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Preimplantation genetic testing for aneuploidy in unexplained recurrent pregnancy loss: a systematic review and meta-analysis

Sezcan Mumusoglu, M.D.,[a,b] Savci Bekir Telek, M.D.,[c] and Baris Ata, M.D., M.Sc.[d,e]

[a] Department of Obstetrics and Gynecology, Hacettepe University School of Medicine, Ankara, Turkiye; [b] Anatolia IVF and Women Health Center, Ankara, Turkiye; [c] Department of Obstetrics, Gynecology and Reproductive Sciences, Yale School of Medicine, New Haven, Connecticut; [d] ART Fertility Clinics, Dubai, United Arab Emirates; [e] Department of Obstetrics and Gynecology, Koc University School of Medicine, Istanbul, Turkiye

Importance: Preimplantation genetic testing for aneuploidy (PGT-A) to deselect aneuploid embryos in assisted reproductive technology (ART) treatment cycles may hold promise by augmenting pregnancy rates per transfer and reducing pregnancy loss rates for patients with unexplained recurrent pregnancy loss (RPL).
Objective: To explore effectiveness of PGT-A in managing unexplained RPL by evaluating several key aspects: the likelihood of live birth in a subsequent spontaneous pregnancy, whether women with unexplained RPL have a higher rate of aneuploidy, whether euploid blastocysts offer comparable live birth rate (LBR) in patients with unexplained RPL, whether the endometrium is less selective in unexplained RPL loss, and whether PGT-A increases the LBR or reduces pregnancy losses until delivery.
Data sources: PubMed and Cochrane Library databases were searched from inception until June 2024.
Study selection and synthesis: Studies involving patients with ≥ 2 unexplained RPL who underwent ART with or without PGT-A or expectant management were included.
Main Outcome Measures: The primary outcome measure was the LBR. Secondary outcome measures were aneuploidy rate, clinical pregnancy rate, and clinical pregnancy loss rate.
Results: Whether couples with unexplained RPL have higher embryo aneuploidy rates remains equivocal. Euploid blastocyst transfers yielded comparable clinical pregnancy loss rate (odds ratio [OR], 1.10; 95% confidence interval [CI], 0.57–2.13) and LBR (OR, 1.04; 95% CI, 0.74–1.44) in patients with and without unexplained RPL. Comprehensive chromosome analysis of products of conception shows similar aneuploidy rates between patients with and without RPL and does not support the less selective endometrium hypothesis. Preimplantation genetic testing for aneuploidy decreased clinical pregnancy loss rate (OR, 0.42; 95% CI, 0.27–0.67) and enhanced LBR per transfer (OR, 2.17; 95% CI, 1.77–2.65) and LBR per patient (OR, 1.85; 95% CI, 1.18–2.91) in patients with unexplained RPL.
Conclusion and relevance: Current low-quality evidence suggests that PGT-A enhances LBR per transfer and per patient in unexplained RPL. Well-designed randomized controlled trials comparing ART with PGT-A vs. expectant management for unexplained RPL are warranted.
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El resumen está disponible en Español al final del artículo.

Key Words: Recurrent pregnancy loss, aneuploidy, preimplantation genetic testing, in vitro fertilization, expectant management

Pregnancy loss, a common and distressing pregnancy complication, affects 15%–25% of pregnant women (1). Approximately 80% of losses occur during the first trimester of pregnancy (2). A smaller percentage of women experience the more distressing condition of recurrent pregnancy loss (RPL). Previously, RPL was defined as the loss of ≥ 3 consecutive clinical pregnancies. However, the recent European Society for Human Reproduction and Embryology and American Society for Reproductive Medicine (ASRM) guidelines state that the definition can include ≥ 2 consecutive or nonconsecutive pregnancy losses, encompassing biochemical pregnancies and pregnancies of unknown location (1, 3). With the former definition, the reported prevalence of RPL was 0.8%–1.4%; however, with

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Correspondence: Baris Ata, M.D., M.Sc., ART Fertility Clinics, ART Fertility Clinics, Jumeirah Street 869, Umm Suqeim 3, Dubai, United Arab Emirates (E-mail: barisata@ku.edu.tr).

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the expanded definition, it could increase to 2%–3% (4).

The impact of pregnancy loss is not limited to physical risks like infection, bleeding, or potential complications of medical procedures but also includes significant psychological effects (5, 6). Although certain causes of RPL, including parental chromosomal abnormalities (e.g., balanced translocations) (7), uterine malformations (8), endocrine (9) and immunologic disorders (10), have been documented in various studies, more than half of the cases remain unexplained (1, 3). In the absence of a recognized etiology for pregnancy loss, the condition is often dubbed unexplained RPL. Comprehensive chromosomal analysis (CCA) of products of conception (POC) indicated comparable aneuploidy rates in pregnancy losses arising from natural conceptions (56.8%), conceptions through assisted reproductive technology (ART) (53.6%), women with a single prior loss (54.4%), and women experiencing three or more losses (52.1%) (11). Yet, a study, including 100 women with ultrasound or histopathology, documented RPL reported that the combination of CCA of POC using a 24-chromosome microarray with the standard evaluation suggested by the ASRM explained the etiology of pregnancy losses in >90% of cases (12, 13). Intriguingly, >90% of the patients who had a normal ASRM RPL workup had a chromosome abnormality in the POC, highlighting the relevance of CCA of POC and the role of aneuploidy in RPL (13, 14).

The deselection of aneuploid embryos by preimplantation genetic testing for aneuploidy (PGT-A) enhances pregnancy rate per embryo transfer (ET) and decreases the pregnancy loss rate in patients undergoing ART (15). Because >50% of early pregnancy losses are attributable to aneuploidy (16), many clinicians propose employing ART with PGT-A for women experiencing RPL (17). However, there are few studies investigating the use of PGT-A in women with a history of RPL, and no guidelines or recommendations are available regarding the use of PGT-A for couples with unexplained RPL. Whether PGT-A can benefit patients with unexplained RPL hinges on several factors: the likelihood of live birth (LB) in a subsequent pregnancy, whether women with unexplained RPL produce aneuploid blastocysts at a higher rate, whether euploid blastocysts offer a similar LB rate (LBR) in women with unexplained RPL, whether the endometrium is less selective in unexplained RPL, and whether PGT-A increases LBs or limits pregnancy losses until delivery. These points will be thoroughly discussed.

MATERIALS AND METHODS

This systematic review was conducted following the preferred reporting items for systematic reviews and meta-analysis guidelines. The protocol was registered (CRD42024522745) on international prospective register of systematic reviews (www.crd.york.ac.uk/prospero).

Information sources and search strategy

A systematic literature search was conducted in PubMed and Cochrane databases from inception to March 2024. The following search terms were used: ("unexplained recurrent pregnancy loss" OR "idiopathic recurrent miscarriage" OR "recurrent spontaneous abortion") AND ("in vitro fertilization [IVF]" OR "intracytoplasmic sperm injection") AND ("preimplantation genetic testing for aneuploidy" OR "next generation screening" OR "array-based comparative genomic hybridization" OR "trophectoderm biopsy" OR "blastocyst biopsy").

Study selection and data extraction

Studies involving patients with two or more spontaneous pregnancy losses (including biochemical losses), and who underwent ART with PGT-A, ART without PGT-A, or expectant management were included. Only studies that used trophectoderm biopsy and CCA for PGT-A were included. All retrieved publications were imported into EndNote X9, and duplications were removed. Two investigators (S.M. and S.B.T.) independently screened the remaining articles for titles and abstracts. A cross-reference check was performed to identify additional relevant studies. Only original articles and abstracts in English were included. Disagreements were resolved by discussion and consensus with the senior investigator (B.A.).

The following data were extracted from each study: the first investigator's last name, year of publication, country of study, study design, number of participants in study and control groups, clinical pregnancy rate per ET and per patient, clinical pregnancy loss rate, LBR per ET and per patient, as well as limitations and specific remarks of the studies.

Risk of bias assessment of included studies

The Newcastle-Ottawa Scale (NOS) quality assessment form for cohort studies was used to evaluate the methodological quality of the included studies. To evaluate the quality of evidence for the main outcome measure LBR, we used the Grading of Recommendations, Assessment, Development, and Evaluations framework for observational studies (18). Two reviewers (S.M. and S.B.T.) independently assessed the NOS scoring of the included studies. Any disagreements were resolved by discussion with the senior investigator (B.A.).

Outcome measures and synthesis of results

The primary outcome measure was the LBR per ET and per patient when available. The secondary outcome measures were clinical pregnancy rate and clinical pregnancy loss rate.

Mantel–Haenszel odds ratios (ORs) with 95% confidence interval (CI) were used for reproductive outcome measures. A random effects model was used. We assessed statistical heterogeneity using forest plots and I^2 (%) statistics; I^2 >50% was interpreted as substantial heterogeneity. All statistical analyses were performed using RevMan 5.3 (Cochrane Collaboration). A qualitative approach was taken when pooled analysis was not feasible.

Sensitivity analyses

Several prespecified sensitivity analyses were performed. The estimates of the fixed-effects meta-analysis were compared with random-effect models to check the robustness of the conclusions. Other sensitivity analyses assessed

the potential impact of study weight and the year of publication by visual inspection of the forest plot displayed in ascending order of study weight and year of publication. A sensitivity analysis was performed by only including studies reporting data per patient or deemed good and fair quality according to NOS.

RESULTS

The literature search revealed 118 potentially eligible publications after removal of the duplicates and those that did not match the inclusion criteria; a total of 18 studies were included in the analysis, with one study (19) providing data for both comparisons. Among the included studies, data comparing reproductive outcomes in patients with unexplained RPL and non-RPL undergoing ART with PGT-A were available in eight studies (19–26), whereas data comparing reproductive outcomes in patients with RPL undergoing ART with PGT-A vs. ART without PGT-A were available in 11 studies (19, 27–36) (Supplemental Fig. 1, available online). The list of excluded studies and the reasons for their exclusion are provided in Supplemental Table 1 (available online). Risk of bias and quality of evidence assessments are presented in Supplemental Tables 2–4, respectively.

Likelihood of achieving an LB in the next spontaneous pregnancy in patients with unexplained RPL

The risk of pregnancy loss depends on the number of prior pregnancy losses (37, 38). A prospective registry-based cohort study conducted in Norway assessed the risk of recurring pregnancy losses after consecutive losses. The study included 21,005 pregnancy losses among the 156,584 pregnancies between 2009 and 2013. Pregnancy loss rates were as follows: 11.6% in patients with no previous pregnancies, 19.8% in patients with one previous loss, 27.7% in those with two previous losses, and 41.9% in individuals with three or more previous losses. The effect of maternal age on the risk of pregnancy loss was accounted for in an adjusted analysis, and the OR for pregnancy loss increased with the number of previous losses: 1.54 (95% CI, 1.48–1.60) after one loss, 2.21 (95% CI, 2.03–2.41) after two, and 3.97 (95% CI, 3.29–4.78) after three consecutive losses (37).

A systematic review, which also included data from two high-quality randomized controlled trials (RCT), namely progesterone in recurrent miscarriage (39) and progesterone in spontaneous miscarriage (40), in addition to 20 other studies, was in agreement with the Norwegian study and reported the risk of pregnancy loss as follows: 11.3% (95% CI, 6.6–17.0; 7 studies; n = 362,285) for a patient with no history of pregnancy loss, 17.0% (95% CI, 9.0–27.0; 7 studies; n = 70,283) for those with one, 28.0% (95% CI, 20.1–36.4; 22 studies; n = 16,717) for two or three, 39.6% (95% CI, 34.9–44.3; 20 studies; n = 2,105) for four, 47.2% (95% CI, 36.2–58.3; 14 studies; n = 792) for five, and could increase up to 63.9% (95% CI, 54.4–2.9; 10 studies; n = 315) after six or more losses (38).

Do patients with unexplained RPL have a higher aneuploidy rate?

Lack of female age-stratified data and variations in genetic platforms across studies prevented pooling data and a qualitative approach was taken. Six retrospective studies compared blastocyst aneuploidy rates between patients with RPL and non-RPL controls. Although two studies (23, 41) reported higher aneuploidy rates in patients with RPL, the other four reported comparable rates (24–26, 42).

Kort et al. (41) compared aneuploidy rates between women with infertility, RPL, and fertile controls. Although it is not explicitly mentioned that all etiology for RPL was ruled out, carriers of structural rearrangements were excluded; hence, the RPL group can be considered as unexplained RPL for assessment of euploidy rates. A total of 3,378 PGT-A treatment cycles and 18,387 trophectoderm biopsies with 644 patients with RPL were included. The aneuploidy rate was significantly higher (OR, 1.33; 95% CI, 1.132–1.565; $P<.001$) in the RPL group than in the fertile controls who underwent PGT-A for sex selection (41). However, patients in the RPL group were older (37.2 ± 4.2 vs. 34.7 ± 4.2). Yet, the multivariate analysis was adjusted for maternal age. Liu et al. (23) retrospectively compared aneuploidy rates between patients undergoing PGT-A for unexplained RPL (n = 62 patients, 101 PGT-A cycles) and patients undergoing PGT for monogenic disorders (n = 212 patients, 311 PGT for monogenic disorders treatment cycles), who could be considered fertile. Among women aged <35 years (n = 30), the aneuploidy rate was significantly higher in the unexplained RPL group (48.9% vs. 36.9%, respectively, $P<.001$), but among women aged >35 years (n = 32), the difference was not significant (66.9% vs. 61.4%, respectively, $P=.175$) (23).

In contrast, a retrospective study involving the first ART cycles of 294 patients, 56 with a history of RPL, and 238 infertile couples reported similar aneuploidy rates (55% ± 31% vs. 54% ± 34%, respectively). Patients with structural rearrangements were excluded, and there were only four patients with suspected and treated etiology for RPL; thus, the group can be considered unexplained RPL with regard to euploidy rate analysis. The findings remained consistent even after adjusting for age, antimüllerian hormone levels, and different infertility diagnoses using a linear mixed-effects model (26). Another retrospective study investigated whether the euploidy rate was correlated with the number of prior losses. The study included 180 oocyte retrieval cycles of 166 women with unexplained RPL, all of whom were aged <35 years old. When patients were stratified by the number of previous losses, baseline demographic characteristics, and embryological characteristics revealed no statistically significant differences. Euploidy rates were 63.3%, 58.2%, and 58.5% for women with 2, 3, and >3 prior losses, respectively ($P=.477$) (42).

Cimadomo et al. (25) retrospectively investigated 2,676 patients (2,676 treatment cycles producing 8,151 blastocysts) undergoing PGT-A. Because female age at oocyte retrieval was significantly associated with euploidy rate, patients

were stratified into five clusters (<35, 35–37, 38–40, 40–42, and >42 years) based on their age. To further investigate the effect of reproductive history, including the number of pregnancy losses, on euploidy rate, patients were categorized as having no pregnancy loss (n = 1,989), 1 pregnancy loss (n = 436), and ≥2 pregnancy losses (n = 251, RPL group). Similar euploidy rates were found in each age subgroup for the number of previous pregnancy loss categories. The euploidy rate per cohort of biopsied blastocysts was independent of the number of previous pregnancy losses in linear regression analysis (25).

Euploid blastocyst transfer and LBR in patients with RPL

A total of eight retrospective cohort studies (19–26) consisting of 8,203 ET cycles (1,713 in the RPL group and 6,490 in the non-RPL group) were included. Table 1 (19–26, 31) presents the main characteristics of the included studies.

Pooled estimates for clinical pregnancy rate per euploid ET, clinical pregnancy loss rate, and LBR per ET are shown in Figure 1 (19–26). Patients with RPL compared with those without RPL had similar clinical pregnancy rates (OR, 0.97; 95% CI, 0.84–1.12; I^2, 3%; seven studies; 7,791 cycles; very low-quality evidence) (Fig. 1A), numerically higher but statistically similar clinical pregnancy loss rates (OR, 1.42; 95% CI, 0.90–2.24; I^2, 46%; six studies; 4,945 pregnancies; very low-quality evidence) (Fig. 1B), and lower LBR (OR, 0.80; 95% CI, 0.65–0.99; seven studies; I^2, 48%; 8,203 cycles; very low-quality evidence) (Fig. 1C).

A sensitivity analysis including only good quality studies showed (21, 25, 26) (Supplemental Fig. 2) similar pooled estimates for clinical pregnancy rate (OR, 1.00; 95% CI, 0.74–1.35; I^2, 0; three studies; 2,057 cycles; low-quality evidence) and clinical pregnancy loss rate (OR, 1.10; 95% CI, 0.57–2.13; I^2, 0; two studies; 996 pregnancies; low-quality evidence). The only difference was noted in the comparison of LBR; contrary to overall estimates, similar LBRs (OR, 1.04; 95% CI, 0.74–1.44; I^2, 0; two studies; 1,774 cycles; low-quality evidence) were observed in women with RPL compared with those without RPL.

Overall, according to low-quality evidence from observational studies, the transfer of euploid blastocysts likely yields comparable clinical pregnancy rate, clinical pregnancy loss rate, and (based on the sensitivity analysis) LBR in RPL and non-RPL patients.

Is the endometrium less selective in patients with RPL?

Comprehensive chromosomal analysis of POC reveals comparable aneuploidy rates in POC between patients with RPL and non-RPL (11). When CCA of POC was employed, comparable aneuploidy rates were noted in pregnancy losses between natural (56.8%) and IVF conceptions (53.6%), as well as between women with a single prior loss (54.4%) and women with three or more losses (52.1%) (11).

Does PGT-A benefit patients with unexplained RPL compared with expectant management or ART without PGT-A?

Only a few studies to date have assessed the benefit of PGT-A specifically among women with RPL. Murugappan et al. (43) retrospectively analyzed reproductive outcomes in patients with RPL (defined as ≥2 losses) with normal parental karyotypes and compared those treated with PGT-A (112 couples and 198 attempts) and those managed expectantly (188 couples and 202 attempts). Expectant management was defined as attempting to conceive for 6 months, and the success of PGT-A cycles was assessed as per intention-to-treat and per attempt. The intention-to-treat analysis showed no difference in clinical pregnancy, clinical pregnancy loss, and LBRs. However, in the per attempt analysis, 100 patients who completed PGT-A cycles with euploid transfer had significantly higher clinical pregnancy (72% vs. 51%, respectively, P=.0008) and LB (57% vs. 34%, respectively, P=.0001) and lower pregnancy loss rates, albeit the latter was short of statistical significance (14% vs. 24%, respectively, P=.12) (43). However, the analysis was not adjusted for maternal age, despite female age being significantly higher in the PGT-A arm (37.1 ± 4.1 vs. 35.7 ± 3.9, P=.004), and PGT-A was arbitrarily canceled when the embryo yield or quality was deemed low by the investigators (44).

Regarding the comparison of reproductive outcomes per ET in patients with RPL undergoing ART with and without PGT-A, a total of 11 studies comprising 11,205 ET cycles (6,006 in the PGT-A group and 5,199 in the non-PGT-A group) were included in the current meta-analysis (19, 27–36). Nine studies were retrospective cohorts (19, 28, 30–36), one was a prospective cohort (27), and one was an RCT (29). Table 2 (19, 27–36) presents the main characteristics of the included studies.

Pooled estimates for clinical pregnancy rate per ET, clinical pregnancy loss rate, and LBR per ET are shown in Figure 2 (19, 27–29, 31–35). Compared with those without PGT-A, patients undergoing ART with PGT-A had higher clinical pregnancy rate (OR, 1.76; 95% CI, 1.57–1.98; I^2, 8%;10 studies; 11,093 cycles; low-quality evidence) (Fig. 2A), lower clinical pregnancy loss rates (OR, 0.42; 95% CI, 0.27–0.67; I^2, 69%; nine studies; 5,850 pregnancies; low-quality evidence) (Fig. 2B), and higher LBR (OR, 2.17; 95% CI, 1.77–2.65; I^2, 46%; 10 studies; 11,133 cycles; low-quality evidence) (Fig. 2C) per ET.

A sensitivity analysis limited to good quality studies showed similar estimates for clinical pregnancy rate, clinical pregnancy loss rates, and LBR and did not change the overall conclusions (27–29, 31, 33, 34) (Supplemental Fig. 3).

Regarding the comparison of reproductive outcomes per patient, data were available only from four of the 11 included studies (27, 29, 33, 34). Patients with RPL undergoing ART with PGT-A compared with those without PGT-A had a higher clinical pregnancy rate per patient (OR, 1.53; 95% CI, 1.07–2.18; I^2, 0; four studies; 540 patients; very low-quality evidence) (Fig. 3A) (27–29, 31, 33, 34), similar clinical pregnancy loss rates (OR, 0.25; 95% CI, 0.04–1.72; I^2, 76%;

TABLE 1

Studies comparing reproductive outcomes between patients with unexplained recurrent pregnancy loss and those without recurrent pregnancy loss after euploid blastocyst transfer.

Author, year, and country	Study design	Study population, n Definitions	Genetic platform	Clinical pregnancy rate per embryo transfer, n/n (%)	Clinical pregnancy loss rate, n/n (%)	Live birth rate per embryo transfer, n/n (%)	Remarks/limitations and RoB assessment score; quality
Lee et al. (20), 2019, and Taiwan	Retrospective cohort	Non-RPL: n = 42 patients' oocyte donation cycles RPL: n = 68 ≥2 miscarriages	Array-CGH	Non-RPL: 30/42 (71.4%) RPL: 43/68 (63.2%)	Non-RPL: 5/30 (16.7%) RPL: 3/43 (7.0%)	Non-RPL: 24/42 (57.1%) RPL: 38/68 (55.9%)	- No baseline differences between groups were observed. - Only the first IVF treatment cycle of each patient was included. - All cycles involved SET. RoB score: 5; poor quality
Wang et al. (21), 2019, and United States	Retrospective cohort	Non-RPL: n = 242 patients with no or one miscarriage, diagnosed with different infertility reasons such as male factor, decreased ovarian reserve, endometriosis, and others etc. RPL: n = 41 ≥2 miscarriages	NGS	Non-RPL: 130/242 (53.7%) RPL: 18/41 (43.9%)	NA	NA	- Ongoing pregnancy was defined as a fetal heartbeat seen on ultrasound at 8–12 wks. - No baseline differences between groups were observed. - Only the first IVF treatment cycle of each patient was included. - All treatment cycles involved SET. RoB score: 8; good quality
Kim et al. (19), 2019,[a] and United States	Retrospective cohort	Non-RPL: n = 3,975 patients with no or one miscarriage. RPL: n = 660 ≥2 miscarriages	NA	Non-RPL: 2,859/3975 (72%) RPL: 480/660 (73%)	Non-RPL: 335/2,859 (12%) RPL: 72/480 (15%)	Non-RPL: 2,524/3,975 (63%) RPL: 408/660 (62%)	- Meeting abstract - All treatment cycles involved frozen-thawed SET. - Each patient was included in one treatment cycle. RoB score: 5; fair quality.
Boynukalin et al. (22), 2020, and Turkey	Retrospective cohort	Non-RPL: n = 539 Patients with no or one miscarriage. Most patients are diagnosed with recurrent implantation failure. RPL: n = 168 ≥2 miscarriages	NGS	NA	NA	Non-RPL: 320/539 (59.4%) RPL: 83/168 (49.4%)	- Baseline comparison data for female age, BMI, and day of biopsy are lacking. - The number of previous miscarriages independently predicts live births in regression. - Data on the inclusion of only the first treatment cycle per woman are absent; all treatment cycles entail frozen-thawed SET. RoB score: 6; fair quality.
Liu et al. (23), 2020, and China	Retrospective cohort	Non-RPL: n = 212 Patients with monogenic disorders (311 PGT-M cycles) RPL: 62 patients ≥2 miscarriages (101 PGT-A cycles)	SNP and NGS	Non-RPL: 128/201 (63.7%) RPL: 45/89 (50.6%)	Non-RPL: 9/128 (7.0%) RPL: 11/45 (24.4%)	Non-RPL: 119/201 (59.2%) RPL: 34/89 (38.2%)	- Mean paternal and maternal ages were higher in the RPL group. No adjustment was made for age, BMI, or day of biopsy for direct comparison. - Age subgroup analysis: >35 and ≤35 y old. - Subsequent treatment cycles were included in the analysis. RoB score: 5; poor quality

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TABLE 1

Continued.

Author, year, and country	Study design	Study population, n Definitions	Genetic platform	Clinical pregnancy rate per embryo transfer, n/n (%)	Clinical pregnancy loss rate, n/n (%)	Live birth rate per embryo transfer, n/n (%)	Remarks/limitations and RoB assessment score; quality
Ni et al. (24), 2020, and China	Retrospective cohort	Non-RPL: n = 103 (129 cycles) patients with one miscarriage or ≤2 implantation failures or ≤1 biochemical loss RPL: n = 177 ≥2 miscarriages or biochemical pregnancy loss	Array-CGH and NGS	Non-RPL: 76/129 (58.9%) RPL: 338/570 (59.2%)	Non-RPL: 7/76 (9.2%) RPL: 69/338 (20.4%)	Non-RPL: 69/129 (53.5%) RPL: 269/558 (48.2%)	- Baseline comparison data for female age, BMI, and day of biopsy are lacking. - Some patients underwent multiple embryo transfer cycles, including a few with double transfers. - Patients with ≥4 miscarriages showed significantly higher miscarriage rates and lower live birth rates. RoB score: 7; poor quality
Cimadomo et al. (25), 2021, and Italy	Retrospective cohort	Non-RPL: n = 730 Patients with no or one miscarriage. RPL: n = 1,444 ≥2 miscarriages PGT-SR, PGT-M, and donation cycles were not included.	qPCR and NGS	Non-RPL: 730/1444 (50.5%) RPL: 72/136 (52.9%)	Non-RPL: 99/730 (13.6%) RPL: 11/72 (15.3%) Aside from live births, all other pregnancies were classified as miscarriages.	Non-RPL: 631/1,444 (43.7%) RPL: 61/136 (44.9%)	- Only the first IVF treatment cycle of each patient was included. - All treatment cycles involved SET. RoB score: 8; good quality
Bhatt et al. (31), 2021, and United States	Retrospective cohort Data from SART-CORS between 2010 and 2016	Non-RPL: n = 471 patients with tubal factor infertility RPL: n = 3,351 ≥3 pregnancy losses	NA	Not reported	Not reported	Numeric data not reported Comparable live birth rate	- Lack of numeric data to add to meta-analysis.
Kornfield et al. (26), 2022, and United States	Retrospective cohort	Non-RPL: n = 238 patients with infertility and no or one miscarriage RPL: n = 56 patients ≥2 miscarriages	Array-CGH and NGS	Non-RPL: 149/238 (62.6%) RPL: 33/56 (58.9%)	Non-RPL: 4/160 (2.5%) RPL: 0/34 (0.0%)	Non-RPL: 133/238 (55.8%) RPL: 28/34 (50.0%)	- Small sample size - Only the first IVF treatment cycle of each patient was included. - The number of transferred embryos is not equal to one. There is no data regarding the difference between the two groups. RoB score: 8; good quality

Note: BMI = body mass index; CGH = comprehensive genomic hybridization; FET = frozen-thawed embryo transfer; IVF = in vitro fertilization; NA = not available; NGS = next generation sequencing; PGT-A = preimplantation genetic testing for aneuploidy; qPCR = quantitative polymerase chain reaction; RoB score = risk of bias score using New castle Ottawa for observational studies; RPL = recurrent pregnancy loss; SART-CORS = Society for Assisted Reproductive Technology Clinic Outcome Reporting System; SET = single embryo transfer; SNP = single nucleotide polymorphism.

[a] Studies reporting per patients' reproductive outcomes data.

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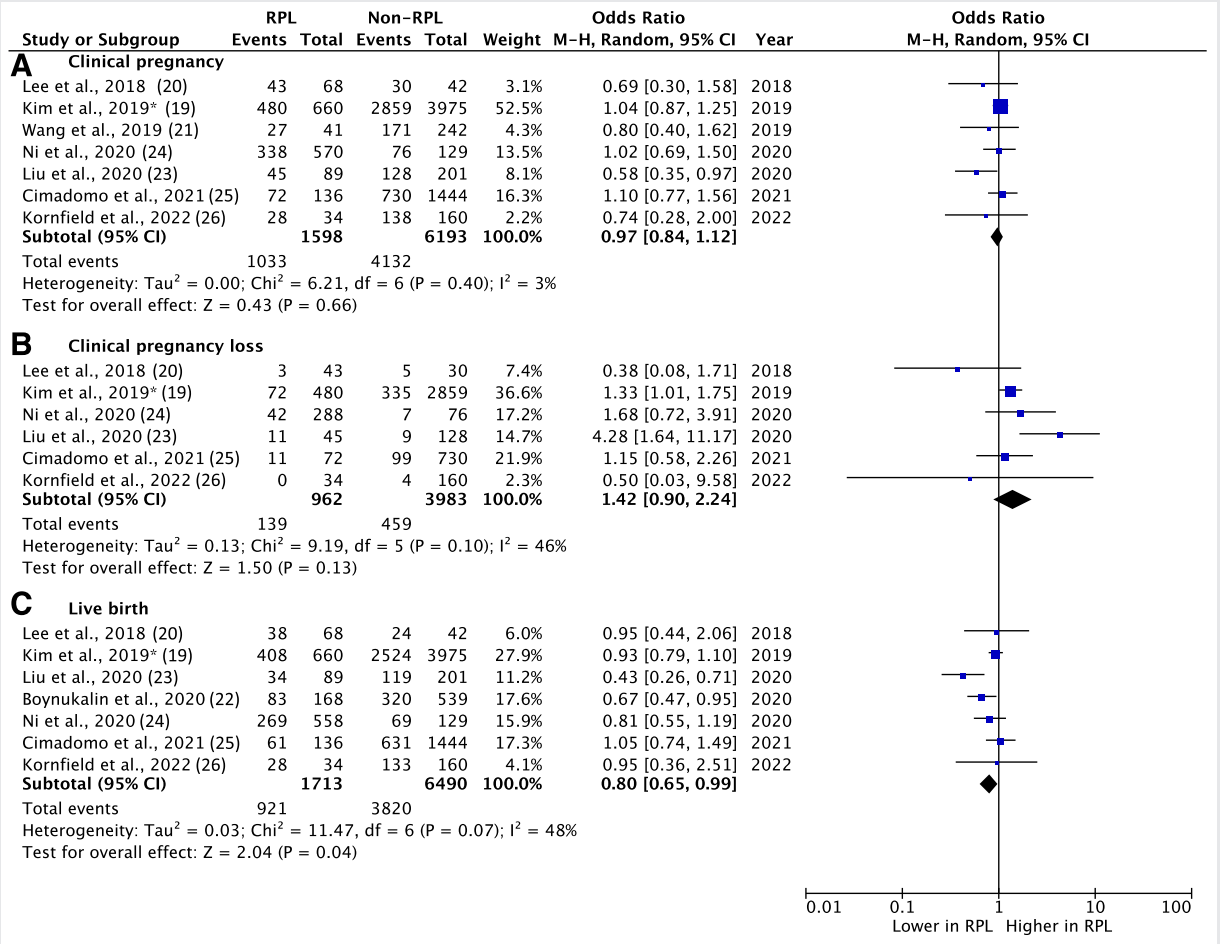
FIGURE 1



Forest plot comparing reproductive outcomes after euploid blastocyst transfer between unexplained recurrent pregnancy loss and nonrecurrent pregnancy loss patients; (**A**) clinical pregnancy rates, (**B**) clinical pregnancy loss rates, (**C**) live birth rates. CI = confidence interval; M–H = Mantel–Haenszel; RPL = recurrent pregnancy loss. *Indicate meeting abstract.

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four studies; 217 pregnancies; very low-quality evidence) (Fig. 3B), and higher LBRs (OR, 1.85; 95% CI, 1.18–2.91; I^2, 18%; four studies; 540 patients; very low-quality evidence) (Fig. 3C) per patient.

Overall, low-quality evidence from observational studies (19, 27, 28, 31–33, 43) and an RCT (29) suggest that, in patients with unexplained RPL, PGT-A could increase LBR per transfer (27, 31, 43, 45) and per patient (27, 29, 33, 45) and decrease clinical pregnancy loss rate (27, 29, 43, 45). Because the chance of LB after expectant management of patients with RPL is approximately 60%–70% (37), sufficiently powered RCTs comparing PGT-A vs. expectant management for RPL are warranted.

DISCUSSION

Our findings suggest that patients with unexplained RPL have a decent chance of LB with expectant management, although the risk of a subsequent pregnancy loss increases with the number of prior losses. Whether patients with unexplained RPL have a higher blastocyst aneuploidy rate remains uncertain, but outcomes of euploid blastocyst transfers are similar between women with and without unexplained RPL. Preimplantation genetic testing for aneuploidy seems to provide higher LBR per cycle and per patient.

Although it is encouraging that individuals experiencing RPL have the potential for a subsequent successful pregnancy through expectant management, with LBRs approximately 60%–70%, depending on maternal age and the number of previous losses (37). It is noteworthy that studies demonstrate a biologic gradient, i.e., increasing risk of subsequent pregnancy loss with increasing number of previous losses, suggesting a causal relationship. In theory, one persistent factor causing repetitive pregnancy losses can be higher aneuploidy rates or lower endometrial selectivity for euploid embryos.

Studies comparing euploidy rates between women with and without RPL yielded contradictory results. However, we have some concerns regarding the two studies that reported

TABLE 2

Studies comparing reproductive outcomes in patients with unexplained recurrent pregnancy loss undergoing in vitro fertilization treatment with and without preimplantation genetic testing for aneuploidy.

Author, year, and country	Study design	Study population, n Definition of RPL	Genetic platform	Clinical pregnancy rate per embryo transfer, n/n (%)	Clinical pregnancy loss rate, n/n (%)	Live birth rate per embryo transfer, n/n (%)	Remarks/limitations and RoB score; quality
Sato et al. (27), 2019,[a] and Japan	A multicenter prospective study	n = 79 ≥2 miscarriages without any live births, with at least one case of aneuploidy having been ascertained through prior products of conception testing.	Array-CGH	PGT-A: 14/21 (66.7%) Non-PGT-A: 10/37 (29.7%)	PGT-A: 2/14 (14.3%) Non-PGT-A: 2/10 (20.0%)	PGT-A: 11/21 (52.4%) Non-PGT-A: 8/37 (21.6%)	- Small sample size - Each patient was included in one cycle. - All treatment cycles were frozen-thawed SET. RoB score: 9; good quality
Kim et al (19)., 2019,[b] and United States	Retrospective cohort	n = 761 ≥2 pregnancy losses It is unclear whether biochemical losses are included and whether patients with RPL are unexplained.	NA	PGT-A: 480/660 (72.7%) Non-PGT-A: 62/101 (61.4%)	PGT-A: 72/480 (15.0%) Non-PGT-A: 20/62 (32.3%)	PGT-A: 408/660 (62%) Non-PGT-A: 42/101 (41%)	- Meeting abstract - Each patient was included in one treatment cycle. - All treatment cycles were frozen-thawed SET. - Female age was not matched between groups. RoB score: 5; poor quality
Lei et al. (28), 2019, and China	Retrospective cohort	n = 506 ≥2 failed clinical pregnancies occurring between 6 and 24 wk of gestation.	SNP microarray	PGT-A: 89/167 (53.3%) Non-PGT-A: 133/346 (38.4%)	PGT-A: 12/89 (13.5%) Non-PGT-A: 46/133 (34.6%)	PGT-A: 75/167 (44.9%) Non-PGT-A: 87/346 (25.1%)	- More than one treatment cycle per patient. - PGT-A group: SET - Non-PGT-A group: one or two embryos on day 3 or day 5/6 (fresh or frozen). RoB score: 8; good quality
Sui et al. (29), 2021,[a] and China	Single-center randomized controlled trial	n = 207 ≥2 failed clinical pregnancies. Patients with a previous pregnancy loss because of chromosomal abnormalities were excluded.	SNP microarray	PGT-A: 59/115 (51.3%) Non-PGT-A: 49/156 (31.4%)	PGT-A: 2/59 (3.4%) Non-PGT-A: 18/49 (36.7%)	PGT-A: 50/115 (43.5%) Non-PGT-A: 29/156 (18.6%)	- More than one treatment cycle per patient. - PGT-A group: SET - Non-PGT-A group: One or two embryos on day 3 or day 5/6 (fresh or frozen). RoB score: 9; good quality
Mantravadi et al. (30), 2021,[b] and India	Retrospective cohort	n = 112 ≥2 failed clinical pregnancies. Lack of detailed description of the RPL definition.	NGS	NA	NA	PGT-A: 27/82 (32.3%) Non-PGT-A: 9/30 (30.0%)	- Meeting abstract - Small sample size - No data regarding whether more than one treatment cycle per patient was analyzed. - PGT-A group: SET - Non-PGT-A group: two blastocyst transfer RoB score: 5; poor quality

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TABLE 2

Continued.

Author, year, and country	Study design	Study population, n Definition of RPL	Genetic platform	Clinical pregnancy rate per embryo transfer, n/n (%)	Clinical pregnancy loss rate, n/n (%)	Live birth rate per embryo transfer, n/n (%)	Remarks/limitations and RoB score; quality
Bhatt et al. (31), 2021, and United States	Retrospective cohort of SART-CORS from 2010–2016	n = 8,404 ≥3 previous pregnancy losses. The SART database does not provide clinical details regarding a specific cause for the RPL.	NA	PGT-A: 2,510/4,288 (58.4%) Non-PGT-A: 1,898/4,116 (46.1%)	PGT-A: 463/2,510 (18.4%) Non-PGT-A: 517/1,898 (27.2%)	PGT-A: 2,047/4,288 (47.7%) Non-PGT-A: 1,381/4,116 (33.5%)	- No data regarding whether more than one treatment cycle per patient was analyzed. - All treatment cycles are FET. - No data regarding the number and days of embryos transferred per treatment cycle. RoB score: 9; good quality
Pavlovic et al. (32), 2023,[b] and United States	Retrospective multicenter cohort	n = 589 ≥2 failed clinical pregnancies	NA	PGT-A: 260/442 (58.8%) Non-PGT-A: 67/147 (45.6%)	PGT-A: 64/260 (24.6%) Non-PGT-A: 20/67 (29.9%)	PGT-A:196/442 (44.3%) Non-PGT-A: 47/147 (32%)	- Meeting abstract - No data regarding whether more than one cycle per patient was analyzed. - All treatment cycles were FET and SET - No data regarding the number and day of embryos transferred per treatment cycle RoB score: 5; poor quality
Kato et al. (33), 2023,[a] and Japan	Retrospective cohort	n = 14 ≥2 failed clinical pregnancies without any live birth and at least one case of aneuploidy had been ascertained through prior products of conception testing.	WGA/Microarray	PGT-A: 5/5 (100%) Non-PGT-A: 5/9 (55.6%)	PGT-A: 1/5 (20%) Non-PGT-A: 5/5 (100%)	PGT-A: 4/5 (80%) Non-PGT-A: 0/9 (0%)	- Small sample size - Each patient was included in one treatment cycle. - All treatment cycles were SET and FET. RoB score: 9; good quality
Shi et al. (34), 2023,[a] and China	Retrospective cohort	n = 232 ≥2 pregnancy losses (ESHRE RPL guideline definition)	NGS	PGT-A: 69/120 (57.5%) Non-PGT-A: 34/102 (33.3%)	PGT-A: 15/69 (21.7%) Non-PGT-A: 5/34 (14.7%)	PGT-A: 54/120 (45.0%) Non-PGT-A: 29/102 (28.4%)	- More than one cycle per patient. - First-cycle data per patient is also available. - All cycles were SET. - Non-PGT-A group: Fresh embryo transfer. - No data regarding the day of embryos transferred in the non-PGT-A arm. RoB score: 7; Good quality

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TABLE 2

Continued.

Author, year, and country	Study design	Study population, n Definition of RPL	Genetic platform	Clinical pregnancy rate per embryo transfer, n/n (%)	Clinical pregnancy loss rate, n/n (%)	Live birth rate per embryo transfer, n/n (%)	Remarks/limitations and RoB score; quality
Mei et al. (35), 2024, and China	Retrospective cohort	n = 72 ≥2 pregnancy losses	NGS	PGT-A: 38/49 (77.5%) Non-PGT-A : 15/23 (70.3%)	NA	NA	- Ongoing pregnancy was defined as viable intrauterine pregnancy persisting for 12 wks after embryo transfer. - Small sample size - Each patient was included in only one FET treatment cycle. - PGT-A group: SET - Non-PGT-A group: one or two cleaved embryos or blastocysts were transferred in the FET treatment cycle. RoB score: 5; poor quality
Kim et al. (36), 2024, and Korea	Retrospective cohort	n = 212 ≥2 pregnancy losses before 20 wks of gestation.	Array-CGH or NGS	PGT-A: 36/57 (63.2%) Non-PGT-A: 70/132 (53.0%)	PGT-A: 6/36 (16.7%) Non-PGT-A: 35/70 (50.0%)	PGT-A: 28/57 (49.1%) Non-PGT-A: 32/132 (24.2%)	- Each patient was included with only the first FET treatment cycle. - One or two blastocysts were transferred in both groups. RoB score:5; poor quality

Note: BMI = body mass index; CGH = comprehensive genomic hybridization; ESHRE = European Society of Human Reproduction and Embryology; FET = frozen-thawed embryo transfer; NA = not available; NGS = next generation sequencing; PGT-A = preimplantation genetic testing for aneuploidy; RoB score = risk of bias score using New castle Ottawa for observational studies; RPL = recurrent pregnancy loss; SART-CORS = Society for Assisted Reproductive Technology Clinic Outcome Reporting System; SET = single embryo transfer; SNP = single nucleotide polymorphism; WGA = whole genome amplification.

[a] Studies reporting per patients' reproductive outcomes data.

[b] Studies presented as a meeting abstract.

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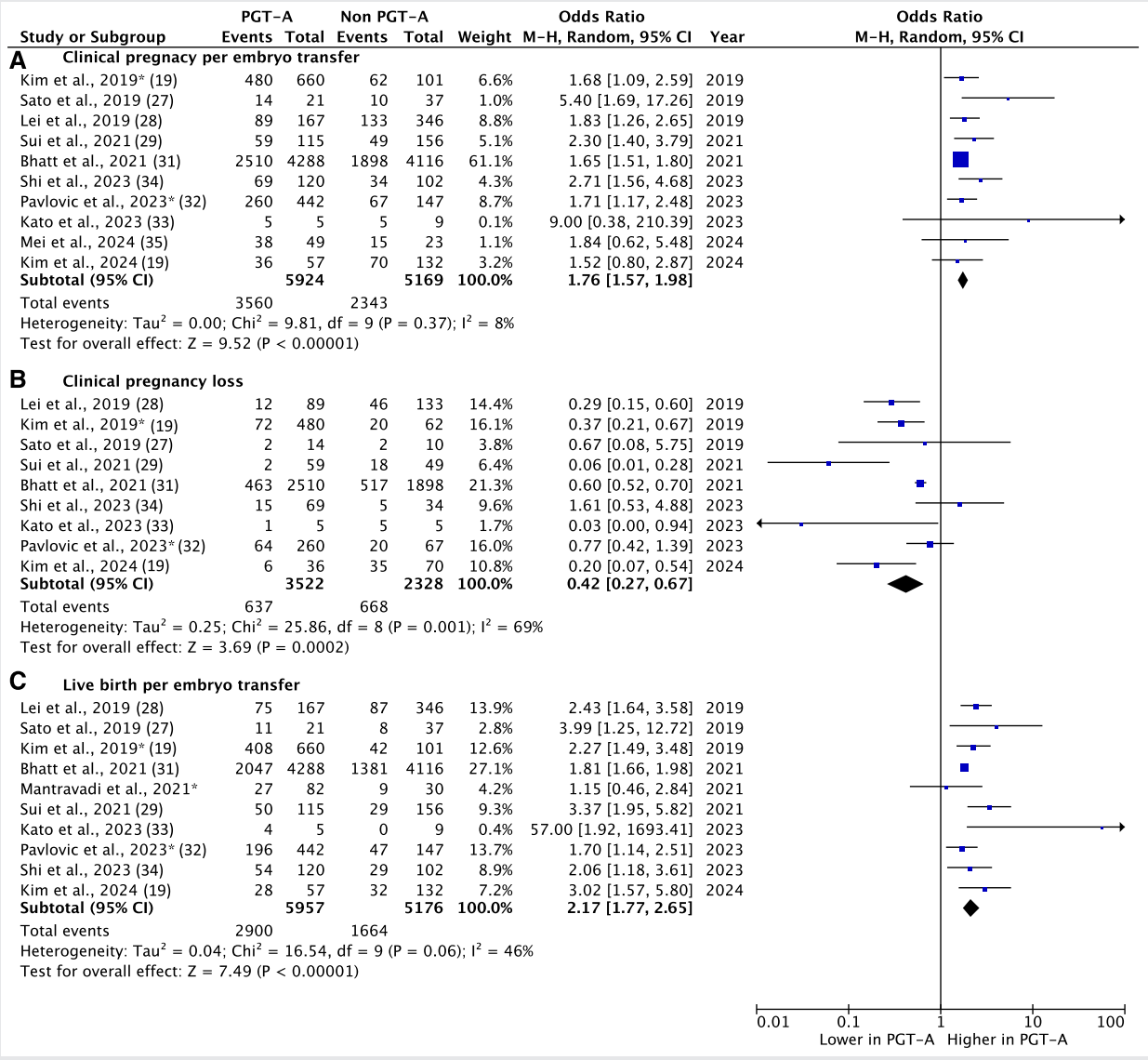
FIGURE 2



Forest plot comparing reproductive outcomes per embryo transfer in patients with unexplained recurrent pregnancy loss undergoing in vitro fertilization treatment with and without preimplantation genetic testing for aneuploidy (PGT-A); (**A**) clinical pregnancy rates, (**B**) clinical pregnancy loss rates, (**C**) live birth rates. CI = confidence interval; M–H = Mantel–Haenszel; RPL = recurrent pregnancy loss. *Indicate meeting abstract.

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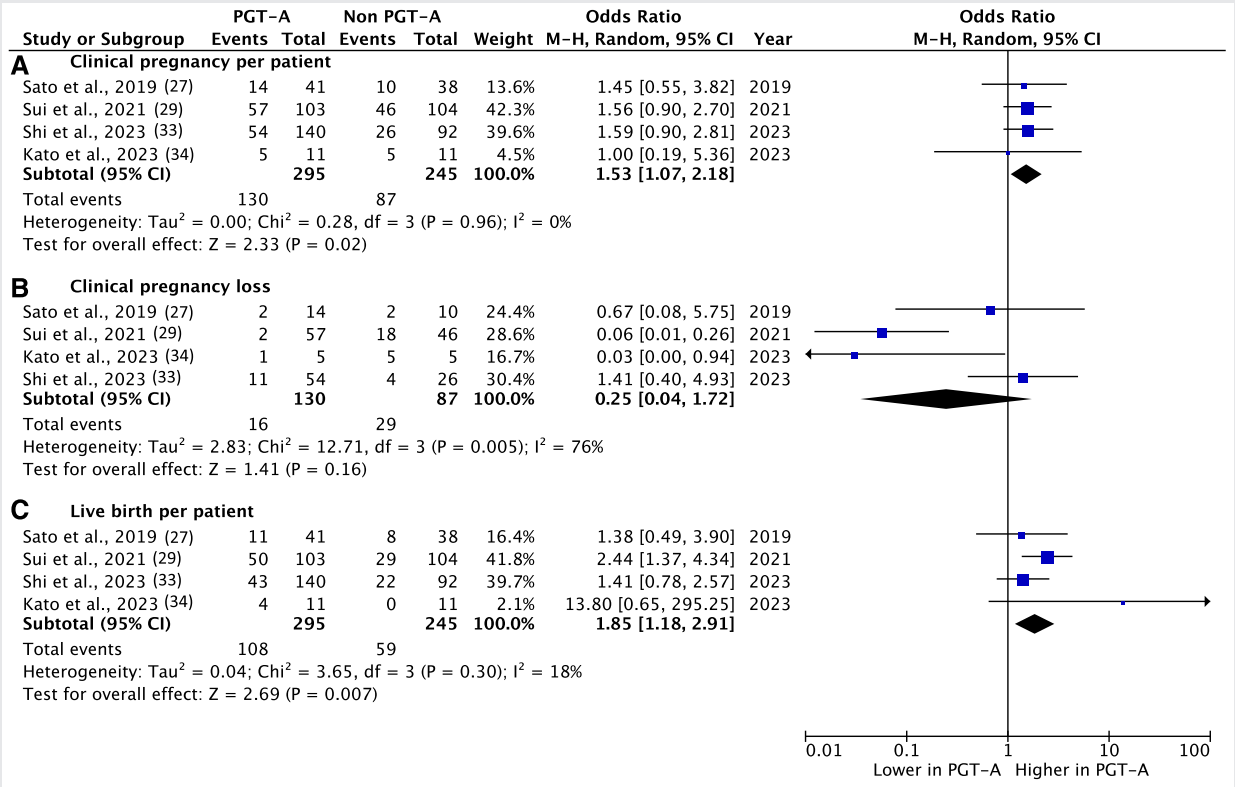
higher aneuploidy in patients with RPL (23, 41). Results by Kort et al. (41) can be questioned because patients with RPL were significantly older, and whether such a strong confounder as age can be adequately adjusted for by a regression model or a 2.5-year difference alone would lead to an approximately 30% increase in aneuploidy rate is debatable. The study by Liu et al. (23) had a limited sample size, involved patients with multiple cycles, and reported unadjusted analyses. Overall, we think the available evidence trends in favor of similar euploidy rates between patients with and without RPL. High-quality large prospective studies comparing euploidy rates between unexplained RPL and non-RPL controls undergoing ART with PGT-A are still needed. The comparators should be similar for other factors that can also affect aneuploidy and pregnancy loss rates, such as female age. When the answer is affirmative, PGT-A might offer a potential solution for unexplained RPL.

Although our meta-analysis suggests similar clinical pregnancy and pregnancy loss rates but lower LBR with euploid blastocysts in women with unexplained RPL, sensitivity analysis with good quality studies suggests similar LBRs. Our impression is the latter is closer to the truth. Bhatt and colleagues analyzed

FIGURE 3



Forest plot comparing reproductive outcomes per patient in patients with unexplained recurrent pregnancy loss undergoing in vitro fertilization treatment with and without preimplantation genetic testing for aneuploidy (PGT-A); (**A**) clinical pregnancy rates, (**B**) clinical pregnancy loss rates, (**C**) live birth rates. CI = confidence interval; M–H = Mantel–Haenszel; RPL = recurrent pregnancy loss. *Indicate meeting abstract.

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data from the Society of Assisted Reproductive Technologies Clinical Outcomes Reporting System, for frozen ET (FET) cycles conducted between 2010 and 2016 in the United States. A total of 12,631 FET cycles of 10,060 couples with RPL were included. A total of 4,287 cycles with an indication for tubal factor comprised the control group (31). This large study was not included in the meta-analysis because the figures were not presented in the manuscript; however, similar LB, clinical pregnancy, pregnancy loss, ectopic pregnancy, and biochemical pregnancy loss rates after a euploid ET between patients with RPL and tubal factor were reported. The findings remained consistent in adjusted analyses. The sample size of this study is larger than the total sample included in the meta-analysis and had the results been reported in an extractable manner and included in the meta-analysis, it would almost certainly change the pooled estimate, especially given the fact that the upper boundary of the CI was already 0.99. A similar LB assumption is also consistent with the observed similar clinical pregnancy and pregnancy loss rates.

Demonstration of similar aneuploidy rates in POC by CCA does not support the "checkpoint hypothesis," which posits that a less selective endometrium allows implantation of incompetent embryos and leads to RPL. More than half of all pregnancy losses, including those in women with RPL, are attributed to numeric chromosome errors, with trisomy being the most common, especially with advancing maternal age, followed by polyploidy and monosomy X (46). These "aneuploid" pregnancy losses are believed to occur randomly, implying that the risk of a subsequent pregnancy loss would not be increased. In contrast, "euploid" pregnancy losses are more frequently diagnosed with an increasing number of previous pregnancy losses. Specifically, the risk of euploid pregnancy losses increases in parallel with the number of previous losses, whereas the risk of pregnancy losses from sporadic aneuploidies remains mostly constant (38, 47). These observations may suggest the presence of another embryonic factor than aneuploidy, rather than an endometrial factor for RPL.

Because most pregnancy losses are due to aneuploidy (45), PGT-A can be expected to decrease their incidence. As an embryo deselection tool, PGT-A with trophectoderm biopsy and 24-chromosome analysis offers several advantages in the general ART population. These include facilitating a single ET (48) irrespective of female age and number of previous ART attempts, enhancing LBR per single ET (15, 49), reducing pregnancy loss rates (15, 49, 50), expediting the time to achieve a singleton LB (20), and potentially decreasing drop-out rates. However, it is important to consider potential drawbacks such as the risks of misdiagnosis depending on genetic laboratory

performance (51), embryo damage inflicted by biopsy (52), increased costs (53), and PGT-A does not necessarily improve the cumulative delivery rate per aspiration cycle in the general ART population (54).

In theory, PGT-A is expected to decrease pregnancy loss rates because of aneuploidy in patients with unexplained RPL. On the basis of a global survey, most respondents believe that PGT-A might enhance LBRs in patients with unexplained RPL, despite the ongoing debate and the lack of robust evidence (17). Although Kutteh et al. (12) suggest that PGT-A should only be considered for patients with aneuploid RPL after a period of attempts at spontaneous conception, some authorities caution against the premature adoption of PGT-A and recommend the current standard of care for the management of unexplained RPL, which is expectant management (55). It is possible that PGT-A might still benefit couples with poor embryo quality, challenging the conclusions of Murugappan et al. (43), who arbitrarily excluded poor quality embryos from PGT-A.

Although awaiting more robust studies, the current evidence provides insights as to which patient populations may benefit from PGT-A for the management of unexplained RPL. Patients with adequate ovarian reserve who are already undergoing IVF may find PGT-A beneficial because they are expected to have an adequately high number of gametes amenable for PGT-A, potentially reducing the time to LB. The observed trend toward lower pregnancy loss with PGT-A suggests that, in the long term, PGT-A may decrease the number of pregnancy losses until LB is achieved in such patients. Patients of advanced age who have a high incidence of aneuploidy may be considered suitable candidates to avoid the risk of repetitive aneuploid pregnancy losses. Patients with a history of previous aneuploid loss could also benefit from PGT-A, as suggested by Kutteh et al. (12). Additionally, the coexistence of other indications for PGT-A might further increase the potential benefits for patients.

Future research perspectives on embryo selection for patients with unexplained RPL patients undergoing ART

With the current technology, invasive interventions are employed for genetic testing of embryos. A prospective multicenter nonselection study found no adverse impact of trophectoderm biopsy on sustained implantation rates (56). However, concerns persist regarding the potential detrimental effect of biopsy and increased costs, driving the exploration of noninvasive assessment methods (57). After the initial observation of DNA in embryo culture medium (58), several studies investigating chromosomal ploidy in culture medium (59, 60) or blastocoelic fluid (61) have emerged, such as the first report of a noninvasive chromosome screening (NICS) assay by Xu et al. (62). Xi et al. (63) conducted the first large cohort study to assess the efficacy of NICS as a diagnostic tool for the prediction of ART outcomes in women with a history of RPL (63). Of the 173 patients with RPL, 84 underwent ART with NICS, and 89 underwent ART without NICS. In the non-NICS group, selection relied on blastocyst morphology. In total, 113 FET cycles were performed in the NICS group, with 136 high-quality blastocysts transferred to 89 patients in the non-NICS group. The study revealed statistically significant differences, with the NICS group exhibiting higher ongoing pregnancy rates (40.7% vs. 25.0%, P=.037), LBRs (38.9% vs. 20.6%, P=.008), and lower pregnancy loss rates (17.9% vs. 42.6%, P=.038) per FET cycle. These differences remained significant in an adjusted analysis. Artificial intelligence models on the basis of morphokinetic characteristics of embryos are also under study as noninvasive embryo selection tools to predict embryo ploidy and risk of pregnancy loss (64).

Xiang et al. (65) performed whole-exome sequencing analysis in 100 patients with RPL to more comprehensively investigate potential genetic variants associated with unexplained RPL. However, given the complexity of the implantation process and the potential involvement of many genes in pregnancy losses, verification of candidate genes through experiments is necessary. In the future, studies exploring the causal genetic defects for unexplained RPL can enable calculation of an individual's risk for pregnancy loss (66).

Although promising results have been reported with these novel techniques, future studies evaluating reproductive outcomes, including comparison with expectant management, are necessary to determine their efficacy.

CONCLUSION

Despite some data suggesting similar aneuploidy rates in patients with unexplained RPL, uncertainty remains because of low-quality evidence. The transfer of euploid blastocysts likely yields comparable LBRs in patients with unexplained RPL and non-RPL. Pooled data from observational studies indicate that PGT-A could increase the LBR per ET and per patient while reducing the clinical pregnancy loss rate in patients with unexplained RPL. Although it may not be offered to every patient, arguably patients with adequate ovarian reserve undergoing ART may find PGT-A beneficial because it increases the number of gametes available for conception, potentially reducing the time to LB for couples capable of producing competent embryos. Advanced age patients, who have a high incidence of aneuploid embryos, can be also considered suitable candidates to avoid the risk of repetitive aneuploid pregnancy loss and developing infertility because of age-related fertility decline. Patients with a previous aneuploid pregnancy loss history can also consider PGT-A.

The clinical guidelines from ASRM and European Society for Human Reproduction and Embryology do not recommend PGT-A for management of unexplained RPL (1, 3). Given the fact that these patients are not infertile and do not need ART in the first place and the absence of direct and high-quality evidence for the benefit of PGT-A, this stance is understandable from a strictly evidence-based perspective. On the other hand, unexplained RPL is a multifaceted distressing condition for patients, and it seems unlikely that the anticipated high-quality evidence from conclusive RCTs comparing PGT-A vs. expectant management will become available soon. Meanwhile, CCA of POC, another investigation that is not recommended in the current guidelines, can be considered to provide the patient with an explanation of the problem, and PGT-A will remain a choice that can be considered on an individual basis.

CRediT Authorship Contribution Statement

Sezcan Mumusoglu: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. Savci Bekir Telek: Investigation, Writing – original draft. Baris Ata: Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

Declaration of Interests

S.M. has nothing to disclose. S.B.T. has nothing to disclose. B.A. has nothing to disclose.

REFERENCES

1. Practice Committee of the American Society of Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. Fertil Steril 2020;113:533–5.
2. Roberts SCM, Beam N, Liu G, Upadhyay UD, Leslie DL, Ba D, et al. Miscarriage treatment-related morbidities and adverse events in hospitals, ambulatory surgery centers, and office-based settings. J Patient Saf 2020;16:e317–23.
3. ESHRE Guideline Group on RPL, Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, et al. ESHRE guideline: recurrent pregnancy loss: an update in 2022. Hum Reprod Open 2023;2023:hoad002.
4. Larsen EC, Christiansen OB, Kolte AM, Macklon N. New insights into mechanisms behind miscarriage. BMC Med 2013;11:154.
5. Musters AM, Koot YE, van den Boogaard NM, Kaaijk E, Macklon NS, van der Veen F, et al. Supportive care for women with recurrent miscarriage: a survey to quantify women's preferences. Hum Reprod 2013;28:398–405.
6. Quenby S, Gallos ID, Dhillon-Smith RK, Podesek M, Stephenson MD, Fisher J, et al. Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. Lancet 2021;397:1658–67.
7. Franssen MT, Korevaar JC, Leschot NJ, Bossuyt PM, Knegt AC, Gerssen-Schoorl KB, et al. Selective chromosome analysis in couples with two or more miscarriages: case-control study. Br Med J 2005;331:137–41.
8. Rikken JF, Kowalik CR, Emanuel MH, Mol BW, Van der Veen F, van Wely M, et al. Septum resection for women of reproductive age with a septate uterus. Cochrane Database Syst Rev 2017;1:CD008576.
9. Dong AC, Morgan J, Kane M, Stagnaro-Green A, Stephenson MD. Subclinical hypothyroidism and thyroid autoimmunity in recurrent pregnancy loss: a systematic review and meta-analysis. Fertil Steril 2020;113:587–600.e1.
10. Bramham K, Hunt BJ, Germain S, Calatayud I, Khamashta M, Bewley S, et al. Pregnancy outcome in different clinical phenotypes of antiphospholipid syndrome. Lupus 2010;19:58–64.
11. Zhu X, Li J, Zhu Y, Wang W, Wu X, Yang Y, et al. Application of chromosomal microarray analysis in products of miscarriage. Mol Cytogenet 2018;11:44.
12. Kutteh WH, Papas RS, Maisenbacher MK, Dahdouh EM. Role of genetic analysis of products of conception and PGT in managing early pregnancy loss. Reprod Biomed Online 2024;49:103738.
13. Popescu F, Jaslow CR, Kutteh WH. Recurrent pregnancy loss evaluation combined with 24-chromosome microarray of miscarriage tissue provides a probable or definite cause of pregnancy loss in over 90% of patients. Hum Reprod 2018;33:579–87.
14. de Assis V, Giugni CS, Ros ST. Evaluation of recurrent pregnancy loss. Obstet Gynecol 2024;143:645–59.
15. Rubio C, Bellver J, Rodrigo L, Castillon G, Guillen A, Vidal C, et al. In vitro fertilization with preimplantation genetic diagnosis for aneuploidies in advanced maternal age: a randomized, controlled study. Fertil Steril 2017;107:1122–9.
16. Maisenbacher MK, Merrion K, Levy B, Kutteh WH. Single nucleotide polymorphism (SNP) array analysis of 63,277 products of conception (POC) samples: a 10-year laboratory experience. Fertil Steril 2020;114:e47.
17. Weissman A, Shoham G, Shoham Z, Fishel S, Leong M, Yaron Y. Preimplantation genetic screening: results of a worldwide web-based survey. Reprod Biomed Online 2017;35:693–700.
18. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Br Med J 2008;336:924–6.
19. Kim JG, Murugappan G, Lathi RB, Kort JD, Hanson BM, Tiegs AW, et al. Preimplantation genetic testing for aneuploidy (PGT-A) reduces miscarriage and improves live birth rates in recurrent pregnancy loss patients. Fertil Steril 2019;112:e401.
20. Lee CI, Wu CH, Pai YP, Chang YJ, Chen CI, Lee TH, et al. Performance of preimplantation genetic testing for aneuploidy in IVF cycles for patients with advanced maternal age, repeat implantation failure, and idiopathic recurrent miscarriage. Taiwan J Obstet Gynecol 2019;58:239–43.
21. Wang A, Kort J, Westphal L. Miscarriage history association with euploid embryo transfer outcomes. Reprod Biomed Online 2019;39:617–23.
22. Boynukalin FK, Gultomruk M, Cavkaytar S, Turgut E, Findikli N, Serdarogullari M, et al. Parameters impacting the live birth rate per transfer after frozen single euploid blastocyst transfer. PLoS One 2020;15:e0227619.
23. Liu XY, Fan Q, Wang J, Li R, Xu Y, Guo J, et al. Higher chromosomal abnormality rate in blastocysts from young patients with idiopathic recurrent pregnancy loss. Fertil Steril 2020;113:853–64.
24. Ni T, Wu Q, Zhu Y, Jiang W, Zhang Q, Li Y, et al. Comprehensive analysis of the associations between previous pregnancy failures and blastocyst aneuploidy as well as pregnancy outcomes after PGT-A. J Assist Reprod Genet 2020;37:579–88.
25. Cimadomo D, Capalbo A, Dovere L, Tacconi L, Soscia D, Giancani A, et al. Leave the past behind: women's reproductive history shows no association with blastocysts' euploidy and limited association with live birth rates after euploid embryo transfers. Hum Reprod 2021;36:929–40.
26. Kornfield MS, Parker P, Rubin E, Garg B, O'Leary T, Amato P, et al. Patients with recurrent pregnancy loss have similar embryonic preimplantation genetic testing aneuploidy rates and in vitro fertilization outcomes to infertility patients. F S Rep 2022;3:342–8.
27. Sato T, Sugiura-Ogasawara M, Ozawa F, Yamamoto T, Kato T, Kurahashi H, et al. Preimplantation genetic testing for aneuploidy: a comparison of live birth rates in patients with recurrent pregnancy loss due to embryonic aneuploidy or recurrent implantation failure. Hum Reprod 2019;34:2340–8.
28. Lei CX, Ye JF, Sui YL, Zhang YP, Sun XX. Retrospective cohort study of preimplantation genetic testing for aneuploidy with comprehensive chromosome screening versus nonpreimplantation genetic testing in normal karyotype, secondary infertility patients with recurrent pregnancy loss. Reprod Dev Med 2019;3:205–12.
29. Sui YL, Lei CX, Ye JF, Fu J, Zhang S, Peng XD, et al. In vitro fertilization with single-nucleotide polymorphism microarray-based preimplantation genetic testing for aneuploidy significantly improves clinical outcomes in infertile women with recurrent pregnancy loss: a randomized controlled trial. Reprod Dev Med 2020;4:32–41.
30. Mantravadi K, Mathew S, Soorve S, Rao DG, Karunakaran S. Does Preimplantation genetic testing for aneuploidy optimise the reproductive outcomes in women with idiopathic recurrent pregnancy loss? Fertil Steril 2020;114:e437.
31. Bhatt SJ, Marchetto NM, Roy J, Morelli SS, McGovern PG. Pregnancy outcomes following in vitro fertilization frozen embryo transfer (IVF-FET) with or without preimplantation genetic testing for aneuploidy (PGT-A) in women with recurrent pregnancy loss (RPL): a SART-CORS study. Hum Reprod 2021;36:2339–44.
32. Pavlovic ZJ, Gallahan S, Papri S, New EP, Sprague R, Silva C, et al. Analysis of pregnancy outcomes in patients with idiopathic recurrent pregnancy loss who utilized preimplantation genetic testing for aneuploidy. Fertil Steril 2023;120:e77–8.
33. Kato K, Kuroda T, Yamadera-Egawa R, Ezoe K, Aoyama N, Usami A, et al. Preimplantation genetic testing for aneuploidy for recurrent pregnancy loss and recurrent implantation failure in minimal ovarian stimulation cycle for women aged 35-42 years: live birth rate, developmental follow-up of children, and embryo ranking. Reprod Sci 2023;30:974–83.
34. Shi X, Tang Y, Liu C, Li W, Lin H, Mao W, et al. Effects of NGS-based PGT-a for idiopathic recurrent pregnancy loss and implantation failure: a retrospective cohort study. Syst Biol Reprod Med 2023;69:354–65.

35. Mei Y, Wang Y, He L, Zheng J, Lin Y, Wang F. Performance of preimplantation genetic testing for aneuploidy for patients with unexplained recurrent pregnancy loss and repeated implantation failure. Heliyon 2024;10:e31983.
36. Kim JW, Lee SY, Hur CY, Lim JH, Park CK. Clinical outcomes of preimplantation genetic testing for aneuploidy in high-risk patients: a retrospective cohort study. Clin Exp Reprod Med 2024;51:75–84.
37. Magnus MC, Wilcox AJ, Morken NH, Weinberg CR, Håberg SE. Role of maternal age and pregnancy history in risk of miscarriage: prospective register based study. Br Med J 2019;364:l869.
38. Coomarasamy A, Devall AJ, Brosens JJ, Quenby S, Stephenson MD, Sierra S, et al. Micronized vaginal progesterone to prevent miscarriage: a critical evaluation of randomized evidence. Am J Obstet Gynecol 2020;223:167–76.
39. Coomarasamy A, Williams H, Truchanowicz E, Seed PT, Small R, Quenby S, et al. PROMISE: first-trimester progesterone therapy in women with a history of unexplained recurrent miscarriages - a randomised, double-blind, placebo–controlled, international multicentre trial and economic evaluation. Health Technol Assess 2016;20:1–92.
40. Coomarasamy A, Devall AJ, Cheed V, Harb H, Middleton LJ, Gallos ID, et al. A randomized trial of progesterone in women with bleeding in early pregnancy. N Engl J Med 2019;380:1815–24.
41. Kort JD, McCoy RC, Demko Z, Lathi RB. Are blastocyst aneuploidy rates different between fertile and infertile populations? J Assist Reprod Genet 2018;35:403–8.
42. Turgut NE, Boynukalin FK, Gultomruk M, Yarkiner Z, Abali R, Bahceci M. The number of prior pregnancy losses does not impact euploidy rates in young patients with idiopathic recurrent pregnancy loss. Arch Gynecol Obstet 2023;308:1567–75.
43. Murugappan G, Shahine LK, Perfetto CO, Hickok LR, Lathi RB. Intent to treat analysis of in vitro fertilization and preimplantation genetic screening versus expectant management in patients with recurrent pregnancy loss. Hum Reprod 2016;31:1668–74.
44. Rienzi L, Capalbo A, Vajta G, Ubaldi FM. PGS for recurrent pregnancy loss: still an open question. Hum Reprod 2017;32:476–7.
45. Pantou A, Mitrakos A, Kokkali G, Petroutsou K, Tounta G, Lazaros L, et al. The impact of preimplantation genetic testing for aneuploidies (PGT-A) on clinical outcomes in high risk patients. J Assist Reprod Genet 2022;39:1341–9.
46. Stephenson MD, Awartani KA, Robinson WP. Cytogenetic analysis of miscarriages from couples with recurrent miscarriage: a case-control study. Hum Reprod 2002;17:446–51.
47. Ogasawara M, Aoki K, Okada S, Suzumori K. Embryonic karyotype of abortuses in relation to the number of previous miscarriages. Fertil Steril 2000;73:300–4.
48. Franasiak JM, Forman EJ, Hong KH, Werner MD, Upham KM, Treff NR, et al. The nature of aneuploidy with increasing age of the female partner: a review of 15,169 consecutive trophectoderm biopsies evaluated with comprehensive chromosomal screening. Fertil Steril 2014;101:656–63.e1.
49. Forman EJ, Hong KH, Ferry KM, Tao X, Taylor D, Levy B, et al. In vitro fertilization with single euploid blastocyst transfer: a randomized controlled trial. Fertil Steril 2013;100:100–7.e1.
50. Yang Z, Liu J, Collins GS, Salem SA, Liu X, Lyle SS, et al. Selection of single blastocysts for fresh transfer via standard morphology assessment alone and with array CGH for good prognosis IVF patients: results from a randomized pilot study. Mol Cytogenet 2012;5:24.
51. Bardos J, Kwal J, Caswell W, Jahandideh S, Stratton M, Tucker M, et al. Reproductive genetics laboratory may impact euploid blastocyst and live birth rates: a comparison of 4 national laboratories' PGT-A results from vitrified donor oocytes. Fertil Steril 2023;119:29–35.
52. Scott RT Jr, Upham KM, Forman EJ, Zhao T, Treff NR. Cleavage-stage biopsy significantly impairs human embryonic implantation potential while blastocyst biopsy does not: a randomized and paired clinical trial. Fertil Steril 2013;100:624–30.
53. Murugappan G, Ohno MS, Lathi RB. Cost-effectiveness analysis of preimplantation genetic screening and in vitro fertilization versus expectant management in patients with unexplained recurrent pregnancy loss. Fertil Steril 2015;103:1215–20.
54. Yan J, Qin Y, Zhao H, Sun Y, Gong F, Li R, et al. Live Birth with or without preimplantation genetic testing for aneuploidy. N Engl J Med 2021;385:2047–58.
55. Perfetto CO, Murugappan G, Lathi RB. Time to next pregnancy in spontaneous pregnancies versus treatment cycles in fertile patients with recurrent pregnancy loss. Fertil Res Pract 2015;1:5.
56. Tiegs AW, Tao X, Zhan Y, Whitehead C, Kim J, Hanson B, et al. A multicenter, prospective, blinded, nonselection study evaluating the predictive value of an aneuploid diagnosis using a targeted next-generation sequencing-based preimplantation genetic testing for aneuploidy assay and impact of biopsy. Fertil Steril 2021;115:627–37.
57. Cornelisse S, Zagers M, Kostova E, Fleischer K, van Wely M, Mastenbroek S. Preimplantation genetic testing for aneuploidies (abnormal number of chromosomes) in in vitro fertilisation. Cochrane Database Syst Rev 2020;9:CD005291.
58. Stigliani S, Anserini P, Venturini PL, Scaruffi P. Mitochondrial DNA content in embryo culture medium is significantly associated with human embryo fragmentation. Hum Reprod 2013;28:2652–60.
59. Shamonki MI, Jin H, Haimowitz Z, Liu L. Proof of concept: preimplantation genetic screening without embryo biopsy through analysis of cell-free DNA in spent embryo culture media. Fertil Steril 2016;106:1312–8.
60. Yeung QSY, Zhang YX, Chung JPW, Lui WT, Kwok YKY, Gui B, et al. A prospective study of non-invasive preimplantation genetic testing for aneuploidies (NiPGT-A) using next-generation sequencing (NGS) on spent culture media (SCM). J Assist Reprod Genet 2019;36:1609–21.
61. Gianaroli L, Magli MC, Pomante A, Crivello AM, Cafueri G, Valerio M, et al. Blastocentesis: a source of DNA for preimplantation genetic testing. Results from a pilot study. Fertil Steril 2014;102:1692–9.e6.
62. Xu J, Fang R, Chen L, Chen D, Xiao JP, Yang W, et al. Noninvasive chromosome screening of human embryos by genome sequencing of embryo culture medium for in vitro fertilization. Proc Natl Acad Sci U S A 2016;113:11907–12.
63. Xi H, Qiu L, Yao Y, Luo L, Sui L, Fu Y, et al. Noninvasive chromosome screening for evaluating the clinical outcomes of patients with recurrent pregnancy loss or repeated implantation failure. Front Endocrinol (Lausanne) 2022;13:896357.
64. Bamford T, Barrie A, Montgomery S, Dhillon-Smith R, Campbell A, Easter C, et al. Morphological and morphokinetic associations with aneuploidy: a systematic review and meta-analysis. Hum Reprod Update 2022;28:656–86.
65. Xiang H, Wang C, Pan H, Hu Q, Wang R, Xu Z, et al. Exome-sequencing identifies novel genes associated with recurrent pregnancy loss in a Chinese cohort. Front Genet 2021;12:746082.
66. Polyakov A, Amor DJ, Savulescu J, Gyngell C, Georgiou EX, Ross V, et al. Polygenic risk score for embryo selection-not ready for prime time. Hum Reprod 2022;37:2229–36.

Test genéticos preimplantacionales para aneuploidía en abortos recurrentes de causa inexplicable: una revisión sistemática y metanálisis

Importancia: Los test genéticos preimplantacionaes para aneuploidías (PGT-A) para descartar embriones aneuploides en los ciclos de reproducción asistida (ART) pueden ser prometedores al aumentar las tasas de embarazo por transferencia y reducir las tasas de abortos para pacientes con pérdida recurrente del embarazo (RPL) de causa inexplicable.

Objetivo: Explorar la efectividad de PGT-A en el manejo de RPL inexplicable mediante la evaluación de varios aspectos clave: la probabilidad de recién nacido vivo en un embarazo espontáneo posterior, si las mujeres con RPL inexplicable tienen una tasa superior de aneuploidía, si los blastocistos euploides ofrecen una tasa de nacidos vivos (LBR) comparable en pacientes con RPL inexplicable, ya sea porque el endometrio sea menos selectivo en RPL de causa inexplicable y si el PGT-A aumenta el LBR o reduce las pérdidas gestacionales hasta el parto

Selección y síntesis de estudios: estudios que incluyeron pacientes con $\geq$ 2 RPL de causa inexplicable que se sometieron a TRA con o sin PGT-A o con manejo expectante.

Principales medidas de resultado: El objetivo principal fue el LBR. Los objetivos secundarios fueron la tasa de aneuploidía, la tasa clínica de embarazo y tasa de pérdida de embarazo clínico.

Resultados: Sigue siendo contradictorio si las parejas con RPL inexplicable presentan tasas más elevadas de aneuploidías embrionarias. Las transferencias de blastocistos euploides mostraron una tasa de pérdida de embarazo clínico comparable (odds ratio [OR], 1,10; intervalo de confianza [IC] del 95 %, 0,57–2,13) y LBR (OR, 1,04; 95 % IC, 0,74–1,44) en pacientes con y sin RPL inexplicable. Un análisis cromosómico exhaustivo de los productos de la concepción muestra tasas de aneuploidía similares entre pacientes con y sin RPL y no respalda la hipótesis del endometrio menos selectivo. Los test genéticos preimplantacionales para detectar aneuploidía disminuyeron la tasa de pérdida clínica gestacional (OR, 0,42; IC 95 %, 0,27–0,67) y mejoraron LBR por transferencia (OR, 2,17; IC 95 %, 1,77–2,65) y LBR por paciente (OR, 1,85; IC 95 %, 1,18–2,91) en pacientes con RPL de causa inexplicable.

Conclusión y relevancia: La evidencia actual de baja calidad sugiere que PGT-A mejora el LBR por transferencia y por paciente en RPL inexplicable. Ensayos controlados aleatorios bien diseñados que comparen TRA con PGT-A versus manejo expectante para RPL inexplicables estarían justificados.