Anesthetic management for oocyte retrieval: An exploratory analysis comparing outcome in *in vitro* fertilization cycles with and without pre-implantation genetic diagnosis

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ABSTRACT

PURPOSE: To date, there has been no comparison of outcomes in women undergoing anesthesia for *in vitro* fertilization (IVF) oocyte retrieval for the purpose of pre-implantation genetic diagnosis (PGD) because of their or their partner's genetic disease relative to the outcome in women requiring IVF because of fertility issues. **MATERIALS AND METHODS:** A prospective observational study, wherein all demographic and anesthetic management data were collected from IVF and PGD units' records for a 6-month period. Descriptive analyses and parametric tests were employed. **RESULTS:** There were 307 cases IVF and 76 cases PGD: most (97.4% and 99.7%, respectively) received general anesthesia with propofol and fentanyl ± dipyrone (90.5% and 93.3%, respectively) with no adverse effects. The only statistically significant difference between IVF and PGD groups that was potentially clinically significant was post-procedure recovery time (23.0 ± 20.4 vs. 29.4 ± 35.8 min, respectively; $P < 0.0001$), but is explainable as greater caution by Anesthesiologists for higher-risk PGD cases having autosomal dominant diseases that may impact anesthesia management (myotonic dystrophy, neurofibromatosis, Marfan's); two of these cases also recovered in the general post-anesthesia care unit, as a precaution for early diagnosis and treatment of potential post-procedural complication. **CONCLUSIONS:** Results of this first-ever survey of anesthesia for PGD compared with IVF cases imply that propofol-and-fentanyl-based anesthesia is safe and can be recommended, bearing in mind that with patients who have autosomal dominant diseases impacting anesthetic management it is prudent to be more cautious post-recovery.

KEY WORDS: Autosomal dominant diseases, general anesthesia, *in vitro* fertilization, maternal outcome, neonatal outcome, pre-implantation genetic diagnosis, recovery time

INTRODUCTION

Assisted reproductive technologies offer the opportunity for couples at risk of having babies with genetic abnormalities to circumvent the trauma of (potentially many) pregnancies with adverse outcomes. Pre-implantation genetic diagnosis (PGD) is a process of identifying embryos that do not have the genetic defect of the parent(s) that would lead to an affected child;[1] these couples do not necessarily have a fertility problem.

In vitro fertilization (IVF) was developed primarily for couples with infertility issues to maximize the possibility of a viable pregnancy. IVF, whether for the purpose of PGD or infertility, entails many stages of which the step of (trans-vaginal) follicular aspiration and oocyte retrieval is among the most delicate technically. The cumulative live-birth rate per woman is about 50% although rates in PGD are often lower.[2]

Anesthesia/analgesia for the oocyte retrieval procedure is required, but should be of minimal duration so as preclude impacting optimal oocyte and embryo quality. Early experience with general anesthesia, in particular nitrous oxide, appeared to be correlated with adverse effects on rates of

pregnancy and live-births.[3] A decade later, propofol and remifentanil were recommended[4] as acceptable options, preferably by intravenous administration.[5] A relatively recent metaanalysis of studies regarding types of anesthesia for oocyte retrieval showed that conscious sedation was easy to administer and safe for the mother, as well as being the best option for preserving embryo quality;[6] a combination of propofol, fentanyl, and midazolam has been popular.[6]

To date, there has been no comparison of outcomes in women undergoing anesthesia for IVF oocyte retrieval for the purpose of PGD relative to that in women requiring IVF for fertility issues. The objective of the current prospective observation study is to evaluate maternal outcomes after anesthesia for IVF in a large cohort of women from a single tertiary-care institution with its own IVF and PGD Units. The underlying objective is to evaluate whether women with concurrent diseases for which PGD is required will have a different outcome than otherwise healthy women requiring IVF because of infertility.

MATERIALS ANDMETHODS

This is a prospective observational study, wherein all demographic data and specifics regarding anesthetic management were collected from the medical records of the IVF Unit and PGD Unit, respectively.

All women who underwent IVF and PGD at our institution from 01 November 2010 to 01 May 2011 (6 months) were included.

The reason for infertility in the IVF cases and diagnosis of a genetic condition for the PGD cases were noted as were any other associated diseases (chronic or intercurrent). Age, body weight, body mass index (BMI), as well as hemoglobin, platelet counts, coagulation profile International normalized ratio (INR) and other relevant lab tests were available. Type and duration of anesthesia, all other medications taken at the time of surgery and anesthetic outcomes were collected as recorded in real-time. Previous pregnancy histories and previous IVF treatment were collected from the patient files.

Statistical analysis

The descriptive tests and the Student's *t*-test and Fisher's exact test were employed. All tests were two-tailed and 5% was pre-designated statistically significant.

RESULTS

There were 307 cycles of IVF in 261 women and 76 cycles of PGD in 52 women during the study period. Table 1 presents the demographic characteristics of the two groups. The only statistically significant differences between groups was in mean ages (older in the IVF group) and in INR (prothrombin time test), which is not considered to be clinically significant.

The reason for IVF included female infertility in 69.4% and male-only infertility in the remainder.

Among the PGD group, there were 9 cycles (in 6 women) that were considered to be higher anesthetic risk because of autosomal dominant diseases that could effect administration of anesthesia. These were: 4 cycles (in 3 women) with myotonic dystrophy, 4 cycles (in 2 women) with neurofibromatosis type 1; and one cycle in one woman with Marfan's syndrome. There was also a single cycle in a woman with Marfan's syndrome among the IVF cycles who did not perform PGD since the female was heterozygote for two different mutations on both alleles of the FBN1 gene. The other PGD cycles, which were not considered at increased anesthesia risk were due to: Autosomal dominant female carriers (5, all carriers of BRCA mutations); autosomal dominant diseases in males (13); autosomal recessive carriers (26 couples); females carriers of an X-linked disease (14); male carrier of an X-linked disease (1); translocations in the female (1); translocations in the male (4); and a female mosaic (1).

The most common co-morbidities found in women in both cohorts were hypothyroidism, and obesity, the percentages of which were not statistically different between groups [Table 1].

Approximately half the women in the IVF group had previous pregnancies: Half of these were spontaneous and the other half was by IVF. More than 75% of the women in the PGD group had previous pregnancies: 50% had spontaneous pregnancies where most of the fetuses/babies were affected and/or died and the other 25% had undergone PGD previously [Table 1].

Table 2 presents data regarding the use of anesthesia for oocyte retrieval in both cohorts. Anesthetic management was comparable in the two cohorts. Mean anesthesia times were nearly identical and <25 min. Mean procedure times were comparable and <17 min in each group.

The most commonly used combination for anesthesia during oocyte retrieval was propofol plus fentanyl plus dipyrone (and sometimes a fourth drug like lidocaine). The most commonly used analgesics for post-procedure pain in both groups were dipyrone and paracetamol. There were no apparent differences among the groups for anesthetic management pre- and post-procedure other than spinal anesthesia for two PGD patients with clinically significant symptoms of myotonic dystrophy, whereas in the IVF group no patient underwent spinal anesthesia.

Table 1: Demographic characteristics of the two cohorts and comparison for statistical significance

	IVF	PGD	*P* value
Total number women	261	52	
Total number cycles	307	76	
Mean±SD age (years)	34.1±6.2 (18-45)	30.2±4.9 (19-41)	0.0181
Mean±SD weight (kg)	66.6±13.5 (43-110)	65.5±12.2 (40-98)	NS
Mean±SD BMI	24.8±4.7 (17-38)	24.9±4.1 (17-40)	NS
Mean±SD hemoglobin (g/dL)	12.8±1.0 (9.5-14.9)	12.7±1.0 (9.4-15.1)	NS
Mean±SD platelets ($\times 10^3/mm^3$)	258.6±63.8 (129-485)	261.9±68.3 (42-483)	NS
Mean±SD INR	1.01±0.09 (0.80-1.40)	1.02±0.11 (0.87-1.48)	0.0181
Male issues for procedure (%)	94 (30.6)	11 (14.5)	
Co-morbidity: All (%)	103 (33.6)	19 (25)	
Co-morbidity: Hypothyroid (%)	26 (25.2)	6 (31.6)	
Co-morbidity: Obesity (%)	15 (15.6)	4 (21.1)	
Previous spontaneous pregnancies (%)	82 (26.7) 1-5 pregnancies	38 (50) 1-6 pregnancies*	
Previous IVF/PGD pregnancies (%)	72 (23.5) 1-6 pregnancies	21 (27.6) 1-4 pregnancies	NS
Mean±SD previous IVF/PGD	3.08±2.15	3.12±2.32	NS

*Most with dead or affected babies. SD=Standard deviation; NS=Not significant using Fisher's exact test; IVF=*In vitro* fertilization; PGD=Pre-implantation genetic diagnosis; INR=International normalized ratio; BMI=Body mass index

Table 2: Description of data related to anesthesia of the two cohorts and comparison for statistical significance

	IVF	PGD	*P* value
Number	307	76	
Prior anesthesia consultation (%)	307 (100)	76 (100)	NS
Standard monitoring (%)	307 (100)	76 (100)	NS
Anesthesia: General (%)	306 (99.7)	74 (97.4)	NS
Anesthesia: Spinal (%)	1 (0.3)	2 (2.6)	NS
Anesthesia medications: Propofol only (%)	1 (0.3)	1 (1.3)	NS
Anesthesia medications: Fentanyl only (%)	2 (0.6)	0	NS
Anesthesia medications: Propofol and fentanyl (%)	61 (19.9)	15 (19.7)	NS
Anesthesia medications: Propofol and fentanyl and dipyrone (±others)	159/243 (65.4)	41/60 (68.3)	NS
Mean±SD time anesthesia (min)	23.5±7.8 (10-50)	23.7±7.3 (12-43)	NS
Mean±SD procedure time (min)	15.6±6.2 (5-38)	16.1±7.1 (5-35)	NS
Mean±SD recovery time (min)	23.0±20.4 (20-240)	29.4±35.8 (20-270)	<0.0001
Unusual anesthesia	0	0	
Extra anesthesia	0	0	
Recovery in general PACU (%)	0	2 (2.6)	
Analgesia during recovery for pain (dipyrone/paracetamol/other) (%)	63 (20.5)	15 (19.7)	NS
Complications during recovery	0	1 (1.3%)…fainted	NS

SD=Standard deviation; NS=Not significant using Fisher's exact test; General PACU=General post-anesthesia care unit; IVF=*In vitro* fertilization; PGD=Pre-implantation genetic diagnosis

The only statistically significant difference between the IVF and PGD groups was in mean post-procedure recovery time, which was more prolonged for the PGD group; although, mean times were <30 min in both groups.

When the PGD group was further analyzed, comparing the cases of autosomal dominant who are considered to be at higher anesthesia risk because of the impact of diseases on their physical condition compared with the other PGD cases, there was an apparent difference in the length of the procedure time (16.5 ± 7.1; range 5-35 min vs. 13.9 ± 7.1; range 5-28 min) as well as in recovery times (35.8 ± 29.6; range: 20-120 min vs. 28.5 ± 25; range: 20-270 min), but sample sizes were too small for statistical power. Similarly, the only two patients (among both groups) who were transferred to the general post-anesthesia care unit were two women, each with an autosomal dominant disease.

DISCUSSION

This is the first survey comparing the use of anesthesia for oocyte retrieval in women whose reason for IVF was primarily because of infertility (male or female) compared with women undergoing PGD/IVF because of carriership/existence of a genetic disease (male or female).

The data show that in our institution there was no statistically significant difference between these groups with regard to the demographics and/or the use and outcome of anesthesia except for a prolonged post-procedure recovery time on average among women who had undergone PGD;

this is explained in large measure because of a few cases with autosomal dominant diseases.

Comparable percentages of women in both groups who underwent general anesthesia received comparable drug combinations and the same excellent safety profile was seen in both cohorts.

As noted in the literature, for oocyte retrieval there is a preference for general anesthesia with a combination of propofol, fentanyl and midazolam, which induces conscious sedation;[6] however, our team uses dipyrone as the third component in the drug combination, which is approved in Israel and Europe, but not approved by the American Food and Drug Administration. Beyond this unavoidable limitation in choice of a drug, our results with standard general anesthesia highlight good outcome. Moreover, even the addition of dipyrone is not necessarily seen as a requisite to good sedation, and as such, the classic duet of propofol and fentanyl is equally effective in our hands for oocyte retrieval.

Our explanation for the putatively prolonged procedure and post-procedure recovery times for the PGD group was because of skewing due to the extra care taken with nine cases of women with autosomal dominant diseases that made them higher risk for anesthetic management. Our team of Anesthesiologists were more cautious with this cohort and allowed them more time under supervision.

It had been the objective of this survey to ascertain whether the existence of diseases in the woman, especially those affecting the skeleton and cardiovascular systems such as myotonic dystrophy and Marfan's syndrome, would impact the safety of anesthesia outcome in the PGD group compared with the IVF group. This is especially cogent because even in the case of such co-morbidities as obesity,[7] which may affect the administration of anesthesia, the cohorts were not significantly different: Thus the single important variable was the carrier status or existence of a genetic disease in the PGD cohort. Although PGD itself is fraught with technical complexities,[8] it is not clear if the fact that underlying diseases in many of the women who apply for PGD induces a greater risk for the actual procedure of IVF than in healthy women. Thus, with regard to the anesthetic management, women needing PGD seem to fare as well as otherwise healthy (albeit infertile) women. This was further corroborated when comparing women who suffered from diseases potentially impacting anesthesia administrations (9 cycles) relative to women who were either carriers or partners of carriers of recessive or other genetic diseases (67 cycles).[9,10]

CONCLUSION

The results of this first-ever survey of anesthesia for PGD cycles versus IVF cycles imply that standard anesthetic procedures are safe and can be recommended bearing in mind that with patients who have autosomal diseases that impact systemic management it is prudent to be more cautious in the peri-procedural period.

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