reproductive outcomes in programs that are using propofol anesthesia for PROST procedures.

The current investigation did not specifically address the controversy of nitrous oxide administration during PROST. There are conflicting data on the exposure of preimplantation embryos to nitrous oxide. Chetkowski *et al.*[6] reported that nitrous oxide had no effect on the development of mouse two-cell embryos to the blastocyst stage after exposure *in vitro*. In contrast, Warren *et al.*[17] found that 30 min of nitrous oxide exposure inhibited the development of mouse two-cell embryos when given just before the expected onset of cleavage. Our findings add support to the use of nitrous oxide (especially when given with isoflurane) in women anesthetized for embryo transfer procedures.

We acknowledge that other factors might have contributed to the observed difference in reproductive success between groups. For example, thiopental was given to all women in the isoflurane group, and metoclopramide was used nearly 10 times as often in the isoflurane group as in the propofol group. Although we find it unlikely that any anesthetic drug increases the probability of reproductive success after PROST, we cannot exclude this possibility. Also, women in the propofol group ambulated sooner than their counterparts in the isoflurane group. It is conceivable that premature ambulation in the propofol group led to extratubular embryo migration.

We observed that patients in the isoflurane group were more likely to experience emesis and receive metoclopramide than were women in the propofol group. However, nausea measurements did not differ significantly between the two groups at any time, and no patient required overnight admission for persistent nausea and vomiting. This indicates that, although women in the isoflurane group were more likely to have emesis, their symptoms often resolved rapidly—either spontaneously or in response to metoclopramide. Exogenous hormonal stimulation may have contributed to the lack of severe, persistent nausea in the current study. Beattie *et al.*[18] observed that perioperative nausea and vomiting were less likely among women who were not close to their time of menstrual bleeding compared to women who were perimenstrual (*i.e.,* cycle days 25 through 4). All women in the current study were in the periovulatory phase (*i.e.,* cycle days 12–16) of their menstrual cycle as a result of exogenous hormonal stimulation to induce superovulation. Thus, intractable postoperative nausea requiring overnight admission is not a likely event after laparoscopic PROST with either isoflurane or propofol anesthesia.

In summary, women who received propofol/nitrous oxide anesthesia had less postoperative sedation and vomiting than similar women given isoflurane/nitrous oxide anesthesia for PROST. However, the clinical and ongoing pregnancy rates after isoflurane/nitrous oxide anesthesia were higher than those after propofol/nitrous oxide anesthesia. Hence, the marginal benefits of

propofol anesthesia on postoperative recovery appear trivial given the possibility that propofol unfavorably affects the probability of achieving pregnancy after PROST. These results have prompted us to suspend the use of propofol anesthesia for laparoscopic PROST procedures until the effects of propofol on human preimplantation embryos are better understood.

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