Early pregnancy

Intent to treat analysis of in vitro fertilization and preimplantation genetic screening versus expectant management in patients with recurrent pregnancy loss

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STUDY QUESTION: In an intent to treat analysis, are clinical outcomes improved in recurrent pregnancy loss (RPL) patients undergoing IVF and preimplantation genetic screening (PGS) compared with patients who are expectantly managed (EM)?

SUMMARY ANSWER: Among all attempts at PGS or EM among RPL patients, clinical outcomes including pregnancy rate, live birth (LB) rate and clinical miscarriage (CM) rate were similar.

WHAT IS KNOWN ALREADY: The standard of care for management of patients with RPL is EM. Due to the prevalence of aneuploidy in CM, PGS has been proposed as an alternate strategy for reducing CM rates and improving LB rates.

STUDY DESIGN, SIZE, DURATION: Retrospective cohort study of 300 RPL patients treated between 2009 and 2014.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Among two academic fertility centers, 112 RPL patients desired PGS and 188 patients chose EM. Main outcomes measured were pregnancy rate and LB per attempt and CM rate per pregnancy. One attempt was defined as an IVF cycle followed by a fresh embryo transfer or a frozen embryo transfer (PGS group) and 6 months trying to conceive (EM group).

MAIN RESULTS AND THE ROLE OF CHANCE: In the IVF group, 168 retrievals were performed and 38 cycles canceled their planned PGS. Cycles in which PGS was intended but cancelled had a significantly lower LB rate (15 versus 36%, P = 0.01) and higher CM rate (50 versus 14%, P < 0.01) compared with cycles that completed PGS despite similar maternal ages. Of the 130 completed PGS cycles, 74% (n = 96) yielded at least one euploid embryo. Clinical pregnancy rate per euploid embryo transfer was 72% and LB rate per euploid embryo transfer was 57%.

Among all attempts at PGS or EM, clinical outcomes were similar. Median time to pregnancy was 6.5 months in the PGS group and 3.0 months in the EM group.

LIMITATIONS, REASONS FOR CAUTION: The largest limitation is the retrospective study design, in which patients who elected for IVF/PGS may have had different clinical prognoses than patients who elected for expectant management. In addition, the definition of one attempt at conception for PGS and EM groups was different between the groups and can introduce potential confounders. For example, it was not confirmed that patients in the EM group were trying to conceive for each month of the 6-month period.

WIDER IMPLICATIONS OF THE FINDING: Success rates with PGS are limited by the high incidence of cycles that intend but cancel PGS or cycles that do not reach transfer. Counseling RPL patients on their treatment options should include not only success rates with PGS per euploid embryo transferred, but also LB rate per initiated PGS cycle. Furthermore, patients who express an urgency to conceive should be counseled that PGS may not accelerate time to conception.

STUDY FUNDING/COMPETING INTERESTS: None.

TRIAL REGISTRATION NUMBER: N/A.

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Introduction

Recurrent pregnancy loss (RPL) is a multifactorial disorder defined by the American Society for Reproductive Medicine (ASRM) as two or more clinical miscarriages (CMs). The formal definition of RPL has varied within the literature, with RPL defined as either two or three prior early pregnancy losses with inconsistent inclusion of ectopic, molar or biochemical pregnancies (Shahine and Lathi, 2015). There is currently no uniformly agreed upon definition of RPL, and European and US guidelines differ with European guidelines defining recurrent miscarriage as three consecutive prior pregnancy losses (The Royal College of Obstetricians and Gynaecologists Green-Top Guideline, 2011). The ASRM recommends that a clinical evaluation for RPL commence following two early pregnancy losses, and that a threshold of three prior pregnancy losses be utilized for epidemiologic studies (The Practice Committee of the American Society for Reproductive Medicine, 2012).

Although the overall incidence of RPL is low and estimated at <5% of women (The Practice Committee of the American Society for Reproductive Medicine, 2012), it presents a significant diagnostic and treatment challenge for both patients and clinicians. Guidelines for the evaluation of patients with RPL include evaluation of the uterine cavity and blood work to determine parental karyotypes and the presence of anti-phospholipid antibodies (APLA). In at least 50% of patients, however, an etiology for RPL is not identified (Stirrat, 1990; Stephenson, 1996; Stephenson and Kutteh, 2007; The Practice Committee of the American Society for Reproductive Medicine, 2012). The ASRM recommends expectant management as the current standard of care for patients with unexplained RPL (The Practice Committee of the American Society for Reproductive Medicine, 2012). Counseling patients with unexplained RPL to pursue expectant management presents several challenges. Patients often feel an urgency to conceive and expectant management can feel like a passive and time-consuming approach to conception. In addition, patients often carry a significant amount of guilt and grief in association with miscarriage. Attempting spontaneous conception can feel emotionally vulnerable; despite reassurance of good prognosis, patients doubt that a subsequent pregnancy will be successful (Lachmi-Epstein et al., 2012). For all of these reasons, IVF and preimplantation genetic screening (PGS) have been investigated as a treatment strategy in RPL patients with the goals of shortening time to pregnancy, decreasing CM rates and increasing live birth (LB) rates.

The role of aneuploidy in CM is well known, with over 50% of pregnancy losses attributed to fetal chromosomal abnormalities (Viaggi et al., 2013). Furthermore, for patients greater than 35 years of age with RPL, fetal aneuploidy is responsible for up to 80% of first trimester losses (Marquard et al., 2010). Due to the prevalence of aneuploidy in first trimester losses and in the RPL population, PGS has been proposed as a method for reducing miscarriage by selecting only euploid embryos for transfer (Shahine and Lathi, 2014). The ultimate effect of PGS on increasing LB rates in the RPL population and the time interval to conception are areas of ongoing investigation. Neither longitudinal prospective studies nor well-powered randomized clinical trials comparing IVF and PGS to the current standard of care, expectant management, have been performed to date for the treatment of RPL patients. Current studies are largely retrospective in design with several limitations. Inconsistent definitions of CM and RPL are employed. In addition, the treatment group (IVF and PGS) has been compared with a variety of control groups including IVF without PGS, a control infertile population, or to predicted LB and CM rates based on age and clinical history, but has not been compared with expectant management, the current standard of care (Shahine and Lathi, 2014). Finally, the majority of studies report clinical outcomes only of patients who reach PGS biopsy and/or embryo transfer, so all possible cycle outcomes are not captured (Hodes-Wertz et al., 2012). The objective of this study is to perform an intent to treat analysis comparing IVF and PGS to expectant management in fertile RPL patients.

Materials and Methods

Study population and participants

This is a retrospective cohort study of fertile RPL patients who were treated at two academic fertility centers between 2009 and 2014. RPL was defined as a history of at least two prior CMs occurring between 6 and 20 weeks gestational age, excluding biochemical pregnancies and intrauterine fetal demise. All patients had a complete RPL workup as recommended by the ASRM including blood work for parental karyotypes and to detect the presence of APLA including anti-cardiolipin antibody, lupus anticoagulant and β-2-glycoprotein as well as a uterine cavity evaluation. Patients were also routinely screened for hypothyroidism and hyperprolactinemia with serum thyroid-stimulating hormone and prolactin. Patients who were known to be translocation carriers (either maternal or paternal) were excluded. Patients who tested positive for one or more anti-phospholipid antibody (APLA) or were found to have a uterine cavity anomaly, and unexplained RPL patients were included. Patients with the APLA syndrome were offered low dose aspirin and prophylactic heparin. Patients with uterine cavity anomalies including a uterine septum, intramural fibroids or uterine polyps were offered hysteroscopy and transection of the uterine septum, myomectomy or polypectomy, respectively. All patients were followed for at least 6 months from the initial clinic visit. The treatment group consisted of patients who underwent an oocyte retrieval with the intent to perform PGS. The control group consisted of patients who elected to try and conceive spontaneously. Patients in the expectant management group were routinely offered vaginal progesterone supplementation.

Study methods

Patients in both treatment and control groups were allowed multiple attempts at conception during the study interval. In the treatment group, one attempt at conception was defined as an IVF cycle and oocyte retrieval followed by a single fresh embryo transfer or a single frozen embryo transfer. PGS was implemented as 24-chromosome screening of embryos.
using array comparative genomic hybridization (aCGH) from Day 5 trophoetoderm biopsy. PGS samples were processed at Genesis Genetics, Inc or Natera, Inc. Cycle parameters including number of oocytes retrieved, embryo stage, number of embryos biopsied and number of euploid embryos from each PGS cycles were recorded. For each patient, the number of surplus embryos in either 2PN or blastocyst stage was recorded. For cycles that completed PGS, surplus embryos were frozen only in the blastocyst stage. For cycles that canceled PGS, surplus embryos were frozen in the 2PN or blastocyst stage. In the control group, one attempt at conception was defined as 6 calendar months trying to conceive spontaneously. The main study outcomes were pregnancy rate per attempt, LB rate per attempt and CM rate per pregnancy.

A pregnancy was defined as a serum quantitative hCG level > 5 mIU/ml and the presence of a gestational sac on transvaginal ultrasound at 6–7 weeks of gestation. Pregnancies were then followed by weekly ultrasound until transfer of care at 10 weeks gestational age. A patient with a serum hCG level >5 mIU/ml that never progressed to a gestational sac on transvaginal ultrasound was diagnosed with a biochemical pregnancy (BC). A patient with a serum hCG level >5 mIU/ml and an extra-uterine gestational sac was diagnosed with an ectopic pregnancy. A CM was defined as a loss of an intrauterine pregnancy after a gestational sac had been identified on ultrasound and between 6 and 20 weeks gestational age. LBs were defined as birth of a neonate at or beyond 24 weeks gestation and were documented by patient report. When results were not available, patients were individually contacted for follow-up. Pregnancy rate and LB rates were calculated per attempt and CM rates were calculated per pregnancy. Time to pregnancy was calculated from date of new patient visit to date of positive β hCG result in both groups.

### Statistical analyses

Continuous data with a normal distribution was reported as a mean value with standard deviation. The unpaired two-tailed student t-test was used to analyze the difference between means. Categorical data were presented as percentages and the Fisher exact test was used to test the differences between the two groups. A P-value of <0.05 was considered statistically significant.

### Ethical approval

This study was approved by the Institutional Review Boards of Stanford Hospital and the Western Institutional Review Board.

### Results

#### Patient demographics

A total of 300 RPL patients met inclusion criteria. Of these, 112 patients elected for IVF/PGS and formed the treatment group while 188 patients elected for expectant management and formed the control group. Within the treatment group, one patient (0.9%) tested positive for the APLA syndrome, and three patients (2.7%) had uterine cavity anomalies including one patient with a submucosal myoma and two patients with a uterine septum. All three patients underwent hysteroscopic resection prior to starting treatment. Within the control group, seven patients (3.7%) tested positive for the APLA syndrome and eight patients (4.3%) had uterine cavity anomalies. One patient had an arcuate uterus, one patient had Asherman’s syndrome, five patients had a uterine septum that were resected hysteroscopically and one patient had a submucosal myoma that was resected hysteroscopically. The treatment and control groups did not differ significantly in terms of patients carrying a diagnosis of APLA or uterine cavity anomalies (P = 0.27 and 0.55, respectively). Patients with known chromosomal translocations were excluded from both groups as previously noted.

Baseline demographics in both treatment and control groups are shown in Table 1. All patients in the treatment group had a prior spontaneously conceived pregnancy. Patients in the treatment group were significantly older with an average age of 37.1 ± 4.1 years compared with 35.7 ± 3.9 in the control group (P < 0.01). Patients in the treatment and control groups had similar mean BMI (23.5 ± 3.0 and 24.3 ± 4.8, respectively, P = 0.14), similar number of prior CMs (2.8 ± 1.0 in both groups, P = 0.53) and a similar number of prior LBs (0.6 ± 0.7 and 0.5 ± 0.7, respectively, P = 0.20).

#### Treatment group outcomes

In the treatment group, there were a total of 198 attempts (168 retrievals and 30 frozen embryo transfers without an additional retrieval) among 112 patients. Patients had an average of 1.5 ± 1.0 retrievals and 1.1 ± 1.0 embryo transfers. Thirty-four percent of patients (n = 38) had more than one retrieval. On average, there were 1.4 ± 0.8 embryos per transfer. Fifty-six percent (n = 110) of cycles had at least one surplus embryo, with a cumulative average of 2.3 ± 3.1 surplus embryos per patient.

Of the 168 retrievals performed, 77% (n = 130) completed PGS and 38 cycles canceled their planned PGS due to poor embryo yield or quality. Of the 130 completed PGS cycles, 74% (n = 103) yielded at least one euploid embryo and 21% (n = 27) did not proceed to transfer of a euploid embryo during the study interval. Among all patients with the intent to perform IVF and PGS, a total of 128 transfers were performed with 88 pregnancies, 63 LBs, 18 CMs, 5 biochemical pregnancies and 2 ectopic pregnancies. Outcomes were available for all pregnancies in

### Table 1 Baseline patient demographics in treatment (PGS) and control (expectant management) groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment (n = 112 patients)</th>
<th>Control (n = 188 patients)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (year)</td>
<td>37.1 ± 4.1</td>
<td>35.7 ± 3.9</td>
<td>0.004*</td>
</tr>
<tr>
<td>Maternal BMI (kg/m²)</td>
<td>23.5 ± 3.0</td>
<td>24.3 ± 4.8</td>
<td>0.14</td>
</tr>
<tr>
<td>Number of Prior CMs</td>
<td>2.8 ± 1.0</td>
<td>2.8 ± 1.0</td>
<td>0.53</td>
</tr>
<tr>
<td>Number of prior LBs</td>
<td>0.6 ± 0.7</td>
<td>0.5 ± 0.7</td>
<td>0.20</td>
</tr>
<tr>
<td>Anti-phospholipid antibodies n (%)</td>
<td>1 (0.9)</td>
<td>7 (3.7)</td>
<td>0.27</td>
</tr>
<tr>
<td>Uterine factor n (%)</td>
<td>3 (2.7)</td>
<td>8 (4.3)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Data are mean ± SD unless stated otherwise.

*Statistically significant for P < 0.05, two-tailed Student’s t-test.
this group. Of the 18 CMs in the treatment group, 10 occurred after transfer of a euploid embryo, with the remaining 8 miscarriages occurring in IVF cycles that canceled the planned PGS. Of the 10 CMs that occurred after transfer of a euploid embryo, karyotype information for products of conception (POC) was available for 5 cases. There were three normal karyotypes, one abnormal mosaic karyotype and one sample which was insufficient for diagnosis. Of the eight miscarriages that occurred in cycles that canceled PGS, karyotype information for POC was available for two cases, which were both abnormal (46XX + 22, 46XX-8p23.1).

**Control group outcomes**

In the control group, patients were allowed to attempt spontaneous conception for a 6-month period. During this time period, there were 202 attempts at spontaneous conception among 188 patients. Seven percent of patients (n = 14) made more than one attempt during the study interval. Following the 6-month interval to attempt spontaneous conception, there were 104 pregnancies, 68 LBs, 25 CMs, 6 biochemical pregnancies, 1 ectopic pregnancy and 4 pregnancies for which the outcome was unknown. Of the 25 miscarriages that occurred in the control group, karyotype information for POC was available for 8 cases. There were three normal karyotypes and five abnormal karyotypes (45XO, 47XX + 2, 47X + 15/48, 47XX + 22, 69XXX). There were 20 additional pregnancies that occurred between 6 and 12 months and 7 additional pregnancies that occurred after 12 months (between 13 and 19 months) that were not included in the primary analysis.

**Comparison of treatment and control groups**

Comparison of clinical outcomes per attempt between treatment and both control groups is shown in Table II. Pregnancy rate per attempt did not differ significantly between treatment and control groups (44 versus 51%, P > 0.05). LB rate per attempt did not differ significantly between treatment and control groups (32 versus 34%, P > 0.05). CM rate per pregnancy also did not differ significantly between treatment and control groups (20 versus 24%, P > 0.05). Similarly, we did not find a difference in BC rates between the groups (6% in both groups, P = 1.00) or ectopic pregnancy rates between the groups (2 versus 1%, P > 0.05). Patients in the treatment group conceived in a median of 6.5 months while patients in the control group conceived in a median of 3.0 months. An additional analysis of clinical outcomes was performed excluding patients with APLA syndrome and uterine factor (i.e. including only patients with unexplained RPL). Pregnancy, LB, and CM rates did not differ significantly from the original patient cohort (Supplementary Table SI).

When the time interval for expectant management was increased from 6 to 12 months, there were 124 pregnancies, 77 pregnancies, 35 CMs, 7 biochemical pregnancies, and 1 ectopic pregnancy, and 4 pregnancies for which the outcome was unknown. Pregnancy rate per attempt was significantly higher in this control group compared with the treatment group (61 versus 44%, respectively, P < 0.01) while LB rate of 38% and CM rate of 28% did not differ significantly from the treatment group (P > 0.05).

**Subgroup analysis #1**

A subgroup analysis was performed within the treatment group by separating attempts in which PGS was completed from attempts in which PGS was planned but subsequently canceled. Among cycles that completed PGS, 21% (n = 27) did not proceed to transfer of a euploid embryo during the study interval. The risk of not reaching euploid transfer was 25% in women under 35 and 37% in women over age 35. Of the PGS cycles that transferred a euploid embryo, average maternal age was 36.2 ± 3.5 years with an average of 2.8 ± 0.8 prior CMs. Mean maternal age and number of prior losses were similar to controls (P = 0.49 and 0.17, respectively). Of the cycles that completed PGS with at least one euploid embryo and proceeded to embryo transfer, 32% were fresh embryo transfers and 68% were frozen embryo transfers. Clinical pregnancy rate per euploid embryo transferred was 72% and LB rate per euploid embryo transferred was 57%, which were significantly higher than the pregnancy and LB rates in the control group (Supplementary Table SI). CM rate for cycles that completed transfer of a euploid embryo did not differ significantly from the CM rate for the control group (14 versus 24%, P = 0.12). Among all attempts that completed PGS (including cycles that did not transfer a euploid embryo), there were a significantly greater number of mean oocytes retrieved (16.6 ± 8.5 versus 11.9 ± 7.9, P < 0.01), greater number of 2PN embryos (9.8 ± 5.5 versus 5.6 ± 5.0, P < 0.01) and greater number of blastocysts (5.7 ± 3.2 versus 1.7 ± 2.3, P < 0.01) with similar maternal ages (37.3 ± 3.9 versus 37.6 ± 4.3, P > 0.05) compared with attempts in which PGS was planned but canceled (Table III). Clinical pregnancy rates per attempt did not differ significantly between the subgroups (46 versus 40%, P > 0.05).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment (n = 198 attempts)</th>
<th>Control (n = 202 attempts)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical pregnancy ratea</td>
<td>88 (44)</td>
<td>104 (51)</td>
<td>0.16</td>
</tr>
<tr>
<td>LB ratea</td>
<td>63 (32)</td>
<td>68 (34)</td>
<td>0.75</td>
</tr>
<tr>
<td>CM rateb</td>
<td>18 (20)</td>
<td>25 (24)</td>
<td>0.61</td>
</tr>
<tr>
<td>Biochemical pregnancy rateb</td>
<td>5 (6)</td>
<td>6 (6)</td>
<td>1.00</td>
</tr>
<tr>
<td>Ectopic pregnancy rateb</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>0.59</td>
</tr>
<tr>
<td>Median time to pregnancy (months)</td>
<td>6.5</td>
<td>3.0</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Table II: Comparison of clinical outcomes between intent to treat (PGS) and control (expectant management) groups.

Data are n (%). P values were calculated using Fisher’s exact test.

a Rate calculated per attempt, where one attempt at conception was defined in the treatment group as an IVF cycle and oocyte retrieval followed by a single fresh embryo transfer or a single frozen embryo transfer. In the control group, one attempt at conception was defined as 6 calendar months trying to conceive spontaneously.

b Rate calculated per pregnancy.
LB rate per attempt was significantly increased (36 versus 15%, \( P < 0.05 \)) and CM rate was significantly reduced (14 versus 50%, \( P < 0.01 \)) in those attempts that completed PGS compared with attempts in which PGS was canceled. Finally, all surplus embryos from PGS cycles were frozen in the blastocyst stage. Surplus embryos from cycles that canceled PGS were frozen almost exclusively in the blastocyst stage, with the exception of 2% of cycles in which embryos were frozen in the 2PN stage. We did not find a difference between the attempts that completed PGS versus attempts that canceled PGS in terms of number of cycles with surplus embryos (56 versus 53%, \( P > 0.05 \)) or mean number of cumulative surplus embryos per patient (2.2 \( \pm \) 2.6 versus 3.0 \( \pm \) 4.6, \( P > 0.05 \)).

**Subgroup analysis #2**

Finally, LB rates were stratified across treatment and control groups by maternal age. For the subgroup of patients who reached euploid transfer, women over age 35 had significantly higher LB rates compared with the control group (59 versus 28%, \( P = 0.0001 \)) and a lower CM rate (14 versus 24%, \( P = 0.05 \)). Age-stratified LB rate and CM rates in the group of patients who reached euploid transfer compared with the control group are shown in Supplementary Figs S1 and S2. Among all attempts at IVF and PGS in the treatment group compared with the control group, LB rates decrease with increasing maternal age and do not differ significantly between treatment and control groups for any subset of maternal age between 25 and 44 years (Fig. 1).

**Discussion**

The goal of this study was to compare clinical outcomes of RPL patients pursuing IVF/PGS and expectant management in an intent to treat analysis. Counseling RPL patients on expectant management can be challenging in the face of sophisticated reproductive technology. Despite the absence of studies comparing PGS to the current standard of care, expectant management, PGS has been suggested as a strategy for decreasing CM rates in RPL patients by selecting euploid embryos for transfer (Shahine and Lathi, 2014). RPL patients, however, typically conceive easily without infertility treatment, and the role of aneuploidy in RPL is unclear. In a landmark prospective study of spontaneous conception in RPL patients published by Brigham et al. in 1999, predicted LB rates per conception range from 84% (CI 77–90%) in a 30-year-old with two prior miscarriages to 69% (CI 57–82%) in a 40-year-old with two prior miscarriages (Brigham et al., 1999). The role of aneuploidy in CM is well recognized and aneuploidy is strongly correlated with increasing maternal age. The role of aneuploidy in RPL, however, is less clearly defined. It has been demonstrated, for example, that the rate of aneuploidy in POC from RPL patients is not significantly higher than aneuploidy rates seen in sporadic miscarriages, suggesting that an additional factor may have a role in contributing to CM in RPL patients (Marquard et al., 2010). Therefore, utilizing PGS to transfer euploid embryos may reduce overall CM rates, but would not be expected to reduce CM in patients whose pregnancy losses are not due to aneuploidy.

In this study, we included all patients with the intent to perform IVF/PGS or conceive spontaneously, regardless of the ultimate outcome,
and compared a single attempt of IVF/PGS with 6 months of expectant management. We chose expectant management as a control group, which differs from previous studies on outcomes in RPL patients, as this is the current standard of care for the management of RPL as recommended by the ASRM (The Practice Committee of the American Society for Reproductive Medicine, 2012). A 6-month interval was chosen for attempting spontaneous conception as this was felt to be a reasonable amount of time to counsel a patient on attempting expectant management. In addition, the median time to pregnancy was 6.5 months in the IVF/PGS group so a similar period of time to attempt spontaneous conception was felt to be appropriate. Among cycles that completed PGS, we report a 72% clinical pregnancy rate per euploid embryo transferred and 57% LB rate per euploid embryo transferred. When looking at all attempts at IVF/PGS, including cycles that did not proceed to transfer, and comparing to one attempt at expectant management, defined as trying to conceive for 6 months, IVF/PGS does not significantly increase pregnancy or LB rates or decrease miscarriage rates compared with expectant management. Pregnancy rate is significantly higher in patients attempting spontaneous conception for 12 months compared with those intending to pursue IVF/PGS. All other clinical outcomes were similar between patients intending to perform IVF/PGS and patients attempting spontaneous conception for either 6 or 12 months. A subgroup analysis within the IVF/PGS group comparing attempts that completed the planned PGS versus those attempts in which PGS was planned but canceled showed more favorable cycle parameters in the attempts that proceeded with PGS including higher mean number of oocytes retrieved, 2PN embryos and blastocysts. LB rate was significantly higher in the subgroup that completed PGS compared with the subgroup that canceled PGS. CM rate was also decreased significantly in the subgroup that completed PGS compared with those attempts that intended but canceled PGS. Our group has previously put forth a cost effectiveness analysis using published data that indicates there may be a benefit in reducing CM rate with IVF/PGS, which is in concordance with the subgroup analysis from this RPL cohort (Murugappan et al., 2015).

In the subgroup of cycles that both completed PGS and transferred a euploid embryo, pregnancy and LB rates were significantly improved compared with the control group. CM rate in this subgroup was 14%, which was lower but not significantly different than the CM rate of 24% in the EM cohort. CM rate of 14% after transfer of a euploid embryo is higher than CM rates from a general IVF/PGS population, which are reported at 11% in a randomized controlled trial comparing pregnancy outcomes with IVF and q-PCR based CCS versus morphology embryo grading (Forman et al., 2013). We believe that the higher than expected miscarriage risk is due to euploid miscarriages and/or mosaicism in embryos, which may be more common in the RPL population as previously mentioned (Marquard et al., 2010). Karyotype information on POC obtained was available for only a small proportion of the CMs that occurred in the treatment and control groups, limiting the ability to form a conclusion regarding possible misdiagnosis of the embryo following PGS.

Age-stratified analysis of outcomes in the subgroup of patients who reached transfer of a euploid embryo suggests that LB rate is significantly improved using PGS in women over age 35 who reach transfer of a euploid embryo compared with the control group. However, when looking at all attempts of PGS, including cycles that intended but canceled PGS and cycles that did not transfer a euploid embryo, pregnancy and LB rates do not differ between treatment or either control group for any subset of maternal age between 25 and 44 years. This suggests that outcomes with PGS and expectant management are similar for young RPL patients, while PGS success rates in older women are limited by the high incidence of cycles that intend but cancel PGS or cycles that do not reach transfer.

While IVF/PGS did not have more favorable clinical outcomes per attempt in this intent to treat RPL population, one may ask if time to pregnancy is decreased in the IVF/PGS group compared with patients trying to conceive spontaneously. In 2014, Perfetto et al. performed a retrospective cohort study of fertile RPL patients and showed that median time to conception was 2 months for those patients who achieved a spontaneous conception, and 88% conceived within 6 months. In comparison, patients using PGS conceived in a median of 5 months (Perfetto et al., 2015). Our findings were similar to those of Perfetto et al. We report that patients intending to perform IVF/PGS conceived in a median of 6.5 months while patients in the expectant management group conceived in a median of 3 months. Thus, patients pursuing PGS do not accelerate the time to conception compared with those who opt for expectant management. We hypothesize that the increased time interval to conception with PGS is likely multifactorial; possible reasons include patients’ ambivalence about the procedure, delays from timing the cycle start due to oral contraceptive pill use or procedure availability and need for adequate patient training and insurance authorization prior to initiating treatment.

The major strength of this study is its structure as an intent to treat analysis, enabling the authors to capture all possible clinical outcomes that occur in a heterogeneous patient population. In order to accomplish this, patients in both treatment and control groups were allowed to perform multiple attempts. In addition, IVF cycles that intended but canceled PGS and cycles with euploid embryos that did not proceed to transfer were included in the analysis. While this captures the difference between perfect use of IVF/PGS and actual use of the technology, including patients with attempts that did not proceed to transfer may introduce a confounding factor that contributes to their lack of success. In addition, patients may have performed transfers after the data collection period. Our hope is that by including all attempts at PGS including those that did not make it to transfer, we represent a more realistic view of outcomes with PGS that can be used to counsel RPL patients. In addition, our choice of expectant management as control group differs from previously published studies and further strengthens the ability to counsel patients by comparing PGS to the current standard of care. An additional strength is limiting the time for attempting expectant management to 6 months, which makes this strategy more palatable for patients who may be reluctant to forgo an intervention and continue to attempt spontaneous conception. Finally, ovarian reserve varies among women with RPL, and many patients may not be candidates for PGS based on diminished ovarian reserve. This study demonstrates that those patients are at particularly high risk of treatment failure with PGS.

The largest limitation is the retrospective study design, in which patients who elected for IVF/PGS may have had different clinical prognoses than patients who elected for expectant management, thus introducing a bias in the study results. For example, the cohort of patients intending to pursue IVF/PGS was older than the expectant management cohort by an average of 1.4 years while the patient cohorts did not differ in terms of maternal BMI, prior CMs or LBs, or prevalence of APLA syndrome or uterine cavity anomalies. The difference in ages between
treatment and control groups may affect clinical outcomes independent of aneuploidy. While the ideal study design to guide management of RPL patients is a randomized controlled trial, the RPL population forms a very small proportion of patients who seek fertility treatment, and prospective studies are time-consuming and limited by cohort size. Establishing the parameters with which the treatment and control groups were compared was challenging and a potential limitation of the study. We compared pregnancy and LB rates from one attempt at IVF/PGS, defined as one retrieval with or without embryo transfer or a frozen embryo transfer, to one attempt at spontaneous conception, defined as 6 calendar months of trying to conceive spontaneously. We did not, however, confirm that patients were trying to conceive during each month of the 6-month period. In addition, 27 additional pregnancies occurred after the 6-month period but within 24 months of expectant management that were not included in the primary analysis. Finally, total cycle potential is increased when there are surplus embryos upon completion of a cycle. We were unable to calculate total cycle potential because at the time of this analysis more than half of patients had surplus embryos. We did not, however, find a difference in terms of number of cycles with surplus embryos or mean number of surplus embryos between the subgroups of treatment cycles completing PGS compared with treatment cycles in which PGS was canceled.

**Conclusion**

PGS has been utilized in the treatment of RPL patients on the basis that selecting euploid embryos for transfer may result in improved CM and LB rates. This study is an intent to treat analysis comparing outcomes among RPL patients intending to pursue PGS and patients who are expectantly managed, the current standard of care for management of RPL. All attempts at PGS, including cycles in which PGS was intended but canceled and cycles that did not proceed to embryo transfer, were included. A single attempt at PGS was compared with 6 months of attempting spontaneous conception. We report that per attempt, PGS is not effective in improving LB rate or decreasing CM rate compared with expectant management except in those PGS cycles that complete transfer of a euploid embryo. Success rates with PGS are limited by the high incidence of cycles that intent but cancel PGS or cycles that do not reach transfer, and a higher no transfer rate is seen in women over 35 years of age. Among cycles in which PGS was planned and completed compared with cycles in which PGS was planned and then canceled, LB rate was significantly increased and CM rate was significantly reduced, suggesting that clinical outcomes may be improved if patients complete the planned PGS cycle as intended. Counseling RPL patients on their treatment options should include not only success rates with PGS per euploid embryo transferred, but also LB rate per initiated PGS cycle. Furthermore, patients who express an urgency to conceive should be counseled that PGS may not accelerate time to conception.

**Supplementary data**

Supplementary data are available at http://humrep.oxfordjournals.org/.

**Authors’ roles**


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No external funds was either sought or obtained for this study.

**Conflict of interest**

None declared.

**References**


