Preimplantation genetic testing for aneuploidy failed to improve cumulative live birth rate in patients with limited good-quality embryos: a retrospective cohort study

Qian Zhang[1], Yueyue Yan[1], Jie Li[1], Yumei Huang[1], Wei Zhou[2], Tianxiang Ni[1], and Junhao Yan[1]

[1]Shandong University
[2]Affiliation not available

January 13, 2023

Abstract

Objectives: To evaluate whether preimplantation genetic testing for aneuploidy (PGT-A) can improve pregnancy and neonatal outcomes for patients with limited good-quality embryos. Design: Retrospective cohort study. Setting: University hospital. Population: A total of 1,553 patients who intended to pursue PGT-A for the first time but obtained only two or less good-quality embryos on day 3 after oocyte retrieval were divided into two groups: 997 in the PGT-A group and 556 in the drop-out group of withdrawing PGT-A due to poor embryological outcome. Results: After adjusting for potential confounding factors, PGT-A group exhibited significantly lower cumulative rates of biochemical pregnancy (19.96% vs. 30.22%, P-adj < 0.001), clinical pregnancy (17.55% vs. 23.38%, P-adj < 0.001) and live birth (14.14% vs. 16.19%, P-adj $= 0.005$) per oocyte retrieval and longer median time to pregnancy and live birth compared with drop-out group. However, significant increases in rates of biochemical pregnancy (72.16% vs. 35.50%, P-adj < 0.001), clinical pregnancy (61.86% vs. 26.98%, P-adj < 0.001), and live birth (48.45 vs. 18.26%, P-adj < 0.001) per transfer were found in the PGT-A group. No significant differences were observed in cumulative miscarriage and ectopic pregnancy rates, number of ETs needed per live birth and neonatal outcomes. Conclusion: PGT-A failed to improve cumulative live birth rate or shorten time to pregnancy, but optimized pregnancy outcomes per transfer for patients with limited good-quality embryos. Keywords: preimplantation genetic testing for aneuploidy, cumulative live birth rate, live birth rate per transfer, neonatal outcomes

Introduction

Preimplantation genetic testing for aneuploidy (PGT-A) has become increasingly utilized in assisted reproduction technology (ART) since the first established normal pregnancies of women with X chromosome-linked diseases in the late 1980s (1). The prevalence of embryo aneuploidy is likely to be responsible for implantation failure or miscarriage (2, 3). PGT-A was demonstrated to be the most effective strategy to minimize adverse pregnancy outcomes due to aneuploidy (4).

PGT-A, was initially introduced to screen embryos for several chromosome abnormalities by fluorescent in-situ hybridization (FISH) in the 1990s (5, 6). Subsequently, several genetic testing technologies were employed in PGT-A, mainly including single nucleotide polymorphism (SNP) and array-based comparative genomic hybridization (aCGH) (7, 8). Furthermore, next-generation sequencing (NGS), provided parallel processing of multiple nucleic acid molecules and efficient chromosomal analysis with high-resolution data (9). Compared with biopsy on Day-3, trophectoderm cell biopsy on blastocyst stage reduced the risk of misdiagnosis and caused less detriment to embryo viability (10, 11).

Indeed, numerous studies have demonstrated that euploid elective single-embryo transfer was helpful to

improve pregnancy outcomes and reduce miscarriage rate, especially in advanced maternal age (AMA) women (12, 13). Besides, PGT-A was feasible for women with repeated implantation failure (RIF) and recurrent miscarriage (RM) to improve the live birth rate per embryo transfer (ET) (14). Logically, PGT-A can also be performed in those with a severe male factor, as some aneuploidies may derive from the spermatozoa (15).

Results on live birth rates in women following PGT-A remain conflicting. Several randomized controlled trials (RCTs) indicated that PGT-A improved the live birth rate among patients with a good prognosis in limited infertile populations (16, 17). On the contrary, one multicenter, randomized and controlled trial suggested that the cumulative live birth rate with conventional in vitro fertilization (IVF) was not inferior to the rate with PGT-A among women with three or more good-quality blastocysts (18). Two other studies reached the similar conclusion that there was no benefit of PGT-A when assessing the cumulative live birth rate per oocyte retrieval (19, 20). Previous studies have predominantly focused on women with good pregnancy prognosis, there is limited data to compare the cumulative pregnancy outcomes with or without PGT-A among women possessing a poor prognosis for a live birth (12, 21, 22). The present study was therefore conducted to compare the cumulative pregnancy outcomes after NGS-based PGT-A or intracytoplasmic sperm injection (ICSI) treatment among patients with few good-quality embryos.

Material and methods

Patients

Ethical approval for this present study was obtained from the Institutional Review Board of Reproductive Medicine, Shandong University. This was a retrospective cohort study in which all patients indicated an intention to pursue PGT-A for the first time but obtained only two or less good-quality embryos on day 3 after oocyte retrieval. Cycles in which PGT-A was intended were assessed from March 2017 to June 2021 and only the first cycles for patients meeting the inclusion criteria were examined. Donor oocyte/sperm recipients were excluded. Patients applying PGT for chromosomal structural rearrangements (PGT-SR) or monogenic/single gene defects (PGT-M) were also excluded.

Two study groups were formed based on patients' choices of persisting in PGT-A or not. The PGT-A group consisted of patients selecting blastocyst culture, trophectoderm biopsy and genetic testing despite low number of good-quality embryos, while the drop-out group involved patients withdrawing PGT-A in favor of ET in line with morphologic criteria. Eventually, 997 oocyte retrieval cycles in the PGT-A group and 556 in the drop-out group were analyzed, leading to 291 and 493 cycles of ET, respectively.

Procedures

The controlled ovarian hyperstimulation (COH) protocols employed in this study involved long and short gonadotropin-releasing hormone agonists, antagonists, and mild stimulation protocols, which were used based on the patient's age and preferences and measures of ovarian reserve. When at least one follicle with a diameter over 18 mm was observed, human chorionic gonadotropin (hCG) was injected subcutaneously. Oocytes were retrieved 36 hours later and the aspirated oocytes were then transferred to embryo culture medium and cultured in an incubator at 37. Subsequently, ICSI was employed for all patients. The embryo morphology for cleavage stage was scored according to the Puissant criteria, and the blastomeres with 7–10 cells and [?] 3 scores were defined as good-quality embryos (23). Especially, patients with [?] 2 good-quality embryos were counseled about the low chances of obtaining euploid blastocysts and let decide whether to continue or withdraw PGT-A on day 3 after oocyte retrieval.

For patients keeping on PGT-A, blastomeres were cultured to blastocyst stage, and only 4BC or better blastocysts would be regarded as good-quality blastocysts judging by the Gardner blastocyst scoring system (24). Then good-quality blastocysts were implemented by multicell trophectoderm biopsy and cryopreserved using vitrification technique by an experienced embryologist. Blastocyst biopsies were genetically screened via NGS. Finally, a single frozen-thawed euploid, mosaic or failed/inconclusive-diagnosed blastocyst was selected for possible transfer after genetic counseling. In the drop-out group, majority of patients underwent

fresh blastomere transfer unless they did not obtain good-quality embryos on day 3 after oocyte retrieval. For those patients, blastomeres were obliged to be cultured to blastocyst stage for fresh embryo transfer on day 5 after oocyte retrieval or vitrified for a future frozen transfer in patients whose embryos were not blastocysts until day 5 or who had contraindications to a fresh transfer (risk of ovarian hyperstimulation syndrome, thin endometrium, premature progesterone elevation).

Generally, extra endometrial preparation was not needed for fresh embryo transfer as the thickness of endometrium would reach its maximum after COH. Luteal phase support with 20 mg of oral dydrogesterone (Duphaston, Abbott, USA) twice a day and 200 mg of vaginal progesterone capsules (Utrogestan, Besins Manufacturing, Belgium) once a day was initiated on the day of oocytes retrieval until the 12th week of gestation in most circumstances. For patients who underwent frozen embryo transfer, endometrial preparation and luteal phase support protocols, as well as blastocyst vitrification–thawing and transfer procedures that followed, were completed as described in a previous study (25).

Outcome measures

The primary outcomes were cumulative rates of biochemical pregnancy, clinical pregnancy, miscarriage, ectopic pregnancy, and live birth per oocyte retrieval. The secondary outcomes included pregnancy outcomes per transfer, number of ETs needed per live birth, median time to pregnancy and live birth, and neonatal outcomes.

Biochemical pregnancy was defined as serum hCG concentration $>$ 25 mIU/mL at 14 days after blastomere transfer or 12 days after blastocyst transfer. Clinical pregnancy was diagnosed as the presence of at least one gestational sac with fetal heart activity visualized by ultrasound around 7^{th} week of gestation. Miscarriage referred to the spontaneous termination of clinical pregnancy before 28 weeks of gestation. Ectopic pregnancy was regarded as the existence of extra-uterine gestational sac diagnosed by ultrasound or laparoscopy. Live birth was known as the delivery of one or more live-born infants after 28 weeks of gestation. The cumulative live birth rate was calculated by the number of deliveries per oocyte retrieval cycle. Number of ETs needed per live birth was identified by the number of transfers required to achieve the first live birth per oocyte retrieval cycle. Neonatal outcomes were assessed among patients with singleton delivery, including preterm rate, newborn's sex ratio and birth weight. Preterm birth was regarded as a live birth before 37 weeks of gestation. Normal and low birth weight were denoted as the birth weight of 2500–4000 g and below 2500 g.

Statistical analysis

All analyses were carried out using the Statistical Package for Social Science (SPSS) software, release 26.0 and figures were completed with GraphPad Prism software, version 9.0.0. Continuous variables with a normal distribution were reported as a mean value with standard deviation and compared through unpaired two-tailed student t-test. Categorical data were presented as numbers with percentages and assessed using Pearson's chi-square test. Binary logistic regression analysis of cumulative pregnancy outcomes was used to control the confounding factors related to the likelihood of achieving a live birth per oocyte retrieval, including maternal age, infertility duration, maternal anti-Müllerian hormone (AMH), number of mature oocytes and indication to PGT-A. Besides, logistic regression with generalized estimating equation (GEE) of clinical outcomes per transfer was carried out to account for intrinsic dependence for the different ETs from the same patient. P-value $<.05$ was considered statistically significant.

Results

A total of 1553 patients who intended PGT-A for the first time were initially enrolled in this study (Figure 1). As presented in Figure 1, 997 oocyte retrieval cycles from the PGT-A group adhered to blastocyst culture and PGT-A, of which 415 (41.62%) did not obtain blastocysts suitable for biopsy, 319 (32.00%) did not receive transferable embryos after genetic testing, and 263 (26.38%) were followed by 291 ET cycles. In the drop-out group, 126 of 556 (22.66%) oocyte retrieval cycles did not receive transferable embryos after morphological grading, and 430 (77.34%) were followed by 493 ET cycles. The cancellation rates of embryo transfer among the two groups were 73.62% and 22.66% ($P<0.001$, Figure 2a).

Basal characteristics, indications for PGT-A and cycle data between PGT-A group and drop-out group were compared in Table I. Of note, female age was significantly higher and infertility duration was longer in the drop-out group. Similarly, AMH level parameters and number of basal follicles were significantly worse in the drop-out group compared with the PGT-A group. Numbers of embryos transferred and good-quality embryos transferred as well as endometrial thickness during transfer cycles were higher in drop-out group. But no significant differences were observed between the two groups in terms of paternal age, maternal body mass index (BMI), number of previous oocyte retrieval cycles, number of good-quality embryos at day 3 after oocyte retrieval and endometrial preparation program of transfer cycles.

Comparison of cumulative pregnancy outcomes, pregnancy outcomes per transfer and neonatal outcomes per live birth between the two groups was displayed in Table II. A multivariate logistic regression analysis for cumulative pregnancy outcomes was conducted to eliminate the potential effects of confounding factors, including maternal age, infertility duration, maternal AMH, number of mature oocytes, indication to PGT-A. What is most striking is that the cumulative live birth rate was lower in the PGT-A group, even after adjustment of several potential confounders (14.14 % vs. 16.19%, P-adj = 0.005). Moreover, the PGT-A group showed significantly inferior cumulative rates of biochemical pregnancy and clinical pregnancy compared with the drop-out group (19.96% vs. 30.22%, P-adj $<$ 0.001; 17.55% vs. 23.38%, P-adj $<$ 0.001; respectively). No significant variations were recorded in the cumulative miscarriage and ectopic pregnancy rates and number of ETs needed per live birth between two groups (Figure 2b). In contrast to our results about cumulative pregnancy outcomes, the rates of biochemical pregnancy, clinical pregnancy and live birth per transfer were higher in the PGT-A group, even after adjusting several potential confounders (72.16% vs. 35.50%, P-adj $<$ 0.001; 61.86% vs. 26.98%, P-adj $<$ 0.001; 48.45% vs. 18.26%, P-adj $<$ 0.001; respectively). The miscarriage and ectopic pregnancy rates per transfer did not differ significantly between PGT-A and drop-out groups. However, the drop-out group spent much shorter time to achieve pregnancy and live birth than the PGT-A group (Figure 2c and Figure 2d). In addition, no significant associations between the two groups were detected in preterm rate, birth sex ratio and weight of newborns per singleton delivery.

Considering the possible effect of mosaic or failed/inconclusive-diagnosed embryos transferred on pregnancy outcomes, the clinical outcomes of only euploid embryos transferred in the PGT-A group were further analyzed, and the results were consistent with the above description (Supplemental Table I).

Discussion

PGT-A is now widely used in the ART field in order to select a single euploid embryo for transfer and access clinical pregnancy and live birth. However, there has been controversy regarding whether PGT-A can improve the overall pregnancy outcomes in specific patients with a good prognosis (16-20, 26). Besides, the question that whether patients with limited good-quality embryos benefit from PGT-A or not also remains unresolved (12, 21, 22). The main goal of this study was to compare the cumulative clinical outcomes of patients insisting on PGT-A and those intended but cancelled PGT-A when two or less good-quality embryos were available on day 3 after oocyte retrieval.

Main findings and interpretation

Our study showed that trophectoderm biopsy of blastocyst-stage embryos combined with NGS-based PGT-A did not significantly improve the cumulative live birth rate in women with poor embryo yield or quality. To our knowledge, one randomized controlled study by Rubio et al. reported that Day-3 embryo biopsy associated with aCGH-based PGT-A was not superior in the cumulative delivery rates per AMA patient compared with ICSI (12). The other observational-cohort study with 2 years follow-up by Sacchi, et al. ounded that the drop-out group showed poorer cumulative live birth rate per oocyte retrieval than the PGT-A group given trophectoderm biopsy and quantitative PCR among AMA patients (9/106, 8.49% vs. 81/308, 26.29%, P¡0.001) (22). The limited sample data pooled from both cleavage and blastocyst stage embryos and/or embryos screened by different genetic testing technologies might account for these inconsistent results in previous studies. In the present cohort, even though the drop-out group was characterized by higher female age, longer infertility duration and poorer ovarian reserve, the lower cumulative live birth rate was

still assessed in PGT-A group after eliminating the potential effects of several confounding factors. Our results were comparable to the previous studies among patients with a good prognosis, namely PGT-A was not beneficial when the cumulative live birth rate was assessed per oocyte retrieval (18-20). Besides, we found that PGT-A did not have more favorable cumulative rates of biochemical pregnancy and clinical pregnancy per retrieval. Several possible explanations may be responsible for the inferior outcome of PGT-A. Firstly, the biopsied trophectoderm cells may not perfectly represent the true chromosomal composition of the inner cell mess, leading to misdiagnosis of embryo karyotype (27, 28). Secondly, although widely used, embryo biopsy may influence embryonic development and PGT-A may lead to abandoning a large number of embryos with potential for normal euploid pregnancies (29). Consequently, the continued employment of PGT-A in poor-prognosis patients may not be reasonable, especially considering the increased financial burden when patients had limited good-quality embryos (30).

However, the data presented in this study demonstrated significant improvements in pregnancy outcomes per transfer in the PGT-A group, including rates of biochemical pregnancy, clinical pregnancy and live birth per transfer. Parallel effects following elective single embryo transfer after trophectoderm biopsy and aneuploidy screening have been reported previously, which showed a higher live birth rate per transfer compared with drop-out group among AMA patients (81/201, 40.30% vs. 9/117, 7.69%, P¡0.001) (22). Likewise, Haviland et al. found that women aged [?] 38 years who used PGT-A were 67% (RR: 1.67; 95% CI: 1.31, 2.13) significantly more likely to have a live birth than women who did not use PGT-A (31). Murugappan et al. also shared the notion that cycles that completed trophectoderm biopsy and aCGH-based PGT-A had a significantly increased live birth rate compared with those in which PGT-A was intended but cancelled due to poor embryo yield or quality among RM patients (57/158, 36.00% vs. 6/40, 15.00%, P¡0.05) (21). Overall, the evidence available so far suggested that PGT-A had a positive effect on the ability to successfully maintain the pregnancy to term and improved delivery rate per transfer.

Furthermore, neonatal outcomes of preterm birth rate, sex ratio and birth weight among poor prognosis patients with singleton delivery were essentially identical between the two groups in this study. Our data was consistent with one observational-cohort study that neither blastocyst culture nor PGT-A assessment resulted in suboptimal neonatal outcomes in AMA patients, as evidenced by the comparable low birthweight rate (5/81, 6.17% vs. 2/10, 20.00%, P¿0.05) and preterm birth rate (6/81, 7.41% vs. 1/10, 10.00%, P¿0.05) between PGT-A and drop-out groups (22). A recent multicenter, randomized and controlled trial also indicated that the incidences of maternal or neonatal complications and congenital anomalies were similar between PGT-A and conventional IVF groups among subfertile women who were aged 20 to 37 years and obtained three or more good-quality blastocysts (18). On the contrary, another RCT discovered that elective single embryo transfer after trophectoderm biopsy and rapid aneuploidy screening improved obstetrical outcomes (including higher birthweight, lower rates of preterm delivery and lower rates of neonatal intensive care unit admission) as compared with untested 2-embryo transfer, which did not target patients with a poor prognosis (32). In addition, there were no differences of the mean number of ETs needed per live birth and time to pregnancy between PGT-A and drop-out group in our cohort. Contrarily, Rubio et al. reported that Day-3 embryo biopsy with aCGH-based PGT-A led to lower number of ETs needed per live birth (1.8 vs. 3.7) and shorter time to pregnancy (7.7 vs. 14.9 weeks) compared with ICSI for AMA patient, which might be explained by different stage embryos tested via different genetic testing technologies (12).

Strengths and Limitations

Indeed, the strength of this study lied in its unique design for women with poor embryo yield or quality, which filled the research gaps in this area. Besides, the current study provided new insights into the relationship of PGT-A and cumulative pregnancy outcomes per started cycle, and accumulated evidence of understanding which group of women are most likely to benefit from PGT-A. Nevertheless, some limitations still existed in our study. As a retrospective cohort analysis, the discrepancies between the two groups might contribute to the current results, even though logistic regression was used to minimize sampling bias and group heterogeneity. In addition, our findings might be subjected to small sample size and only first oocyte retrieval for patients who met the inclusion criteria included. Therefore, caution should be exercised when

interpreting the results, especially for clinical genetic counseling of patient with a poor prognosis in PGT-A treatment.

Conclusion

In summary, although PGT-A provided preferable clinical outcomes per transfer, it did not lead to additional improvement in cumulative live birth rate or shorter time to pregnancy as compared to ICSI without genetic testing. Therefore, the application of PGT-A should be more individualized and carefully, especially for those patients with a poor prognosis for a live birth.

Acknowledgements

The authors would like to thank all the staff of the department of assisted reproduction in Center for Reproductive Medicine, Shandong University for their support and cooperation.

Disclosure of interests

The authors report no conflicts of interest associated with this manuscript.

Contribution to Authorship

J.H.Y. is the guarantor. Q.Z. and Y.Y.Y. conceived the study design, completed the data analysis and wrote the article. J.L. and Y.M.H. took the responsibility for the collection of data. J.H.Y., W.Z. and T.X.N. contributed to the conception of the study design and interpretation of the data. All authors reviewed, provided feedback and approved the final manuscript.

Details of Ethics Approval

Ethical approval for this present study was obtained from the Institutional Review Board of Reproductive Medicine, Shandong University (No.140, Date December 24, 2021).

Funding

This study was funded by National Key Research and Development Program of China (2021YFC2700604), General Program of National Natural Science Foundation of China (82171648), Taishan Scholars Program for Young Experts of Shandong Province (tsqn201812154) and Youth Program of National Natural Science Foundation of China (82101752) for data fee (scientific research informed consent, etc.), paper modification and publication fee, etc.

References

1. Handyside AH, Kontogianni EH, Hardy K, Winston RM. Pregnancies from biopsied human preimplantation embryos sexed by Y-specific DNA amplification. Nature. 1990;344(6268):768-70.

2. Franasiak JM, Alecsandru D, Forman EJ, Gemmell LC, Goldberg JM, Llarena N, et al. A review of the pathophysiology of recurrent implantation failure. Fertil Steril. 2021;116(6):1436-48.

3. 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(10285):1658-67.

4. 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(3):624-30.

5. Verlinsky Y, Cieslak J, Freidine M, Ivakhnenko V, Wolf G, Kovalinskaya L, et al. Pregnancies following pre-conception diagnosis of common aneuploidies by fluorescent in-situ hybridization. Hum Reprod. 1995;10(7):1923-7.

6. Grifo JA, Tang YX, Munne S, Alikani M, Cohen J, Rosenwaks Z. Healthy deliveries from biopsied human embryos. Hum Reprod. 1994;9(5):912-6.

7. Treff NR, Levy B, Su J, Northrop LE, Tao X, Scott RT, Jr. SNP microarray-based 24 chromosome aneuploidy screening is significantly more consistent than FISH. Mol Hum Reprod. 2010;16(8):583-9.

8. Wells D, Alfarawati S, Fragouli E. Use of comprehensive chromosomal screening for embryo assessment: microarrays and CGH. Mol Hum Reprod. 2008;14(12):703-10.

9. Fiorentino F, Biricik A, Bono S, Spizzichino L, Cotroneo E, Cottone G, et al. Development and validation of a next-generation sequencing-based protocol for 24-chromosome aneuploidy screening of embryos. Fertil Steril. 2014;101(5):1375-82.

10. Dokras A, Sargent IL, Ross C, Gardner RL, Barlow DH. Trophectoderm biopsy in human blastocysts. Hum Reprod. 1990;5(7):821-5.

11. Schoolcraft WB, Fragouli E, Stevens J, Munne S, Katz-Jaffe MG, Wells D. Clinical application of comprehensive chromosomal screening at the blastocyst stage. Fertil Steril. 2010;94(5):1700-6.

12. 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(5):1122-9.

13. Ubaldi FM, Cimadomo D, Capalbo A, Vaiarelli A, Buffo L, Trabucco E, et al. Preimplantation genetic diagnosis for aneuploidy testing in women older than 44 years: a multicenter experience. Fertil Steril. 2017;107(5):1173-80.

14. 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. 2020;35(1):255.

15. Colaco S, Sakkas D. Paternal factors contributing to embryo quality. J Assist Reprod Genet. 2018;35(11):1953-68.

16. 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(1):24.

17. Scott RT, Jr., Upham KM, Forman EJ, Hong KH, Scott KL, Taylor D, et al. Blastocyst biopsy with comprehensive chromosome screening and fresh embryo transfer significantly increases in vitro fertilization implantation and delivery rates: a randomized controlled trial. Fertil Steril. 2013;100(3):697-703.

18. 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(22):2047-58.

19. Murphy LA, Seidler EA, Vaughan DA, Resetkova N, Penzias AS, Toth TL, et al. To test or not to test? A framework for counselling patients on preimplantation genetic testing for aneuploidy (PGT-A). Hum Reprod. 2019;34(2):268-75.

20. Kushnir VA, Darmon SK, Albertini DF, Barad DH, Gleicher N. Effectiveness of in vitro fertilization with preimplantation genetic screening: a reanalysis of United States assisted reproductive technology data 2011-2012. Fertil Steril. 2016;106(1):75-9.

21. 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(8):1668-74.

22. Sacchi L, Albani E, Cesana A, Smeraldi A, Parini V, Fabiani M, et al. Preimplantation Genetic Testing for Aneuploidy Improves Clinical, Gestational, and Neonatal Outcomes in Advanced Maternal Age Patients Without Compromising Cumulative Live-Birth Rate. J Assist Reprod Genet. 2019;36(12):2493-504.

23. Puissant F, Van Rysselberge M, Barlow P, Deweze J, Leroy F. Embryo scoring as a prognostic tool in IVF treatment. Hum Reprod. 1987;2(8):705-8.

24. Gardner DK, Lane M, Stevens J, Schlenker T, Schoolcraft WB. Blastocyst score affects implantation and pregnancy outcome: towards a single blastocyst transfer. Fertil Steril. 2000;73(6):1155-8.

25. Shao Y, Li J, Lu J, Li H, Zhu Y, Jiang W, et al. Clinical outcomes of Preimplantation genetic testing (PGT) application in couples with chromosomal inversion, a study in the Chinese Han population. Reprod Biol Endocrinol. 2020;18(1):79.

26. Munne S, Kaplan B, Frattarelli JL, Child T, Nakhuda G, Shamma FN, et al. Preimplantation genetic testing for aneuploidy versus morphology as selection criteria for single frozen-thawed embryo transfer in good-prognosis patients: a multicenter randomized clinical trial. Fertil Steril. 2019;112(6):1071-9 e7.

27. Capalbo A, Rienzi L. Mosaicism between trophectoderm and inner cell mass. Fertil Steril. 2017;107(5):1098-106.

28. Victor AR, Griffin DK, Brake AJ, Tyndall JC, Murphy AE, Lepkowsky LT, et al. Assessment of aneuploidy concordance between clinical trophectoderm biopsy and blastocyst. Hum Reprod. 2019;34(1):181-92.

29. Gleicher N, Orvieto R. Is the hypothesis of preimplantation genetic screening (PGS) still supportable? A review. J Ovarian Res. 2017;10(1):21.

30. Neal SA, Morin SJ, Franasiak JM, Goodman LR, Juneau CR, Forman EJ, et al. Preimplantation genetic testing for aneuploidy is cost-effective, shortens treatment time, and reduces the risk of failed embryo transfer and clinical miscarriage. Fertil Steril. 2018;110(5):896-904.

31. Haviland MJ, Murphy LA, Modest AM, Fox MP, Wise LA, Nillni YI, et al. Comparison of pregnancy outcomes following preimplantation genetic testing for aneuploidy using a matched propensity score design. Hum Reprod. 2020;35(10):2356-64.

32. Forman EJ, Hong KH, Franasiak JM, Scott RT, Jr. Obstetrical and neonatal outcomes from the BEST Trial: single embryo transfer with aneuploidy screening improves outcomes after in vitro fertilization without compromising delivery rates. Am J Obstet Gynecol. 2014;210(2):157 e1-6.

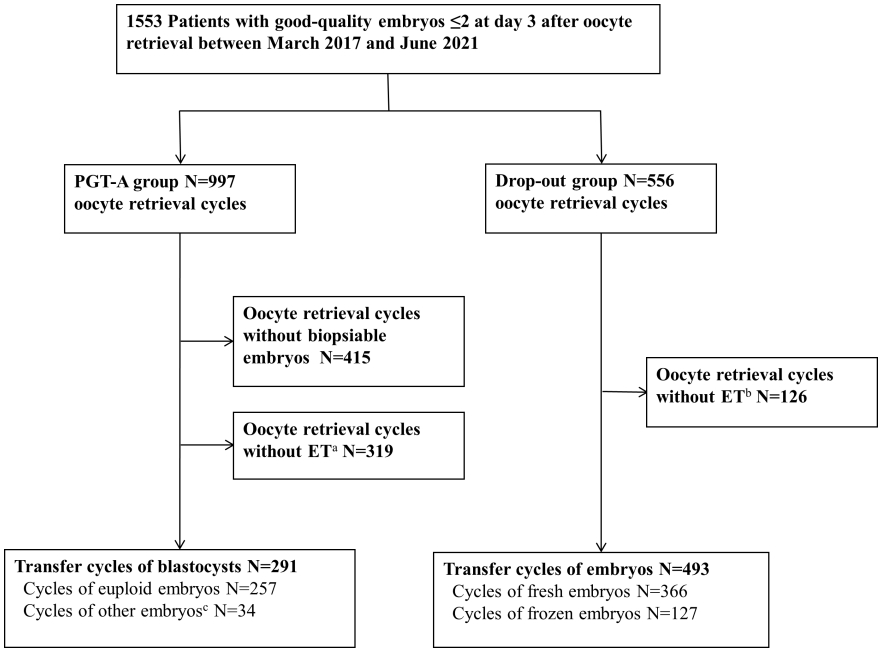
Figure legends

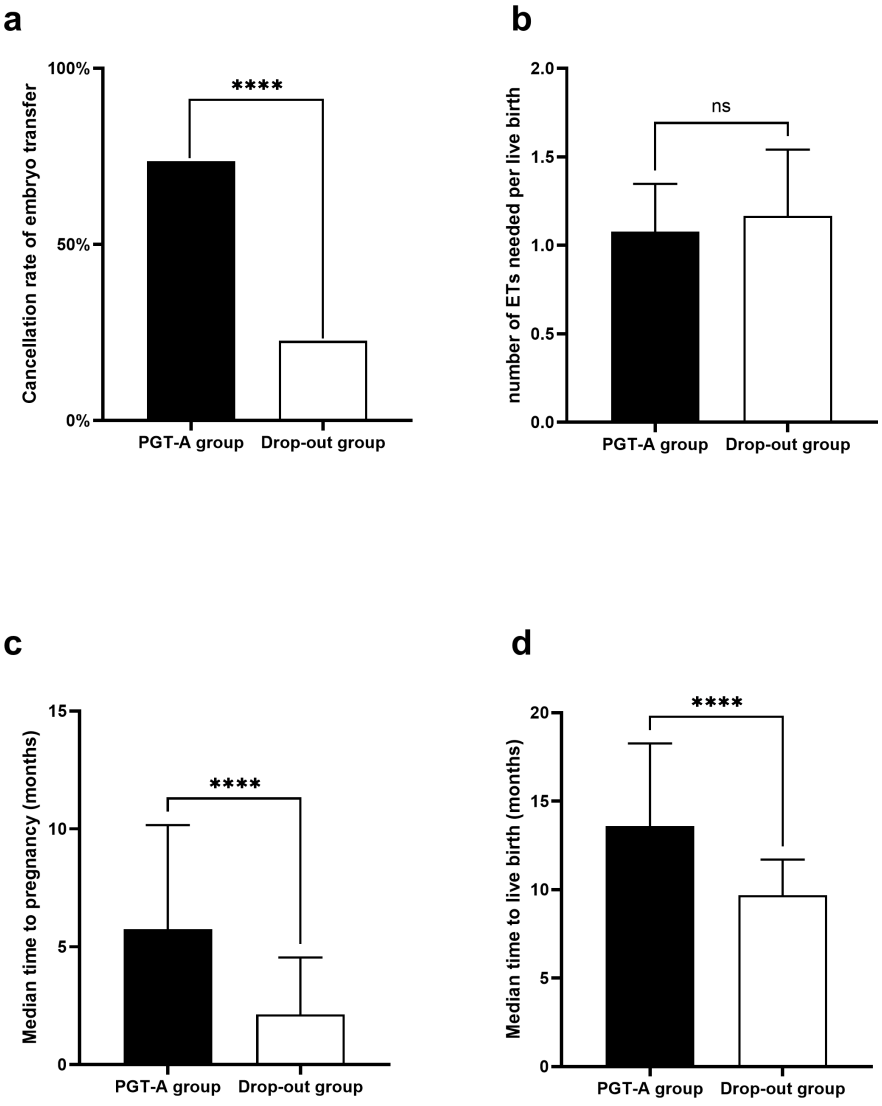
Figure 1. Flow chart of the study.

Note: PGT-A, preimplantation genetic testing for aneuploidy; ET, embryo transfer; a, Oocyte retrieval cycles without transferable embryos after genetic testing; b, Oocyte retrieval cycles without transferable embryos after morphological grading; c, Transfer cycles of mosaic or failed/inconclusive-diagnosed embryos

Figure 2. Comparison of clinical outcomes between two groups.

Note: PGT-A, preimplantation genetic testing for aneuploidy; ET, embryo transfer; ****, P¡0.0001;ns, not significant; a, Results of the cancellation rate of ET; b: Results of number of ETs needed per live birth; c: Results of median time to pregnancy; d: Results of median time to live birth.





Hosted file

Table I.docx available at https://authorea.com/users/460740/articles/618798-preimplantation-genetic-testing-for-aneuploidy-failed-to-improve-cumulative-live-birth-rate-in-patients-with-limited-good-quality-embryos-a-retrospective-cohort-study

Hosted file

Table II.docx available at https://authorea.com/users/460740/articles/618798-preimplantation-genetic-testing-for-aneuploidy-failed-to-improve-cumulative-live-birth-rate-in-patients-with-limited-good-quality-embryos-a-retrospective-cohort-study