ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Role of aneuploidy screening in preimplantation genetic testing for monogenic diseases in young women

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Objective: To investigate whether aneuploidy screening in preimplantation genetic testing (PGT) for monogenic diseases improves the ongoing pregnancy/live birth rate of single frozen/thawed embryo transfer (FET) cycles in young women.
Design: Retrospective cohort study.
Setting: Single university-based fertility center.
Patient(s): From January 2016 to December 2017, 569 FET cycles were selected for analysis. The aneuploidy screening (AS) group included 131 FET cycles from 105 oocyte retrieval cycles in 98 patients who underwent PGT for monogenic diseases with aneuploidy screening, and the non-AS group included 438 FET cycles from 280 oocyte retrieval cycles in 266 patients who underwent PGT for monogenic diseases without aneuploidy screening.
Intervention(s): The patient population was all under the age of 35 years and underwent PGT for monogenic diseases with and without AS.
Main Outcome Measure(s): Ongoing pregnancy/live birth rate, live birth rate, implantation rate, and miscarriage rate.
Result(s): Aneuploidy screening significantly improved the ongoing pregnancy/live birth rate (61.22% vs. 43.98%), implantation rate (64.29% vs. 50.38%), and live birth rate (53.06% vs. 36.09%) of young women carrying monogenic diseases in the first FET cycles. When adjusted for the parity, number of previous miscarriages, and percentage of infertility, the likelihood of implantation was 1.874 times higher (95% confidence interval 1.126–3.119), and an ongoing pregnancy/live birth was 2.139 times more likely (95% confidence interval 1.295–3.534). In addition, the miscarriage rate was significantly decreased (3.17% vs. 11.94%). In the cumulative pregnancy outcomes, the cumulative ongoing pregnancy/live birth rate both per transfer and per patient were significantly higher in the AS group (62.24% vs. 50.38% and 79.59% vs. 68.80%), but no difference existed after adjusting for the parity, number of previous miscarriage, and percentage of infertility. Nevertheless, aneuploidy screening reduced the time interval from the first ET to the achievement a pregnancy.
Conclusion(s): Aneuploidy screening in PGT significantly improved the ongoing pregnancy/live birth rate of young women carrying monogenic diseases in the first FET cycles. (Fertil Steril® 2019;■:■–■. ©2019 by American Society for Reproductive Medicine.)
Key Words: Aneuploidy, genetic testing, in vitro fertilization, live birth, oocyte retrieval

The first instance of successful preimplantation genetic testing (PGT) was reported in 1990 (1). Since then, this technology has been used as an alternative to prenatal diagnosis to avoid transmitting a genetic or chromosomal abnormality to offspring (2). Preimplantation genetic testing enables the identification of embryos with specific disease-causing mutations, such as recessive monogenic disorders, dominant monogenic disorders, and sex-linked disorders, or with chromosomal disorders (3, 4). With the evolution of molecular genetics, an increasing number of monogenic diseases have been identified, which has promoted the rapid development of PGT for monogenic diseases (PGT-M) (5).

A single-cell polymerase chain reaction (PCR)-based mutation detection approach has been established in PGT-M for many years. In recent

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decades, various genetic platforms have been available for PGT-M. The most popularly used platforms include genome-wide, high-throughput technologies, such as karyomapping, which is an indirect mutation detection approach based on haplotype analysis (6, 7), and next-generation sequencing (NGS) with targeted site enrichment for direct mutation detection and linkage analysis (8). In addition to mutation detection, both platforms allow for the simultaneous screening of chromosomal abnormalities (8–10).

Chromosomal abnormalities are the most frequent cause of early pregnancy loss and account for >50% of spontaneous abortions (11). In addition, aneuploidy was found to be one of the main causes of implantation failure during IVF (12), leading to the relatively low efficiency of IVF (13).

Aneuploidy rates are known to increase dramatically with increasing maternal age (14). A study found that almost half of the blastocysts obtained from women aged 35–39 years were aneuploid. It increased to approximately two-thirds of the blastocysts obtained from women aged 40–42 years and approximately 80%–90% of the blastocysts obtained from women aged >42 years (15). Theoretically, selecting euploid embryos could increase the chances of clinical pregnancies, decrease the miscarriage rate, and eventually increase the live birth rate, especially in women aged >35 years. For the last two decades, aneuploidy screening has become of major interest among patients with advanced maternal age. However, the efficacy of preimplantation genetic testing for aneuploidy screening (PGT-A) is undetermined. A multicenter randomized trial found that PGT-A in women between 38 and 41 years of age improved their pregnancy outcomes, with significantly lower miscarriage rates and higher delivery rates after the first transfer attempt, compared with women who underwent blastocyst transfer without aneuploidy screening; however, there was no difference in the cumulative delivery rate between the two groups (16). One of the key considerations was that patients with advanced maternal age did not have an adequate number of embryos for aneuploidy screening (17).

Compared with patients with advanced maternal age, younger patients have more embryos available for screening. In fact, a study by Vanneste et al. revealed that there were high rates of numerical chromosomal abnormalities in embryos from young women, suggesting that these abnormalities were not exclusively attributed to high maternal age (18). Women aged <35 years were found to have an aneuploidy rate of 30%–40% at the blastocyst stage (18). Although numerous studies have focused on the benefits of aneuploidy screening in women of advanced age, few studies have been performed on young women. To date, only one randomized clinical trial has demonstrated the benefits of aneuploidy screening for young women (19). In that study, it was found that aneuploidy screening of blastocysts could significantly increase the implantation rates and could potentially reduce the risk of miscarriage in subsequent frozen/thawed embryo transfer (FET) cycles (19). However, the sample size of that study was small, and the live birth rate, which is considered to be the most significant assessment index of pregnancy outcome, was not available.

The goal of PGT-A is to select embryos before transfer rather than to improve embryo quality. On the one hand, PGT-A likely may increase the implantation rate in the first ET cycles as a result of the aneuploidy screening. On the other hand, PGT-A may result in the loss of embryos that might have implanted owing to both embryo damage during the process of biopsy and vitrification and because of the wastage of embryos that are misdiagnosed or that displayed mosaicism (20).

In the present study we aimed to evaluate whether the application of aneuploidy screening in PGT-M of young women improved pregnancy outcomes during their FET cycles. The control group consisted of young women who underwent cycles with the same blastocyst biopsy procedure but that used only mutation detection without aneuploidy screening. Therefore, the benefit of aneuploidy screening could be evaluated while the impact of an embryo biopsy had been minimized.

MATERIALS AND METHODS

Study Population

This was a retrospective cohort study, including all the oocyte retrieval cycles from young women who underwent PGT-M from January 2016 to December 2017 at the Reproductive Medicine Center of the First Affiliated Hospital of Sun Yat-sen University. The inclusion criteria were as follows: maternal age was younger than 35 years; the first oocyte retrieval cycles were performed between January 2016 and December 2017; all the cycles were biopsied at the blastocyst stage; and at least one FET transfer cycle was performed between January 2016 and December 2017.

Cases were divided into two groups: the aneuploidy screening (AS) group, which included FET cycles that underwent PGT-M with aneuploidy screening, and the non-AS group, which included FET cycles that underwent PGT-M without embryo aneuploidy screening. Our laboratory developed a PCR-based mutation detection platform that has been in use for nearly 18 years, mainly for the detection of α-thalassemia with a southeast deletion genotype, 16 common genotypes of β-thalassemia, and some autosomal dominant diseases, as is shown in our published papers (21). For these indications, we only performed PCR-based mutation detection of PGT-M for young patients. Either karyomapping or NGS were selected for the other genotypes of thalassemias, for thalassemia with probands that needed human leukocyte antigen (HLA) matching, and for rare single-gene diseases besides thalassemias; therefore, these cases consisted of an AS group.

This study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University, China.

Oocyte Retrieval, Embryo Culture, Biopsy, and FET

All the patients underwent controlled ovarian stimulation according to our routine protocols, including the mid-luteal phase long protocol and the antagonist protocol. Recombinant FSH (Gonal-F, Merck-Serono) or a combination of recombinant FSH with hMGs (Menopur, Ferring Pharmaceuticals) was used for ovarian stimulation. Dosages were

individualized for each patient according to the patient's age, weight, and ovarian reserve. Ovulation was triggered using 5,000–10,000 IU hCG when the lead follicles reached 18 mm or when the two follicles reached 17 mm in diameter. Oocytes were retrieved 36 hours later.

Intracytoplasmic sperm injection was used for all the cycles. Embryos were cultured using standard incubation conditions (5% O2 and 6% CO2). Embryos were evaluated on the morning of day 5 using grading criteria that were previously described by Gardner et al. (22), and a trophectoderm biopsy was performed on either postretrieval day 5 or 6, depending on the embryonic development. All the embryos were vitrified separately after the biopsy.

Preimplantation genetic testing with AS was performed using karyomapping or an NGS platform, which was mainly used for rare gene mutation types or when there was a need for HLA matching for probands, and PGT without AS was performed in our preimplantation genetic diagnosis laboratory, mainly for thalassemias using gap-PCR or nested PCR-reverse blot dot (RBD), as described in our previous studies and in the paragraph above describing the study population (8, 10).

In the non-AS group, unaffected embryos included embryos that were normal homozygous for autosomal dominant diseases, embryos that were normal homozygous and heterozygous for autosomal recessive diseases, and embryos that were normal homozygous and heterozygous for X-linked recessive diseases. The unaffected embryos in the AS group also met the criteria that were used for the non-AS group. In addition, the embryos with whole-chromosome aneuploidy and/or segmental imbalance were excluded. Furthermore, we did not suggest that an embryo with more than 30% mosaicism be transferred unless it was the only unaffected embryo.

Once the biopsy results had confirmed that at least one embryo was available for transfer, the patients were scheduled for an FET cycle. Estradiol pills were used during the FET cycles for approximately 12 days, and P in oil was administered when the endometrial thickness reached 8 mm. A single embryo was transferred per cycle, and the transfer was performed under transabdominal ultrasound guidance.

Serum hCG levels were determined 12–14 days after the embryo transfer. Transvaginal ultrasonography was used at 7 to 8 weeks of gestation. Patients were followed from their first frozen/thawed cycles either to the first live birth or until June 2018, regardless of whether all unaffected embryos had been transferred.

Outcome Variables Assessed

Our main outcomes were the ongoing pregnancy/live birth rates, live birth rates, miscarriage rates, and implantation rates.

The implantation rate was defined as the number of gestational sacs visualized on transvaginal ultrasound divided by the total number of embryos transferred. The miscarriage rate was calculated as the number of pregnancy failures after a gestational sac had been documented by transvaginal ultrasound divided by the total number of clinical pregnancies. Any pregnancy that went beyond 20 weeks of gestation was considered an ongoing pregnancy. Monozygotic twins that resulted from a single embryo transfer were counted as one implantation or one ongoing pregnancy or live birth.

Statistical analysis was performed using SPSS software (version 19.0; IBM). Data are presented as mean (SD) or number (percentage). Categorical data were analyzed using Fisher's exact test or χ^2 test, and continuous variables were analyzed using a t test. P values of $< .05$ were considered statistically significant. Relative risk with 95% confidence intervals (CIs) was reported. Odds ratios (ORs) and 95% CIs were estimated for the outcomes in women who underwent PGT with aneuploidy screening compared with the controls. A Cox proportional hazard model was used to evaluate the relative prognostic significance of parity, number of transfer cycles, number of previous miscarriages, percentage of infertility, and number of surplus unaffected embryos in relation to the cumulative live birth rate.

RESULTS

Baseline Characteristics of all Patients

A total of 541 women aged <35 years underwent PGT-M from January 2016 to December 2017. The following cases were excluded, including 47 cases with a history of recurrent pregnancy loss (38 in the AS group and 9 in the non-AS group); 35 cases with endometriosis (29 in the AS group and 6 in the non-AS group); 3 cases with uterine malformation (3 in the AS group and 0 in the non-AS group); 6 cases with thyroid dysfunction (4 in the AS group and 2 in the non-AS group); 42 cases with endometrial problems (37 in the AS group and 5 in the non-AS group); 23 cases without biopsy because there were not enough embryos accumulated for biopsy (17 in the AS group and 6 in the non-AS group); 11 cases in which the transfer cycle was not performed until December 2017 (8 in the AS group and 3 in the non-AS group); and 10 cases without unaffected embryos in the first oocyte retrieval cycles (6 in the AS group and 4 in the non-AS group; all of these cases had unaffected embryos in the subsequent oocyte retrieval cycles, but they did not undergo a transfer cycle between January 2016 and December 2017).

A list of the monogenetic diseases (MGD) in the two groups is presented in Supplemental Table 1, available online. There were 19 couples that needed HLA matching in the AS group. We performed subgroup analysis, and the results are presented in Supplemental Table 2. Because there were no significant differences in pregnancy outcomes between patients who needed HLA matching and the other patients in the AS group, we included the patients who needed HLA matching in the AS group.

The AS group included a total of 47 cycles that used karyomapping and 58 cycles that used NGS. Informative results from the aneuploidy screening were obtained in 646 of the 673 embryos (95.99%) in the AS group. The rate of chromosomal abnormalities was 33.59% (217 of 646), and 20.28% of those with chromosomal abnormalities (44 of 217) displayed mosaicism.

Because PCR-based detection of mutations was used for most of the thalassemia carriers in our laboratory, the percentages of both α- and β-thalassemia were significantly

higher in the non-AS group than in the AS group (98.50% vs. 76.53%; $P<.01$). Couples with thalassemias had a higher number of previous miscarriages (1.31 ± 1.08 vs. 0.74 ± 1.02; $P<.01$) and a lower parity (0.34 ± 0.53 vs. 0.74 ± 0.71; $P=.008$) than those carrying other MGD (Supplemental Table 3), leading to a higher number of previous miscarriages (1.35 ± 1.00 vs. 1.07 ± 1.13; $P=.033$) and a lower parity (0.27 ± 0.51 vs. 0.62 ± 0.58; $P<.01$) in the non-AS group (Table 1).

Table 1 presents the baseline characteristics of all the patients who underwent FET. The AS group had a higher percentage of patients with a history of infertility (42.86% vs. 29.59%; $P=.020$). No differences were observed in the two groups with regard to female age, basal FSH level, basal E2 level, body mass index, gravidity, gonadotropin-initiating dose, number of stimulation days, total gonadotropins, E2 level on the hCG day, number of retrieved oocytes, number of day-3 embryos, total number of blastocysts biopsied, number of day-5 blastocysts biopsied, number of day-6 blastocysts biopsied, number of good-quality blastocysts, and endometrial thickness on the transfer day. The AS group was found to have a lower number of unaffected embryos and a lower number of surplus unaffected embryos, mainly owing to the screening of aneuploid embryos, even though the AS group had a lower number of transfer cycles.

Pregnancy Outcomes of the First ET Attempt

For the first ET attempt, there were 98 FET cycles in the AS group and 266 FET cycles in the non-AS group. Table 2 shows the results of the outcome measures before and after adjustment. The implantation rate was significantly higher in the AS group than in the non-AS group (64.29% vs. 50.38%; $P=.018$). When adjusted for parity, number of previous miscarriages, and percentage of infertility, the likelihood of implantation was 1.874 times higher (95% CI 1.126–3.119; $P=.016$). The miscarriage rate was significantly lower in the AS group than in the non-AS group (3.17% vs. 11.94%; $P=.046$), and it remained significantly different after being adjusted for the factors above, with an OR of 0.177 (95% CI 0.037–0.854; $P=.031$). The live birth rate per patient was significantly higher in the AS group than in the non-AS group (53.06% vs. 36.09%; $P=.003$). When adjusted for parity, number of previous miscarriages, and percentage of infertility, a live birth was 2.073 times more likely (95% CI 1.259–3.411; $P=.004$). The ongoing pregnancy/live birth rate per patient was significantly higher in the AS group compared with the non-AS group (61.22% vs. 43.98%; $P=.004$). When adjusted for the parity, number of previous miscarriages and percentage of infertility, an ongoing pregnancy/live birth was 2.139 times more likely (95% CI 1.295–3.534; $P=.003$).

Cumulative Pregnancy Outcomes

In the AS group, 131 FET cycles from 105 oocyte retrieval cycles in 98 patients were analyzed, and the results were compared with those of 438 FET cycles from 280 oocyte retrieval cycles in 266 patients from the non-AS group. No more than four transfer cycles were performed in the AS

TABLE 1

Baseline characteristics for all patients who underwent FET.

Characteristic	AS group (n = 98)	Non-AS group (n = 266)	*P* value
Female age (y)	29.02 ± 2.52	29.34 ± 2.83	.328
Male age (y)	30.94 ± 3.29	31.38 ± 3.60	.290
Gravidity	1.81 ± 1.26	1.73 ± 1.16	.603
Parity	0.62 ± 0.58	0.27 ± 0.51	.000
No. of miscarriages	1.07 ± 1.13	1.35 ± 1.06	.033
History of infertility	114/266 (42.86)	29/98 (29.59)	.020
Basal FSH, IU/L	5.52 ± 1.37	5.45 ± 1.39	.653
Basal LH, IU/L	3.96 ± 2.53	3.74 ± 1.88	.380
Basal E_2, pg/ml	36.31 ± 20.00	35.99 ± 17.95	.887
Female body mass index (kg/m^2)	20.89 ± 2.82	20.85 ± 2.40	.904
Gonadotropin-initiating dose, IU	189.92 ± 46.66	184.92 ± 47.66	.372
Gonadotropin stimulation days	10.31 ± 1.67	9.99 ± 1.64	.104
Total gonadotropin dosage, pg/ml	2,004.46 ± 699.52	1,864.47 ± 663.32	.081
E_2 level on hCG day, pg/ml	3,026.37 ± 1,212.39	3,094.54 ± 1,359.40	.663
No. of retrieved oocytes	17.92 ± 7.02	17.38 ± 7.56	.539
No. of day 3 embryos	11.05 ± 4.78	11.29 ± 5.45	.702
Total blastocysts biopsied per cycle	7.86 ± 3.88	7.79 ± 4.17	.895
Day 5	4.97 ± 3.53	4.84 ± 3.57	.762
Day 6	2.95 ± 2.05	3.02 ± 2.24	.788
No. of good-quality blastocysts	6.41 ± 3.80	6.33 ± 3.78	.869
No. of unaffected embryos	3.57 ± 2.12	5.48 ± 3.15	.000
No. of surplus unaffected embryos	2.32 ± 2.18	3.91 ± 3.08	.000
No. of transfer cycles	1.34 ± 0.61	1.65 ± 0.85	.000
Endometrial thickness on transfer day (mm)	9.26 ± 1.62	9.16 ± 1.92	.659

Note. Values are mean ± SD or number (percentage).

Hou. Aneuploidy screening in young women. Fertil Steril 2019.

TABLE 2

Pregnancy outcomes of patients undergoing FET with or without aneuploidy screening in the first ET attempt.

Variable	AS group	Non-AS group	*P* value	OR (95% CI)	Adjusted *P* value	Adjusted OR 95% CI
No. of FET cycles	98	266	—	—	—	—
IR, n (%)	63/98 (64.29)	134/266 (50.38)	.018	1.773 (1.099–2.860)	.016	1.874 (1.126–3.119)
Miscarriage rate, n (%)	2/63 (3.17)	16/134 (11.94)	.046	0.242 (0.054–1.086)	.031	0.177 (0.037–0.854)
BPR, n (%)	6/69 (6.12)	17/151 (11.26)	.564	0.751 (0.282–1.996)	.713	0.820 (0.286–2.355)
LBR per patient, n (%)	52/98 (53.06)	96/266 (36.09)	.003	2.002 (1.252–3.200)	.004	2.073 (1.259–3.411)
OP/LBR per patient, n (%)	60/98 (61.22)	117/266 (43.98)	.004	2.011 (1.253–3.227)	.003	2.139 (1.295–3.534)

Note. BPR = biochemical pregnancy rate; IR = implantation rate; OP/LBR = ongoing pregnancy/live birth rate.

Hou. Aneuploidy screening in young women. Fertil Steril 2019.

group, and no more than five cycles were performed in the non-AS group. The live births in each transfer cycle were as follows: the first transfer cycle had 52 live births in the AS group and 96 live births in the non-AS group; the second transfer cycle had 8 live births in the AS group and 32 live births in the non-AS group; the third transfer cycle had 3 live births in the AS group and 3 live births in the non-AS group; the fourth transfer cycle had 3 live births in the non-AS group; and the fifth transfer cycle had no live births. The cumulative live birth rate per patient was slightly higher in the AS group (62.24% vs. 50.38%; $P=.044$), but there was no significant difference after adjusting for the factors listed above. The cumulative ongoing pregnancy/live birth rate per patient was also higher in the AS group (79.59% vs. 68.80%; $P=.043$). However, no significant difference was found after adjusting for the factors listed above (Table 3). The overall implantation rate was significantly higher in the AS group compared with the non-AS group (64.12% vs. 51.60%; $P=.012$). It remained significantly different after adjusting for the factors listed above, and the odds of an implantation were 1.639 times higher (95% CI 1.075–2.499; $P=.022$). The overall miscarriage rate was not significantly different between the groups, but after adjusting for the factors listed above it was significantly different, with an OR of 0.306 (95% CI 0.100–0.934; $P=.038$) (Table 3).

The average time interval from the first ET to an ongoing pregnancy was significantly shorter in the AS group compared with the non-AS group. In addition, the AS group had fewer transfer cycles than the non-AS group (1.34 ± 0.61 vs. 1.65 ± 0.85; $P=.001$) (Table 1). In a competing risk analysis, there was no difference in the cumulative live birth rate between the two groups after adjusting for parity, number of transfer cycles, number of previous miscarriages, percentage of infertility, and number of surplus unaffected embryos (95% CI 0.926–1.843; $P=.13$; Fig. 1).

DISCUSSION

The main finding of this study was that aneuploidy screening in IVF-PGT significantly improved the ongoing pregnancy/live birth rate and implantation rate of young women with MGD in the first FET cycles, whereas it significantly decreased the miscarriage rate. In an intent-to-treat analysis, no difference was found in the cumulative live birth rate between the two groups, but aneuploidy screening in PGT-M reduced the time interval from the first ET to an ongoing pregnancy.

Aneuploidy greatly contributes to a decreased implantation rate and accounts for >50% of spontaneous abortions (11). The number of euploid embryos decreases sharply after 35 years of age, exhibiting a strong inverse linear relationship with age (14). Theoretically, the transfer of euploid embryos would increase the implantation rate and live birth rate. However, the efficacy of PGT-A in patients with advanced maternal age is still debated (23–25). Moayeri et al. (23) held that the regular use of PGT-A in advanced maternal age should not be recommended. However, Elena et al. (24)

TABLE 3

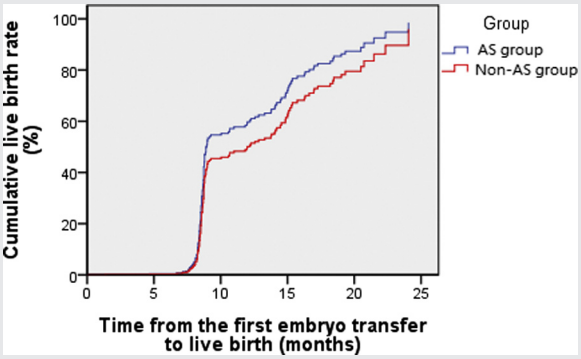
Pregnancy outcomes of patients undergoing FET with or without aneuploidy screening in all transfer attempts.

Variable	AS group (n = 98)	Non-AS group (n = 266)	*P* value	OR 95% CI	Adjusted *P* value	Adjusted OR 95% CI
No. of FET cycles	131	438	—	—	—	—
Time to ongoing pregnancy (mo), mean ± SD	7.06 ± 5.10	8.70 ± 5.55	.11	—	—	—
IR, n (%)	84/131 (64.12)	226/438 (51.60)	.012	1.677 (1.12–2.509)	0.022	1.639 (1.075–2.499)
Miscarriage rate, n (%)	4/84 (4.76)	28/226 (12.39)	.05	0.354 (0.12–1.04)	0.038	0.306 (0.100–0.934)
BPR, n (%)	8/92 (8.70)	25/251 (9.96)	.725	0.861 (0.374–1.984)	0.754	0.868 (0.359–2.099)
OP/LBR per transfer, n (%)	78/131 (59.54)	183/438 (41.78)	.000	2.051 (1.378–3.051)	0.000	2.111 (1.391–3.203)
Cumulative LBR per patient, n (%)	61/98 (62.24)	134/266 (50.38)	.044	1.624 (1.011–2.609)	0.088	1.544 (0.938–2.542)
Cumulative OPR/LBR per patient, n (%)	78/98 (79.59)	183/266 (68.80)	.043	1.769 (1.015–3.083)	0.081	1.681 (0.939–3.011)

Note. BPR = biochemical pregnancy rate; IR = implantation rate; OP/LBR = ongoing pregnancy/live birth rate.

Hou. Aneuploidy screening in young women. Fertil Steril 2019.

FIGURE 1



Comparison of cumulative live birth rates in the two groups.

Hou. Aneuploidy screening in young women. Fertil Steril 2019.

suggested that PGT-A could be recommended as a screening method for all patients of advanced maternal age. A multicenter study reported that women with a good ovarian reserve and who were aged 44 years should be encouraged to use PGT-A (25). A lack of available embryos after aneuploidy screening was considered to be the cause of the high miscarriage rate and low cumulative live birth rate in patients with advanced maternal age (17).

Although studies have weighed the advantages and disadvantages of aneuploidy screening in women of advanced age, few studies have been performed on young women because young women have a relatively low aneuploidy rate. The efficacy of PGT for aneuploidy screening in young patients is also debated. However, a previous study tested 23 good-quality embryos from young women (<35 years old) undergoing IVF and reported a high frequency of chromosomal instability in the cleavage-stage embryos (18). In that study the aneuploidy rate was reported to reach 30%–40% in the blastocysts (8). In our study the rate of chromosomal abnormalities was 33.59% (217 of 646), which was in line with the findings of the previous study. Compared with patients with advanced maternal age, young patients could provide more embryos for aneuploidy screening; therefore, the chance of a lack of available embryos was low.

Another important issue we needed to consider was that all the published randomized controlled trials selected patients without aneuploidy screening for the control groups. This means that no embryo biopsy was performed in the control groups; therefore, the pregnancy outcomes were affected by both embryo biopsy and by aneuploidy screening in the previous randomized controlled trials.

In the present study the control group consisted of young women who underwent cycles that used the same blastocyst biopsy procedure but only used PGT for single-gene diseases (without aneuploidy screening). Therefore, the benefit of aneuploidy screening could be evaluated while the impact of the embryo biopsy had been minimized.

When we restricted our analysis and compared only the first ET attempts in both groups, the implantation rate was significantly higher in the AS group than in the non-AS group. The live birth rate per patient and the ongoing pregnancy/live birth rate per patient were also significantly higher. The miscarriage rate for the group without aneuploidy screening in our study was 12.39% (28 of 226) for younger women (<35 years old), which was significantly higher than that of the AS group after adjusting for parity, number of previous miscarriages, and percentage of infertility. The results agreed with a previous randomized clinical trial in which the aneuploidy screening of blastocysts significantly increased the implantation rates and reduced the risk of miscarriage in subsequent FET cycles (19).

Furthermore, our study revealed that the women in the AS group experienced an ongoing pregnancy in a shorter time interval than the women in the non-AS group. The AS group required fewer ET cycles than the non-AS group to achieve an ongoing pregnancy. Although there were no differences in the cumulative live birth rate and ongoing pregnancy/live birth rate per patient after adjusting for parity, number of previous miscarriages, and percentage of infertility, the issue of cost-effectiveness should be considered. Preimplantation genetic testing with aneuploidy screening costs more (in China, the average cost of a PGT cycle, including biopsy and genetic diagnosis, was 4,667 U.S. dollars more than that of an IVF cycle) (26); however, patients had a higher possibility of having an ongoing pregnancy/live birth in the AS group than in the non-AS group during the first ET attempt. In addition, undergoing multiple transfer cycles increases the stress of the repeated assisted reproductive technology failure associated with transferring aneuploid embryos and delays the time to a live birth (16).

To the best of our knowledge, this is the first retrospective cohort study to evaluate whether aneuploidy screening in PGT for young women carrying MGD would improve pregnancy outcomes after FET. One limitation of this study is that the aneuploidy screening platform was nonuniform, and the sample size was not large enough for us to separately analyze those platforms. Another limitation is that the time interval for the follow-up was not long enough for all the embryos to be transferred. Moreover, the retrospective nature of the study introduces the potential to include confounding variables that may bias our results, although we performed multiple logistic regression analysis to minimize these effects. In addition, the risk of mosaicism in our study was 6.81% (44 of 646), which accounted for 20.28% of the embryos with chromosomal abnormalities. All the mosaic embryos were not transferred in our study owing to the high chance that these embryos will be abnormal (27). However, Greco et al. (28) transferred 18 mosaic embryos (range, 35%–50%), and 6 of the transfers resulted in normal live births. Therefore, the rejection of mosaicism in our study may have led to embryo wastage to a certain extent.

In conclusion, the use of aneuploidy screening in PGT in young women with MGD was found to be associated with a significant improvement in the ongoing pregnancy/live birth rates during the first FET cycles compared with cycles without aneuploidy screening. Studies that are larger, randomized, and/or prospective are needed to confirm these findings.

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