# Patients with Recurrent Pregnancy Loss Have Similar Embryonic Preimplantation Genetic Testing Aneuploidy Rates and In Vitro Fertilization Outcomes to Infertility Patients

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**Objective:** To evaluate aneuploidy rates and in vitro fertilization (IVF)/pregnancy outcomes for patients undergoing IVF and preimplantation genetic testing for aneuploidy (PGT-A) with a recurrent pregnancy loss (RPL) diagnosis compared to infertility diagnoses without RPL.
**Design:** Retrospective cohort study.
**Setting:** Academic fertility center.
**Patient(s):** Of 372 patients undergoing IVF/PGT-A between January 2016-December 2018, 294 patients were included in the analysis: 56 patients with an RPL diagnosis and 238 with infertility diagnoses without RPL.
**Intervention(s):** None.
**Main Outcome Measure(s):** The primary outcome measured was the embryonic aneuploidy rate. Secondary outcomes included fertilization and blastulation rates, number of blastocysts biopsied, cycles without euploid blastocysts, and rates of pregnancy losses, clinical pregnancies, and live births after a euploid embryo transfer.
**Result(s):** The cohort included 56 patients with RPL and 238 patients without RPL, including data from their first IVF cycle within the time period. Aneuploidy rates were similar between the groups, with a mean of 55% (±31%) in RPL and 54% (±34%) in non-RPL cycles. Similar rates persisted after controlling for age, ovarian reserve, and infertility diagnosis. Fertilization and blastulation rates, as well as cumulative clinical pregnancy, pregnancy loss, and live birth rates after the transfer of at least one euploid embryo were also similar between the two groups.
**Conclusion(s):** These results suggest that IVF/PGT-A cycles from patients with an RPL diagnosis have similar IVF and pregnancy outcomes to those of patients with infertility without RPL. This research can help guide counseling for RPL patients considering IVF with PGT-A. (Fertil Steril Rep® 2022;3:342–8. ©2022 by American Society for Reproductive Medicine.)
**Key Words:** recurrent pregnancy loss, preimplantation genetic testing, aneuploidy, in vitro fertilization

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Recurrent pregnancy loss (RPL), defined as two or more pregnancy losses, is a common and clinically significant condition that affects up to 5% of noncontracepting couples (1) and is associated with high rates of stress and depression (2). Patients with RPL are also at risk for adverse perinatal outcomes in subsequent pregnancies (3, 4). Known causes of RPL may be genetic, endocrine, anatomic, or autoimmune. In a previous study of patients with RPL, 3.5% were found to have a structural chromosomal abnormality in at least one partner, most commonly a balanced translocation. For 43% of couples with RPL, a cause cannot be identified, but de novo aneuploidy may explain some of these losses (5).

Early pregnancy loss (EPL) affects 10% of clinically recognized pregnancies in the general population, nearly half of which are because of chromosomal abnormalities (6). For patients in which another cause is not identified, it has been theorized that patients with RPL have a greater proportion of aneuploid conceptions than patients without RPL, which may account for their losses. Studies evaluating the karyotype of the products of conception (POC) in RPL patients' losses have been mixed. One study found that 51.3% of the POC from patients with unexplained RPL had abnormal karyotypes. However, having an increasing number of prior losses was associated with a higher likelihood of euploid POC (7). In a case-control study evaluating POC from patients with RPL compared with those without, 46% of the pregnancy losses from subjects with RPL were aneuploid, similar to a 49% aneuploidy rate in the general population. However, although advanced maternal age (AMA) patients with RPL had similar rates of POC aneuploidy compared with AMA controls, young patients with RPL had lower POC aneuploidy rates than their peers (8). In contrast, a more recent study found that patients with both RPL and infertility diagnoses had higher POC aneuploidy rates than the general population, at 78% (9).

Although analysis of POC has been an important modality for assessing the genetics of EPL, in patients with RPL, it can only evaluate pregnancies that both implant and progress adequately to evaluate tissue. As such, the evaluation of POC is a limited assessment to study whether patients with RPL have higher rates of aneuploid conceptions. Moreover, the contribution of genetics to biochemical pregnancies or recurrent implantation failure in patients with RPL remains unknown. Preimplantation genetic testing for aneuploidy (PGT-A) is a technique that is primarily used in infertility and AMA populations undergoing in vitro fertilization (IVF) to assist in embryo selection. Although PGT-A has been offered to patients with RPL undergoing IVF to select for euploid embryos in hopes of reducing EPL rates, it is unknown if PGT-A improves these patients' pregnancy and live birth rates above and beyond its baseline utility. Moreover, for patients with RPL without infertility—those who otherwise would not have pursued IVF—it is unclear whether IVF to attain PGT-A is worth the investment of time and resources.

Early studies on preimplantation genetics showed promise in reducing EPL rates in patients with RPL, comparable with similarly aged patients without RPL (10, 11). Of patients undergoing PGT for X-linked disease, patients with RPL had higher rates of aneuploidy than patients without RPL and a fertile control group (12). However, these older studies used day 3 biopsies and fluorescence in situ hybridization, as opposed to the current Next Generation Sequencing or single nucleotide polymorphism array technologies, and thus may not be directly translatable to today's PGT-A technology (10–12). A recent study used blastocyst trophectoderm biopsies but looked exclusively at subjects with diminished ovarian reserve (DOR). This study found that women undergoing IVF/PGT-A with both DOR and RPL had higher rates of embryonic aneuploidy and increased risk of no embryo for transfer than DOR patients without RPL, suggesting poorer outcomes for this group (13). Another more recent study from a single lab pooled blastocysts from a cohort of patients with RPL and compared them with those from a fertile control group and found significantly higher adjusted odds of aneuploidy for embryos from patients with RPL but did not perform analysis of patient characteristics or other IVF and pregnancy outcomes (14).

A better understanding of the outcomes from IVF with PGT-A in patients with RPL, including anticipated blastocyst aneuploidy rates, as well as IVF, pregnancy, and birth outcomes, has the potential to guide clinical decision-making and counseling. We sought to identify rates of embryonic aneuploidy for patients with RPL undergoing IVF and PGT-A compared with patients with infertility without RPL.

## MATERIALS AND METHODS

This is a retrospective cohort study of patients who underwent IVF and PGT-A with an RPL diagnosis (including patients with or without infertility), compared with patients with infertility and no RPL diagnosis from January 2016 to December 2018 at the Oregon Health and Science University in Portland, Oregon. This study examined patient aneuploidy rate, IVF and pregnancy outcomes, and live birth rate. The institutional review board at the Oregon Health and Science University approved this study. The selected time period of 36 months was chosen to ensure similar methods of embryo culture and biopsy and increase the availability of pregnancy outcome data, and all patients undergoing IVF/PGT-A during this time period were screened for study inclusion.

### Data Collection and Inclusion Criteria

All patients at our institution who underwent IVF with PGT-A from January 2016 to December 2018 were screened for study inclusion, and information was collected via a review of the electronic health record (EHR). Patients were included if they initiated IVF with infertility and/or RPL diagnosis. Only their first IVF cycle during the time period was included. RPL was defined as two or more prior pregnancy losses at $<$20 weeks, including those detected by human chorionic gonadotropin (hCG) only (biochemical pregnancies) and excluding confirmed ectopic pregnancies, consistent with the guidelines from the European Society of Human Reproduction and Embryology (ESHRE) (15). Patients were excluded if they had parental balanced translocations, were donor oocyte recipients, and did not have infertility or RPL diagnoses based on chart review, or pursued PGT primarily for a specific mutation or for sex selection. The majority of the patients with

RPL had idiopathic RPL, although four had suspected/treated etiologies of RPL. Of these patients, one had diagnosed Antiphospholipid Syndrome but continued to have losses despite treatment; another did not fully meet diagnostic criteria but was treated for presumed recurrent pregnancy loss with pregnancy. One of the patients had a small uterine septum that was identified and resected but did not have a successful pregnancy after this procedure. The remaining patient had two second-trimester losses, one of which was because of suspected cervical insufficiency despite cerclage, and a repeat cerclage was used in a subsequent pregnancy.

Baseline maternal characteristics, including age, BMI, tobacco use status, fertility markers, medical and surgical history, and obstetric history, were collected from all participants' EHR. Infertility diagnosis and primary indication for IVF were obtained from the EHR documentation of IVF details for the Society for Advanced Reproductive Technology reporting. We recorded prior pregnancy losses, biochemical losses (positive hCG test without an ultrasound-confirmed intrauterine pregnancy), ectopic pregnancies (pregnancy outside the uterus; indicated by either the patient's reported history or clinician documentation), and total pregnancy losses at $<$20 weeks (excluding ectopic pregnancies) (Table 1).

The primary outcome was embryonic aneuploidy rate, and secondary outcomes included the following IVF and pregnancy outcomes: number of oocytes retrieved, fertilization rate, blastulation rate, number of blastocysts biopsied, cycles without euploid blastocysts, number of embryo transfers, number of embryos transferred, and pregnancy losses, clinical pregnancies, and live births after a euploid embryo transfer. The fertilization rate was calculated by the total number of two pronuclei (2PN) zygotes divided by the total number of mature oocytes inseminated after retrieval. Blastulation rate was determined by the total number of blastocyst-staged embryos divided by the number of 2PN zygotes. Aneuploidy rate was calculated by dividing the number of aneuploid embryos by the total number of blastocysts biopsied for PGT-A. Embryos with a biopsy result of "no DNA" were excluded from the analysis, and cycles with a single embryo with a "no DNA" PGT-A result were deemed to have no euploid embryos available for transfer.

Among the pregnancy-related outcomes, we analyzed biochemical pregnancy losses (defined as those with positive hCG only without ultrasound findings), ultrasound-confirmed EPL (defined as loss of an ultrasound-confirmed intrauterine pregnancy, without noting a fetal heart rate), clinical pregnancies (defined by an intrauterine pregnancy with a fetal heart rate), and live births (defined as birth of a live infant $\geq$23 weeks' gestation). Records available through our institution's EHR were used to identify if live birth occurred. Twin pregnancies were counted as one clinical pregnancy or live birth.

## Ovarian Stimulation Protocol

Controlled ovarian stimulation protocol was performed using a long GnRH agonist or GnRH antagonist protocol with the administration of follicle-stimulating hormone, human menopausal gonadotropins, or both, or mild stimulation with letrozole with human menopausal gonadotropins as determined by each patient's primary physician. Oocyte maturation was triggered with hCG or leuprolide acetate with 1500 IU of hCG. Trigger usually occurred after at least two follicles measured greater than or equal to 18 mm in size, followed by oocyte retrieval 35 hours later. Given the use of PGT-A, all embryos transferred were biopsied, frozen, and euploid on genetic analysis. Fresh embryo transfers were not included in the analysis. After treatment with oral contraceptives, patients underwent endometrial preparation for embryo transfer with either oral estradiol or leuprolide with estradiol. Intramuscular progesterone was added after endometrial thickness was found to be adequate with a trilaminar appearance. After six days of progesterone exposure, embryo transfer was performed under direct ultrasound guidance. Intramuscular progesterone was continued until 12 weeks of pregnancy.

## Laboratory Protocol

Mature oocytes were inseminated by intracytoplasmic sperm injection (ICSI) 4–6 hours after retrieval. Approximately 16–18 hours after ICSI, fertilization assessments were performed, and normally fertilized zygotes were cultured until day 3 post retrieval. On day 3, laser-assisted hatching was performed, and embryos were transferred to fresh media drops for culture until days 5 and 6 postretrieval. On days 5 and 6, embryos that progressed to expanded blastocysts underwent trophectoderm biopsy and vitrification. Only fair and good quality blastocysts were biopsied, whereas poor quality grade CC on the Gardner scale were excluded (16). Approximately 5–7 trophectoderm cells were biopsied, rinsed in wash buffer, loaded into polymerase chain reaction tubes, frozen, and shipped via courier on dry ice to iGenomix (Torrance, CA) for PGT-A testing using either Microarray (during 2016) or Next Generation Sequencing (from 2016–2018). All embryos were cultured in standard culture conditions (6% $CO_2$, 5% $O_2$, 89% $N_2$, at 37°C and 95% humidity). Commercially available embryo culture media, oil, and vitrification kits were used as specified by the manufacturer for human-assisted reproductive technology (LifeGlobal Group, Guilford, CT).

## Statistical Analysis

We compared baseline demographic information and clinical characteristics of patients with an RPL diagnosis to patients with no RPL diagnosis using a $\chi^2$ test or Fisher's Exact test for categorical variables. As some patients underwent multiple IVF cycles, we included only the first IVF cycle of every patient that underwent IVF during the study time period and met the inclusion criteria for the analysis (Figure 1). Continuous variables were compared using independent two-sample t-tests or Wilcoxon rank sum tests. Categorical variables are presented as frequency (percentage), and continuous variables are presented as mean $\pm$ standard deviation or median (interquartile range).

We used a linear mixed-effects model with random intercept by patient to control for age, AMH, and the presence of an infertility diagnosis in assessing differences in aneuploidy rate in patients with and without RPL. Statistical

## TABLE 1

**Demographics and clinical characteristics of patients with a diagnosis of RPL compared with patients without RPL.**

| Patient demographics and clinical characteristics | RPL (n = 56) | No RPL (n = 238) | P[a] |
|---|---|---|---|
| Age at the time of IVF cycle (y), Mean (SD) | 37.6 (4.0) | 37.8 (3.7) | .67 |
| Body mass index (kg/m$^2$), Mean (SD) | 25.5 (5.8) | 25.3 (5.4) | .89 |
| Anti-Mullerian hormone (ng/mL), Mean (SD) | 3.1 (2.2) | 2.7 (2.5) | .24 |
| Smoker, n (%) | 2 (3.6) | 4 (1.7) | .32 |
| Infertility diagnosis, n (%) | 43 (76.8) | 238 (100.0) | <.001 |
| Primary Indication for IVF, n (%) | | | <.0001 |
| AMA and/or DOR | 13 (23.2) | 64 (26.9) | |
| Embryo banking | 2 (3.6) | 5 (2.1) | |
| Fertility preservation | 1 (1.8) | 2 (0.8) | |
| Male factor | 8 (14.3) | 64 (26.9) | |
| Ovulation disorder | 8 (14.3) | 31 (13.0) | |
| PGT-A | 2 (3.6) | 0 (0.0) | |
| Planning gestational carrier | 1 (1.8) | 1 (0.4) | |
| RPL | 11 (19.6) | 0 (0.0) | |
| Tubal factor | 2 (3.6) | 28 (11.8) | |
| Unexplained | 4 (7.1) | 28 (11.8) | |
| Unknown/not reported | 1 (1.8) | 2 (0.8) | |
| Uterine factor | 3 (5.4) | 13 (5.5) | |
| Prior live births per patient (%) | | | .089 |
| 0 | 34 (60.7) | 178 (75.1) | |
| 1 | 16 (30.4) | 43 (18.1) | |
| 2 | 1 (1.8) | 7 (3.0) | |
| ≥3 | 4 (7.1) | 9 (3.8) | |
| Prior biochemical pregnancy losses, per patient, n (%) | | | <.001 |
| 0 | 32 (57.1) | 226 (95.4) | |
| 1 | 10 (19.6) | 11 (4.6) | |
| 2 | 5 (8.9) | 0 (0.0) | |
| ≥3 | 8 (14.3) | 0 (0.0) | |
| Prior pregnancy losses <20 wk per patient, n (%) | | | <.001 |
| 0 | 0 (0.0) | 179 (75.2) | |
| 1 | 0 (0.0) | 59 (24.8) | |
| ≥2 | 56 (100.0) | 0 (0.0) | |
| Prior ectopic pregnancies, n (%) | | | .79 |
| 0 | 54 (96.4) | 223 (94.1) | |
| 1 | 2 (3.6) | 13 (5.5) | |
| 2 | 0 (0.0) | 1 (0.4) | |

AMA = advanced mother's age; DOR = diminished ovarian reserve; IVF = in vitro fertilization; n = frequency; PGT-A = preimplantation genetic testing for aneuploidy; RPL = recurrent pregnancy loss; SD = standard deviation.
[a] Fisher's exact test/$\chi^2$ test/Independent two-sample t-tests.

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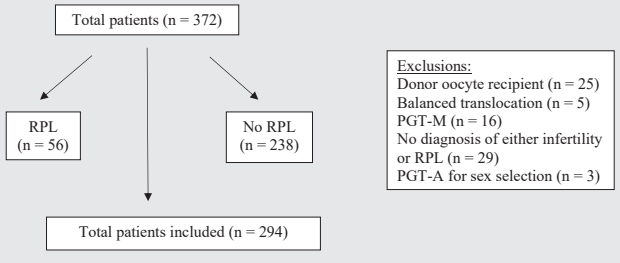
## FIGURE 1




From the 372 patients who underwent oocyte retrievals and PGT-A from January 2016 to December 2018 and were screened for inclusion, 294 patients were approved, 56 with RPL and 238 without RPL. Only their first oocyte retrieval cycle was included in the analysis. RPL = recurrent pregnancy loss.

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significance was set at 0.05. All analyses were performed using Stata version 17 (StataCorp, College Station, TX).

## Results

Of all IVF cycles utilizing PGT-A from January 2016 to December 2018, we reviewed 482 IVF cycles from 372 patients. Of these patients, 283 had only one IVF cycle, 71 had two IVF cycles, 15 had three cycles, and three patients had four IVF cycles. Only the first IVF cycle of each patient was included for analysis. Meeting the above inclusion criteria, the final cohort included a total of 294 patients: 56 patients with RPL and 238 without RPL (Figure 1).

The baseline demographic and clinical characteristics with unadjusted comparisons are presented in Table 1. Patients with RPL, by definition, had a history of significantly

**TABLE 2**

**The IVF cycle outcomes in patients with a diagnosis of RPL compared with patients without RPL**

| | RPL (n = 56) | No RPL (n = 238) | P[a] |
|---|---|---|---|
| Oocyte retrieved, Mean (SD) | 15.2 (6.8) | 13.7 (7.0) | .15 |
| Oocytes undergoing ICSI, Mean (SD) | 12.4 (5.2) | 11.5 (6.2) | .32 |
| Number of oocytes fertilized, Mean (SD) | 9.5 (4.9) | 9.2 (5.1) | .68 |
| Fertilization rate, Mean (SD) | 0.77 (0.15) | 0.80 (0.17) | .32 |
| Number of blastocysts obtained, Mean (SD) | 4.8 (2.7) | 4.8 (3.2) | .88 |
| Blastulation rate, Mean (SD) | 0.52 (0.20) | 0.54 (0.22) | .65 |
| Number of blastocysts biopsied, Mean (SD) | 4.7 (2.8) | 4.7 (3.0) | 1.00 |
| Number of euploid blastocysts, Mean (SD) | 2.3 (2.1) | 2.3 (2.3) | .84 |
| Number of aneuploid blastocysts, Mean (SD) | 2.3 (1.8) | 2.3 (1.8) | .79 |
| Aneuploidy rate, Mean (SD) | 0.55 (0.31) | 0.54 (0.34) | .76 |
| No euploid blastocysts from the current IVF cycle, n (%) | 12 (21.4) | 53 (22.3) | .89 |
| Embryo transfers from IVF cycle, Mean (SD) | 0.79 (0.68) | 0.94 (0.80) | .20 |
| Total embryos transferred from IVF cycle, Median (IQR) | 1 (0-1) | 1 (0-1) | .33 |

SD = standard deviation; IQR = interquartile range; n = frequency; IVF = in vitro fertilization; RPL = recurrent pregnancy loss.
[a] $\chi^2$test/independent two-sample t-tests/Wilcoxon rank sum tests used

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more biochemical pregnancy losses and total pregnancy losses than patients with infertility (P=<.001 for both). Other demographics were similar between the two groups.

The primary outcome, aneuploidy rate, was not significantly different between patients with RPL and patients without RPL (55% ± 31% vs.54% ± 34%; *P*=.76, respectively). After performing a linear mixed-effects model controlling for age, AMH level, and whether the patient had an infertility diagnosis, our findings remained statistically nonsignificant (coefficient=0.03; 95% CI, -0.06–0.12; *P*=.50).

Blastulation rate, number of blastocysts biopsied, and the number of cycles with no euploid blastocysts obtained were similar between the two groups (Table 2). Clinical pregnancy and live birth rates were overall similar between the groups, as were all pregnancy losses, including biochemical losses, ultrasound-confirmed pregnancy losses without fetal heart rate, and losses of previously confirmed clinical pregnancies. There was a nonsignificant trend toward fewer patients having biochemical losses in the RPL group. Of note, only one patient had a pregnancy loss in the RPL group, and this patient had two biochemical losses (Table 3).

## Discussion

This study aimed to evaluate whether patients with RPL had higher rates of aneuploidy than those with infertility without RPL, to gain insight into the early embryonic genetics of these patients and assist them in counseling on anticipated IVF/PGT-A outcomes. We aimed to assess whether we should be counseling our patients with RPL more directivity toward or away from PGT-A compared with how we counsel patients with infertility alone. We found that among patients undergoing IVF/PGT-A, the aneuploidy rate and IVF and pregnancy outcomes were overall similar to the population with infertility.

Whereas a prior study showed a higher rate of embryonic aneuploidy in patients with RPL with DOR, this study suggests that data may not be extrapolated to patients with RPL with normal ovarian reserve (13). Another study by Kort et al. (14) demonstrated an odds ratio of 1.33 for aneuploidy in the population with RPL compared with fertile controls; in that study, the patients with unexplained infertility did not have significantly more aneuploidy than fertile controls. Again, our study differs in that it compared patients with an RPL diagnosis to patients with infertility and no RPL diagnosis but did not find a difference in aneuploidy rate between these groups.

In the present study, patients with RPL who had a euploid embryo transfer had a low rate of pregnancy loss, 2.9%. In contrast, patients with RPL pursuing expectant management are often counseled on a 25% or higher risk of loss in a subsequent pregnancy (17). Given the psychosocial stress associated with RPL, this reduction in pregnancy loss rate for patients pursuing IVF with PGT-A has the potential to be very clinically meaningful for patients. Whereas IVF/PGT-A may not be the right choice for all patients with RPL, for some patients, minimizing the risk of another pregnancy loss may be tantamount. For patients with both infertility and RPL, who may be otherwise counseled to avoid IVF because of the risk of recurrent loss of euploid embryos, our study provides reassuring data that the majority of patients with RPL with euploid embryo transfers will proceed to live birth.

The findings of this study could be interpreted within the "implantation checkpoint" hypothesis: it proposes that the patient with RPL may not produce more aneuploid pregnancies but rather possess an overly receptive endometrium; thus, aneuploid conceptions may implant more readily in this population, accounting for more losses (18). Extrapolating from this theory, patients with RPL may benefit from IVF/PGT-A with the intent to avoid losses through a selection of euploid embryos.

A potential strength of this study is that the RPL group was compared with patients with infertility without RPL, the patients who would usually undergo IVF/PGT-A. The population with infertility offers a useful comparison group, as

## TABLE 3

**Pregnancy and birth outcomes for IVF cycles with a transfer of at least one euploid embryo in patients diagnosed with RPL compared with patients without RPL.**

| | RPL (n = 34) | No RPL (n = 160) | P[a] |
|---|---|---|---|
| Biochemical pregnancy losses, n (%) | | | |
| 0 | 33 (97.1) | 149 (93.1) | |
| 1 | 0 (0.0) | 11 (6.9) | |
| 2 | 1 (2.9) | 0 (0.0) | .060 |
| Ultrasound-confirmed intrauterine pregnancy losses, n (%) | | | |
| 0 | 34 (100.0) | 150 (94.3) | |
| 1 | 0 (0.0) | 8 (5.0) | |
| 2 | 0 (0.0) | 1 (0.6) | .47 |
| Clinical pregnancy losses, n (%) | | | |
| 0 | 34 (100.0) | 156 (97.5) | |
| 1 | 0 (0.0) | 4 (2.5) | 1.00 |
| Total pregnancy losses, n (%) | | | |
| 0 | 33 (97.1) | 138 (86.3) | |
| 1 | 0 (0.0) | 19 (11.9) | |
| 2 | 1 (2.9) | 2 (1.3) | |
| 3 | 0 (0.0) | 1 (0.6) | .059 |
| Clinical pregnancies, n (%) | | | |
| 0 | 6 (17.6) | 22 (13.8) | |
| 1 | 28 (82.4) | 133 (83.1) | |
| 2 | 0 (0.0) | 5 (3.1) | .61 |
| Live births, n (%) | | | |
| 0 | 6 (17.6) | 27 (16.9) | |
| 1 | 28 (82.4) | 129 (80.6) | |
| 2 | 0 (0.0) | 4 (2.5) | 1.00 |

n = frequency; RPL = recurrent pregnancy loss.
[a] $\chi^2$ test /Fisher's exact test, frequency (percentage) reported.

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the greatest body of evidence exists for infertile patients undergoing IVF/PGT-A.

Practical limitations of this study include its retrospective nature and sample size, as many patients with RPL do not undergo IVF in our practice. Additionally, studying RPL is challenging because of the inherent heterogeneity of the population with RPL. There are many potential etiologies for pregnancy loss, recurrent or otherwise, and no universally accepted definition of RPL. For this study, we defined RPL as we do in our clinical practice—two prior losses, including biochemical pregnancies and excluding ectopic pregnancies—consistent with clinical guidelines by ESHRE (15). However, this may limit the applicability of results to clinics that define RPL as three or more losses, include ectopic pregnancy, or only include clinical pregnancy losses. Additionally, among patients with RPL in this study pursuing IVF/PGT-A, the majority had concomitant infertility diagnoses or could have been particularly favorable IVF candidates based on age or ovarian reserve, although these demographics were overall similar to the study control group. Lastly, although the study was powered to detect a large difference in aneuploidy rate and other outcomes, it is underpowered to detect a more subtle difference.

The American Society for Reproductive Medicine practice guideline does not currently address or recommend IVF/PGT-A as management of unexplained RPL (19). In a retrospective cohort study analyzing time to pregnancy among women choosing expectant management or IVF with PGT-A, expectant management (EM) took a median of 3.0 months compared with 6.5 months in the PGT-A group (20). PGT-A is also not cost-effective for increasing live births, mostly because of the high expense of IVF compared with EM (21). However, the psychological impact of pregnancy loss cannot be underestimated (2). A recent pilot study comparing IVF with and without PGT-A in the population with RPL suggested that while PGT-A did not improve live birth rates, it did reduce the incidence of pregnancy loss after embryo transfer (22). For a patient for whom avoiding pregnancy loss is the priority, IVF/PGT-A could be an appropriate option.

Patients must also be counseled about the risk of undergoing an IVF cycle without obtaining a euploid embryo for transfer after both financial and psychological investment. Our study population also included only patients who had embryos available for biopsy, and thus, is limited from addressing patients with canceled IVF cycles. However, the success of obtaining a euploid embryo for transfer was fairly good for patients who did have embryos for biopsy. There is likely significant heterogeneity among causes of RPL, and some groups may have greater success with PGT-A than others; further study is needed to delineate which patients with RPL would benefit most. Taking the limitations of this study into account, these results contribute to the growing body of evidence guiding care for patients with RPL.

## Conclusion

Patients with an RPL diagnosis did not have higher aneuploidy rates or worse IVF or pregnancy outcomes than infertility patients without RPL. These findings can contribute to evidence-based counseling of this patient population. Based on the limited evidence, anticipated outcomes for patients with RPL undergoing IVF and PGT-A are likely similar to infertility patients, including the low risk of pregnancy loss after the transfer of a euploid embryo.

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