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The Use of Propofol, Nitrous Oxide, or Isoflurane Does Not Affect the Reproductive Success Rate following Gamete Intrafallopian Transfer (GIFT)

A Multicenter Pilot Trial/Survey

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Backround: **Whether anesthetic agents administered during gamete intrafallopian transfer (GIFT) affect reproductive outcome is controversial. This multicenter pilot trial and survey had two purposes: to evaluate the effect of propofol, nitrous oxide, midazolam, and isoflurane on pregnancy outcome after GIFT, and to determine if a larger prospective, randomized study is warranted.**

Methods: **A written invitation was mailed to all 50 fertility programs in the United States that are members of the Society for Assisted Reproductive Technology and perform more than 30 GIFT procedures per year. They were invited to contribute information from the medical records of women who underwent GIFT during the calendar years 1993 and 1994. They were asked to document whether propofol, nitrous oxide, midazolam, a potent inhaled anesthetic agent was used during the GIFT procedure; if the woman became pregnant; and if she delivered at least one live neonate.**

Results: **Seven medical centers participated and contributed data from 455 women. The clinical pregnancy rate (number of pregnancies/total number of GIFT procedures) and the delivery rate (number of women who delivered at least one live baby/total number of GIFT procedures) were 35% and 32%, respectively. A statistically significant difference could not be found in the clinical pregnancy or delivery rates between those women who received propofol, nitrous oxide, midazolam, or isoflurane during GIFT and those who did not.**

Conclusions: **No agent-related differences in pregnancy rates were found when propofol, nitrous oxide, isoflurane, or midazolam was used as part of the anesthetic technique for GIFT. Therefore, a more extensive prospective trial does not appear to be warranted. (Key words: Anesthesia; assisted reproductive technique; complications; infertility; obstetrics; outcome.)**

GAMETE intrafallopian transfer (GIFT) is a type of assisted reproductive technique that is usually performed laparoscopically under general anesthesia. Whether the anesthetic drugs administered during the procedure, particularly propofol, nitrous oxide, and the potent inhaled agents affect the success rate is controversial.[1–5] Reported studies are inconclusive because they either had a small study population[2–5] or did not control for possible confounding factors such as patient age or duration of the procedure.[2,4,5] Furthermore, all of the published reports have been from individual hospitals; none were multicentered. Differences in GIFT technique or patient selection among fertility centers may make the conclusions from one center inapplicable to others. The purpose of this multicenter retrospective pilot trial and survey was to assess the effect, if any, of propofol, nitrous oxide, midazolam, and the potent inhaled anesthetic agents on reproductive success after GIFT, and to determine if a larger prospective, randomized study is warranted.

Materials and Methods

The Society for Assisted Reproductive Technology (Birmingham, AL) approved the protocol and gave us a mailing list of all 50 fertility programs that are its members and reportedly performed more than 30 GIFT procedures annually in 1993 and 1994. A written invitation to participate in this multicenter survey study, together with a description and purpose of the study and the survey forms, was sent to each fertility program. The letter requested that the addressee programs give the cover letter and the forms to an investigator who agreed to participate. Approval of the protocol was also obtained from the institutional review board of the Mount Sinai School of Medicine. Each investigator who agreed to participate also obtained approval from their own institutional review board.

Each investigator was asked to collect data from the medical records of all women who underwent GIFT procedures during the calendar years 1993 and 1994. Data collected included patient age, duration of the procedure (the time from entering the operating room until transfer to the postanesthesia care unit), number of oocytes transferred, and outcome with regard to clinical pregnancy and delivery. Clinical pregnancy was defined as the presence of a fetal sac as shown by ultrasonography approximately 21 days after the procedure, and delivery was defined as a pregnancy that resulted in at least one live birth. The data from six fertility centers, along with the anesthesia records (from which patient name and other identifying factors had been removed) were mailed to one investigator (Dr. Beilin) for review and analysis. The anesthesia records from the seventh fertility center were reviewed by a separate investigator (Dr. Vincent), and those data were sent to Dr. Beilin to be included in the analyses.

The anesthesia data collected included the use of propofol (in milligrams), midazolam (in milligrams), nitrous oxide (≥50%), or a potent inhaled anesthetic agent (≥0.3%), and the duration of the procedure. When nitrous oxide, a potent inhaled anesthetic agent, or both were used, generally they were used throughout the procedure.

Gamete Intrafallopian Transfer Technique

Because this was a retrospective chart review study, we could not standardize the GIFT technique. However, after the data had been collected, the investigators at each center provided written descriptions of how the GIFT procedure was performed at their centers. Except for the method of oocyte collection, the GIFT procedure was similar at all participating fertility centers. Ovaries were stimulated with clomiphene citrate alone or in combination with human menopausal gonadotrophin. Ovarian response was monitored by serial ultrasonography and serum estradiol measurements. Once established criteria for follicular maturity had been fulfilled, ovulation was triggered using human chorionic gonadotrophin. Oocytes were collected either laparoscopically (at five centers, n = 354) after creation of a pneumoperitoneum or *via* ultrasound-guided follicular aspiration (at two centers, n = 79). Oocytes and motile sperm were transferred laparoscopically into the fallopian tube. Clinical pregnancy was diagnosed by urine or serum human chorionic gonadotrophin tests and monitored by ultrasonography.

Anesthetic Technique

All GIFT procedures were performed under general anesthesia that was induced with either thiopental or propofol. After administration of a muscle relaxant, the trachea was intubated. Anesthesia was maintained with one or some combination of the following agents in oxygen: propofol, nitrous oxide, a potent inhaled anesthetic agent, fentanyl, and midazolam. All patients received a nondepolarizing muscle relaxant, and at the end of the procedure, residual relaxation was reversed when indicated and the trachea extubated.

Table 1. Number of GIFT Trials and the Clinical Pregnancy and Delivery Rates by Medical Center

Medical Center	Total GIFT	Number of Missing Anesthesia Records	Total in Database	Clinical Pregnancy Rate (%)	Delivery Rate (%)
1	54	5	49	20	19
2	113	0	113	43	41
3	66	6	60	36	33
4	69	11	58	49	42
5	10	0	10	61	50
6	62	0	62	Missing	33
7	81	0	81	17	15
Total	455	22	433	35*	32†

GIFT = gamete intrafallopian transfer; Clinical Pregnancy Rate = number of women who became pregnant / total number of GIFT procedures; Delivery Rate = Number of women who delivered at least one live child / total number of GIFT procedures.

* Based on 371 cases.

† Based on 433 cases.

Data Handling and Statistical Analyses

Data were entered into an Excel database (Microsoft®; Redmond, WA), and converted to a SAS file[6] for analysis. Patient age, procedure duration, and use of anesthetic agents among fertility centers were compared by analysis of variance or the chi-squared test, as appropriate. Each anesthetic agent was considered initially as a binary variable (*i.e.*, either used or not used), and the possible effect of its use or nonuse on the clinical pregnancy rate (number of pregnancies/total number of GIFT procedures) and on the delivery rate (number of women who delivered at least one live neonate/total number of GIFT procedures) was sought using Mantel-Haenszel tests, in which the data were stratified by fertility center.

The delivery rates were analyzed further by introducing age, duration of procedure, and the anesthetic agents into logistic regression analyses while controlling for differences in overall success rates among institutions. This was accomplished by including variables for the institutions in the logistic model. Thus, the logistic regression analyses provide estimates of the odds ratio (relative chance of success) when the anesthetic agent was used *versus* with when it was not used, after accounting for differences among institutions in patient age, duration of procedure, and overall success rates. $P < 0.05$ was considered significant.

Results

Seven of 50 fertility programs invited to participate provided data, representing 455 GIFT procedures. The overall clinical pregnancy rate was 35% and the delivery rate was 32%, but these rates varied considerably among fertility centers (table 1).

Table 2 shows mean patient age, duration of the procedure, and the median number of oocytes transferred at the time of GIFT. Table 3 lists the anesthetic agents used by the medical centers. When propofol and midazolam were used, the minimum total dose was 100 and 1 mg, respectively. For all of the tested parameters (patient age, duration of the procedure, pregnancy and delivery rates, and type of anesthetic used), there was at least one center that differed significantly from the others (by analysis of variance and the chi-squared test, $P < 0.05$).

We could not detect a significant effect resulting from the use of propofol, nitrous oxide, midazolam, isoflurane, or any potent inhaled anesthetic agent, or from the duration of the procedure on the clinical pregnancy or

Table 2. Mean Patient Age, Duration of Procedure, and Number of Oocytes Placed during GIFT, by Center

Medical Center	Age (yr)*	Duration (min)*	Number of Oocytes Placed†
1	32.9 ± 4.7	146.8 ± 36.2	4 (2–9)
2	32.9 ± 4.5	67.1 ± 12.2	5 (2–5)
3	36.2 ± 4.3	88 ± 19.1	6 (4–13)
4	34.9 ± 3.9	Missing	7 (4–12)
5	31.6 ± 3.7	138 ± 17.6	4 (3–6)
6	35.8 ± 4.0	99.8 ± 31.0	5 (2–18)
7	33.4 ± 4.2	109.7 ± 57.4	4 (3–7)
Total	34.1 ± 4.3	97.4 ± 42.7	5 (2–18)

GIFT = gamete intrafallopian transfer.

* Mean ± SD.

† Median (range).

Table 3. The Number (%) of Women Who Received Propofol, N_2O, Midazolam, and Potent Inhaled Anesthetic Agents by Center

Center	n	Propofol	N_2O	Isoflurane	Desflurane	Enflurane	Midazolam
1	49	19 (39)	23 (47)	36 (74)	2 (4)	0	40 (82)
2	113	108 (96)	69 (61)	36 (32)	44 (39)	11 (10)	21 (17)
3	60	44 (73)	56 (93)	44 (73)	0	5 (10)	40 (67)
4	58	50 (86)	0	55 (95)	2 (3)	0	38 (66)
5	10	2 (20)	10 (100)	8 (80)	0	0	10 (80)
6	62	27 (43)	9 (15)	31 (50)	14 (23)	15 (24)	4 (7)
7	81	80 (99)	5 (6)	0	0	0	80 (99)
Total	433	330 (76)	172 (40)	210 (48)	70 (16)	24 (6)	233 (54)

delivery rates (table 4). Although the delivery rate was less than the clinical pregnancy rate, we found no evidence that the magnitude of the difference was related to the use of any anesthetic agent. Table 5 shows the results of the logistic regression analysis that included the effects on the odds of delivery of all the anesthetic agents, the age of the patient, and factors for the individual fertility center. Only patient age was significantly associated with delivery ($P = 0.003$).

Discussion

The effects of anesthetic agents on pregnancy outcome when GIFT is performed under general anesthesia are controversial. We did not find a negative influence of propofol, nitrous oxide, midazolam, or isoflurane on the clinical pregnancy or delivery rates, regardless of whether patient age and procedure duration were considered in the analyses.

In some fertility programs, oocytes are collected laparoscopically and at others they are collected transvaginally. There is no evidence that the collection technique used affects the clinical pregnancy or delivery rates.[7] The GIFT technique has not changed substantially since 1994, except that fewer centers are performing GIFT because the pregnancy success rate for *in vitro* fertilization is greater than that after GIFT. A limitation of our study is our low center response rate. We must also be careful not to draw any definitive conclusions about pregnancy outcome from a retrospective survey study.

Because we collected only the anesthesia record for each patient, rather than the entire medical record, we could not evaluate the effects of other drugs commonly administered in the post anesthesia care unit (*e.g.*, antiemetic agents) on pregnancy outcome. In addition, because patients commonly receive an opioid in the post-anesthesia care unit, we did not try to assess the effect of intraoperative opioid use on pregnancy outcome.

We did not analyze the effect of each anesthetic agent on pregnancy rates by fertility center because there were too few patients in each center to justify such analysis. However, the trend at most centers was that individual anesthetic agents did not affect pregnancy rates (table 4).

Since 1987, the effects of general anesthesia (not the specific agent) on pregnancy outcome after assisted reproductive technology have been disputed. Boyers *et*

Table 4. Delivery Rate (%) by Anesthetic Use*

Fertility Center	Propofol	No Propofol	N_2O	No N_2O	Isoflurane	No Agent	Midazolam	No Midazolam
1	21	20	22	19	17	36	20	22
2	41	40	39	43	44	27	43	37
3	32	44	35	40	34	20	33	40
4	42	25	N/A	41	42	0	34	50
5	50	50	50	N/A	43	50	50	0
6	42	28	44	33	26	0	0	37
7	15	0	0	16	N/A	15	15	0
Total	33	30	35	30	34	20	25	40

N/A = not applicable.

* Delivery rate = number of women who delivered at least one live child / total number of GIFT procedures. Refer to table 4 for the denominators.

Table 5. Estimates of the Influence of Anesthetic Agents on Delivery Rate from Multiple Logistic Regression Analysis

Variable	Adjusted Odds Ratio*	95% Confidence Interval
Propofol	1.33	0.72–2.47
N_2O	1.03	0.56–1.92
Isoflurane	1.45	0.68–3.07
Enflurane or desflurane	2.11	0.94–4.76
Midazolam	0.76	0.43–1.34
Age†	0.92	0.87–0.97

* Odds ratio for each agent is relative to those who did not receive the agent.
† Odds ratio is for each additional year of life.

al.[8] and Hayes *et al.*[9] compared the *in vitro* fertilization and cleavage rates of the first and last preovulatory human oocytes collected laparoscopically under general anesthesia and reported that the last oocytes collected were fertilized less often than the first oocytes collected. However, the carbon dioxide required to produce the pneumoperitoneum may have adversely affected the oocytes.[10] Because we only evaluated women who underwent GIFT under general anesthesia, we cannot draw any conclusions, based on our results, about the effect of general anesthesia on pregnancy outcome.

Several studies have reported that halothane used during assisted reproductive technology has a negative effect on success rate,[11,12] but we are not aware of any study that has evaluated isoflurane. Our finding that nitrous oxide using during GIFT does not have a deleterious effect on pregnancy and delivery rates is consistent with the results of a study by Rosen *et al.*[13] In a prospective, randomized study of women undergoing ovum retrieval, these authors found no difference in the fertilization rates between those who received nitrous oxide and those who did not.

We are not aware of any human clinical studies that have evaluated midazolam or any of the benzodiazepine drugs for an effect on pregnancy outcome, although one laboratory study in mice failed to find a negative influence of midazolam on pregnancy outcome.[14] We did not find any significant influence of midazolam on pregnancy outcome. However, the results of the logistic regression analysis revealed that the adjusted odds ratio for the effect of midazolam on pregnancy outcome was 0.8, and the 95% confidence interval was 0.4 to 1.3. These results suggest that it is possible that, if we had more patients in the study, we might have found a negative effect on pregnancy outcome with midazolam. Additional clinical studies are needed before firm recommendations can be made about the use of midazolam during GIFT.

The use of propofol anesthesia for assisted reproductive technology and its possible effect on pregnancy outcome have probably generated more controversy than the use of any other anesthetic agent. Imoedemhe *et al.*[2] found that propofol, when administered as part of an anesthetic regimen, accumulates in the follicular fluid during oocyte retrieval, but they did not find any negative effect on pregnancy rate. Three other clinical studies have evaluated the effect of propofol on outcome during assisted reproductive technology. Pierce *et al.*[1] did not find any effect of propofol *versus* thiopental when administered for induction of anesthesia for GIFT, and Rosenblatt *et al.*[15] did not find any deleterious effect of propofol on the clinical pregnancy rate during embryo transfer with donor oocytes. In contrast to these findings, Vincent *et al.*[3] found that propofol had a negative effect on pregnancy rate after laparoscopic pronuclear stage transfer. A difference between the results of our and other studies[1,15] that did not find a negative effect of propofol, and those of Vincent *et al.*[3] is that Vincent and colleagues evaluated the effect of propofol on embryos, but the other studies evaluated the effect of propofol on oocytes.

Consistent with the results of other studies, we found that increasing maternal age was associated with a decreasing pregnancy rate.[16] Unlike the results of other studies, the duration of the procedure did not significantly influence pregnancy outcome.[9] However, it is possible that in the study by Hayes *et al.*[9] the carbon dioxide from the pneumoperitoneum, rather than the duration of the procedure, may have caused the decrease in the success rate.

Whenever a study fails to find a statistically significant effect, it is important to consider whether this may be a false-negative finding resulting from an inadequate sample size. In this study, with the exception of midazolam, the adjusted odds ratios for pregnancy and for the delivery rates associated with each of the anesthetic agents is close to 1.0, and their 95% confidence intervals are relatively narrow (table 5). Furthermore, the span of the confidence intervals tends to be more than 1.0. It is therefore unlikely that a larger patient sample size would alter our findings. For example, the adjusted odds ratio for delivery attributable to the use of propofol is 1.3 with the 95% confidence interval (0.7 to 2.3). Analysis of data from a larger patient sample would likely produce a more narrow confidence interval; but all other things being equal, it would be unlikely to show a significant

negative influence of propofol, because that would require an interval with both lower and upper bounds less than 1.0. For midazolam, however, it is possible that a larger patient sample might show a negative influence on pregnancy rate because the confidence intervals tend to be less than 1.0.

Any definitive conclusion that we can draw is limited by the low response rate and retrospective nature of the study, but we could not find any suggestion of an agent-related difference in pregnancy or delivery rates when propofol, nitrous oxide, or isoflurane were used as part of the anesthetic technique for GIFT. We have no reason to believe that a more extensive prospective trial is warranted.

References

1. Pierce ET, Smalky M, Alper MM, Hunter JA, Amrhein RL, Pierce EC: Comparison of pregnancy rates following gamete intrafallopian transfer (GIFT) under general anesthesia with thiopental sodium or propofol. J Clin Anesth 1992; 4:394–8

2. Imoedemhe DAG, Sigue AB, Ghani IA, Abozeid MA, Halim MSA: An evaluation of the effect of the anesthetic agent propofol (Diprivan) on the outcome of human *in vitro* fertilization. J Assist Reprod Genet 1992; 9:488–91

3. Vincent RD, Syrop CH, Van Voorhis BJ, Chestnut DH, Sparks AET, McGrath JM, Choi WW, Bates JN, Penning DH: An evaluation of the effect of anesthetic technique on reproductive success after laparoscopic pronuclear stage transfer. ANESTHESIOLOGY 1995; 82:352–8

4. Rosen MA, Roizen MF, Eger II EI, Glass RH, Martin M, Dandekar PV, Dailey PA, Lawrence L: The effect of nitrous oxide on *in vitro* fertilization success rate. ANESTHESIOLOGY 1987; 67:42–4

5. Critchlow BM, Ibrahim Z, Pollard BJ: General anaesthesia for gamete intra-fallopian transfer. Euro J Anaesth 1991; 8:381–4

6. SAS Institute. SAS User's Guide. Cary, NC, SAS Institute, 1985

7. Lewin A, Margalioth EJ, Rabinowitz R, Schenker JG: Comparative study of ultrasonically guided percutaneous aspiration with local anesthesia and laparoscopic aspiration of follicles in an in vitro fertilization program. Am J Obstet Gynecol 1985; 151:621–5

8. Boyers SP, Lavy G, Russell JB, DeCherney AH: A paired analysis of *in vitro* fertilization and cleavage rates of first—versus last—recovered preovulatory human oocytes exposed to varying intervals of 100% CO_2 pneumoperitoneum and general anesthesia. Fertil Steril 1987; 48:969–74

9. Hayes MD, Sacco AG, Savoy-Moore RT, Magyar DM, Endler GC, Moghissi KS: Effect of general anesthesia on fertilization and cleavage of human oocytes *in vitro*. Fertil Steril 1987; 48:975–81

10. Botta G, D'Angelo A, D'Ari G, Merlino G, Chapman M, Grudzinskas G: Epidural anesthesia in an *in vitro* fertilization and embryo transfer program. J Assist Reprod Genet 1995; 12:187–90

11. Fishel S, Webster J, Faratian B, Jackson P: General anesthesia for intrauterine placement of human conceptuses after *in vitro* fertilization. J In Vitro Fert Embryo Transf 1987; 4:260–4

12. Critchlow BM, Ibrahim Z, Pollard BJ: General anaesthesia for gamete intra-fallopian transfer. Eur J Anaesth 1991; 8:381–4

13. Rosen MA, Roizen MF, Eger EI II, Glass RH, Martin M, Dandekar PV, Dailey PA, Litt L: The effect of nitrous oxide on *in vitro* fertilization success rate. ANESTHESIOLOGY 1987; 67:42–4

14. Swanson RF, Leavitt MG: Fertilization and mouse embryo development in the presence of midazolam. Anesth Analg 1992; 75:549–54

15. Rosenblatt MA, Bradford CN, Bodian CA, Grunfeld L: The effect of a propofol-based sedation technique on cumulative embryo scores, clinical pregnancy rates, and implantation rates in patients undergoing embryo transfer with donor oocytes. J Clin Anesth 1997; 9:614–7

16. Borin A, Bianchi L, Violini F, Maccolini A, Cattoli M, Flamigni C: Oocyte donation program: Pregnancy and implantation rates in women of different ages sharing oocytes from a single donor. Fertil Steril 1996; 65:94–7