ORIGINAL ARTICLE

Live Birth with or without Preimplantation Genetic Testing for Aneuploidy

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ABSTRACT

BACKGROUND

Embryo selection with preimplantation genetic testing for aneuploidy (PGT-A) may improve pregnancy outcomes after initial embryo transfer. However, it remains uncertain whether PGT-A improves the cumulative live-birth rate as compared with conventional in vitro fertilization (IVF).

METHODS

In this multicenter, randomized, controlled trial, we randomly assigned subfertile women with three or more good-quality blastocysts to undergo either PGT-A or conventional IVF; all the women were between 20 and 37 years of age. Three blastocysts were screened by next-generation sequencing in the PGT-A group or were chosen by morphologic criteria in the conventional-IVF group and then were successively transferred one by one. The primary outcome was the cumulative live-birth rate after up to three embryo-transfer procedures within 1 year after randomization. We hypothesized that the use of PGT-A would result in a cumulative live-birth rate that was no more than 7 percentage points higher than the rate after conventional IVF, which would constitute the noninferiority margin for conventional IVF as compared with PGT-A.

RESULTS

A total of 1212 patients underwent randomization, and 606 were assigned to each trial group. Live births occurred in 468 women (77.2%) in the PGT-A group and in 496 (81.8%) in the conventional-IVF group (absolute difference, −4.6 percentage points; 95% confidence interval [CI], −9.2 to −0.0; P<0.001). The cumulative frequency of clinical pregnancy loss was 8.7% and 12.6%, respectively (absolute difference, −3.9 percentage points; 95% CI, −7.5 to −0.2). The incidences of obstetrical or neonatal complications and other adverse events were similar in the two groups.

CONCLUSIONS

Among women with three or more good-quality blastocysts, conventional IVF resulted in a cumulative live-birth rate that was noninferior to the rate with PGT-A. (Funded by the National Natural Science Foundation of China and others; ClinicalTrials.gov number, NCT03118141.)

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During in vitro fertilization (IVF),[1] the selection of the best embryo optimizes the live-birth rate per transfer, especially when only a single embryo is transferred instead of multiple embryos to reduce the likelihood of multiple pregnancy. In addition to the conventional morphologic score, the genetic status of the embryo has been associated with treatment success. The presence of aneuploidy is likely to result in implantation failure or spontaneous abortion.[2-5] Thus, preimplantation genetic testing for aneuploidy (PGT-A) with next-generation sequencing may improve embryo selection.

In women of advanced maternal age, some studies have suggested that PGT-A improved the live-birth rate after the first embryo transfer.[6-8] However, data are lacking on the clinical effectiveness of PGT-A in women with a good prognosis for a live birth. Although some randomized trials have shown a higher frequency of ongoing pregnancy with PGT-A than with conventional IVF,[9,10] two recent trials showed that PGT-A did not improve the frequency of ongoing pregnancy or live birth among women under 35 years of age.[11,12] These studies focused on pregnancy outcomes after the first embryo transfer, rather than the cumulative live-birth rate for a given oocyte-retrieval cycle; however, the cumulative live-birth rate is considered to be the most important patient-centered outcome in evaluating the success of an IVF program.[13] For trials evaluating PGT-A, the cumulative live-birth rate reflects the possible effects of the practice of discarding some embryos that might have led to a live birth if they had been implanted; such data cannot be captured when only the first embryo transfer is analyzed.[14]

To obtain data regarding women with a good prognosis for a live birth, we designed a trial to compare the cumulative live-birth rate after PGT-A on the basis of a combination of morphologic criteria and next-generation sequencing with the rate after conventional IVF on the basis of morphologic criteria alone.

Methods

Trial Design and Oversight

From July 2017 through June 2018, we conducted this multicenter, randomized, controlled, noninferiority trial in 14 academic fertility centers throughout China. The trial was approved by the ethics committee at each trial site. A data and safety monitoring board was established to oversee the trial. All data entry, management, and analyses were conducted at Shandong University, which served as the data coordinating center.

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Patients

Eligible couples had been diagnosed with subfertility, were planning to undergo their first IVF cycle, and were considered to have a good prognosis for a live birth. A good prognosis was defined as a woman's age of 20 to 37 years and the availability of three or more good-quality blastocysts. A blastocyst was considered to be of good quality if the score according to the Gardner morphologic criteria on day 5 of embryo culture was 4BC or better.[15] (Details regarding these criteria are provided in the Supplementary Appendix, available at NEJM.org.)

Exclusion criteria included a known uterine abnormality (e.g., uterine congenital malformation; untreated uterine septum, adenomyosis, or submucous myoma; endometrial polyps; or intrauterine adhesions), the presence of a contraindication to pregnancy, a plan to undergo preimplantation genetic testing for monogenic disease or parental chromosomal structural rearrangements, or the use of donated oocytes or sperm to achieve pregnancy. Couples were counseled by local investigators at the office visit at the time of ovarian hyperstimulation; all couples provided written informed consent on the day of oocyte retrieval. Follow-up of all pregnancies was completed in February 2020.

Procedures

Controlled ovarian hyperstimulation was conducted with the use of a gonadotropin-releasing hormone (GnRH) agonist on the basis of a long or short protocol or with a GnRH antagonist at the discretion of local investigators. The long protocol involved the administration of a GnRH

agonist in the midluteal phase of the previous cycle and the initiation of gonadotropin after satisfactory pituitary desensitization had been achieved. The short protocol involved the administration of a GnRH agonist on day 2 or 3 of the cycle and the administration of gonadotropin 2 days later. The antagonist protocol was performed as reported previously.[16] When at least two follicles had reached a mean diameter of 18 mm or more, clinicians administered human chorionic gonadotropin, a GnRH agonist, or both for final oocyte maturation, followed by oocyte retrieval guided by transvaginal ultrasonography 34 to 36 hours later. Intracytoplasmic sperm injection was used in all IVF procedures, since randomization was not performed until day 5 of embryo culture. All embryos were cultured to the blastocyst stage. According to the Gardner criteria,[15] the blastocyst morphologic score was based on three components: blastocyst expansion, inner cell mass, and trophectoderm development. Details regarding the scoring are provided in the Supplementary Appendix.

On day 5, patients with three or more good-quality blastocysts were assigned to the PGT-A group or to the conventional-IVF group in a 1:1 ratio by means of block randomization. In the PGT-A group, three good-quality blastocysts that had been selected by means of morphologic criteria underwent trophectoderm biopsy, which was performed by the same embryologist at each site. Each center used its preferred next-generation sequencing platform (Illumina NextSeq 550 or Ion PGM/Proton). The procedures that were used for blastocyst biopsy and next-generation sequencing are detailed in the Methods section in the Supplementary Appendix.

All embryos that were obtained were cryopreserved and single frozen-embryo transfers were performed each time in the two groups. In the PGT-A group, a euploid blastocyst was chosen for transfer. In the conventional-IVF group, a blastocyst was chosen on the basis of morphologic criteria. If live birth was not achieved after the initial transfer and there were remaining euploid embryos in the PGT-A group or morphologically transferrable embryos in the IVF group, subsequent single-embryo transfers were performed. Only transfers of scheduled embryos (up to three in each group) that were performed within 1 year after randomization were included.

Endometrial preparation with either a natural ovulation cycle or an artificial regimen or an ovulation-induction cycle and luteal-phase support was performed according to local routine, as reported previously.[16,17] We followed all conceptions that resulted from up to three embryo transfers that were performed within 1 year after randomization through to live birth or pregnancy termination; follow-up could be up to 21 months to capture the live birth for a transfer performed at 1 year after randomization. All pregnancy and neonatal outcomes were recorded in detail.

OUTCOMES

The primary outcome was the cumulative live-birth rate that resulted from up to three embryo transfers performed within 1 year after randomization. The secondary outcomes were the rate of a good birth outcome (defined as a live birth at ≥37 weeks of gestation, with a birth weight between 2500 and 4000 g and without a major congenital anomaly),[18-20] cumulative rates of biochemical and clinical pregnancy and pregnancy loss, multiple pregnancy rate, duration of pregnancy, birth weight, cumulative incidence of maternal and neonatal complications, and the number of embryo transfers needed to achieve a live birth. The tertiary outcomes were the rates of pregnancy, pregnancy loss, and live birth after the initial embryo transfer.

Biochemical pregnancy was defined as a serum human chorionic gonadotropin level of at least 25 mU per milliliter at 14 days after embryo transfer. Clinical pregnancy, ongoing pregnancy, and live birth were defined as reported previously.[16] The cumulative live-birth rate was calculated by dividing the number of women who had a live birth at 28 weeks or more of gestation after transfers of all euploid embryos in the PGT-A group or up to three blastocysts in the conventional-IVF group within 1 year after randomization by the total number of women who were assigned to the group.

STATISTICAL ANALYSIS

We hypothesized that the cumulative live-birth rate after the transfer of euploid blastocysts selected by PGT-A would not be more than 7 percentage points greater than the rate after the serial transfer of up to three blastocysts that did not undergo PGT-A, which equates to a noninferiority margin for comparing conventional IVF

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	PGT-A Group (N=606)	Conventional-IVF Group (N=606)
Age — yr	29.1±3.6	29.2±3.5
Body-mass index†	23.0±3.4	22.9±3.5
Fertility history		
Duration of attempt to conceive — yr	3.3±2.1	3.5±2.3
Previous conception — no./total no. (%)	269/604 (44.5)	244/602 (40.5)
Previous miscarriage — no./total no. (%)	70/606 (11.6)	56/606 (9.2)
Previous live birth — no./total no. (%)	81/606 (13.4)	67/606 (11.1)
Indication for IVF — no. (%)		
Ovulatory dysfunction	41 (6.8)	35 (5.8)
Tubal factor	314 (51.8)	345 (56.9)
Endometriosis	3 (0.5)	2 (0.3)
Male factor	92 (15.2)	94 (15.5)
Combined factors	122 (20.1)	108 (17.8)
Unexplained	34 (5.6)	22 (3.6)
Ultrasonographic findings‡		
Antral follicle count in both ovaries	22.1±10.6	21.9±10.0
Endometrial thickness — mm	7.3±2.8	7.4±2.7
Laboratory testing§		
Follicle-stimulating hormone — IU/liter	6.0±1.6	6.1±1.7
Luteinizing hormone — IU/liter	6.9±4.8	6.7±4.8
Estradiol — pg/ml	40.8±25.9	41.2±24.0
Total testosterone — ng/ml	0.4±0.2	0.4±0.2
Prolactin — ng/ml	17.6±8.9	18.0±9.0

* Plus–minus values are means ±SD. To convert values for estradiol to picomoles per liter, multiply by 3.671. To convert values for testosterone to nanomoles per liter, multiply by 3.467. PGT-A denotes preimplantation genetic testing for aneuploidy, and IVF in vitro fertilization.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Data were missing regarding the antral follicle count in both ovaries in 14 women in the PGT-A group and in 11 in the conventional-IVF group and regarding endometrial thickness in 7 women and 3 women, respectively.

§ The baseline steroid hormones were measured at the early follicular phase, mostly on day 1 to 3 of the menstrual cycle. Data were missing regarding follicle-stimulating hormone and luteinizing hormone in 1 woman in the PGT-A group; regarding estradiol in 6 women in the PGT-A group and 4 women in the conventional-IVF group; regarding total testosterone in 24 women and 29 women, respectively; and regarding prolactin in 25 women and 28 women, respectively.

with PGT-A of 7 percentage points. This calculation took into account the possibility of false positive diagnoses of aneuploidy and the decision not to transfer mosaic embryos in the PGT-A group. We estimated that the cumulative live-birth rate after three single-embryo transfers would be 65% in each group. To be 80% certain that the upper limit of a one-sided 95% confidence interval would exclude a difference in favor of the PGT-A group by more than 7 percentage points, we determined that 575 patients were required in each group. On the assumption that 5% of the patients would withdraw, we determined that an enrollment of 1208 patients would be necessary.

Included in the intention-to-treat analysis were all the patients who had undergone randomization. Continuous baseline characteristics of the patients in the two groups are reported as means (±SD); between-group differences were

Table 2. Outcomes of Controlled Ovarian Hyperstimulation.*

Characteristic	PGT-A Group (N = 606)	Conventional-IVF Group (N = 606)
No. of days of ovarian stimulation	9.9±1.8	9.8±2.0
Gonadotropin dose — IU	1647±700	1651±712
Estradiol level on hCG trigger day — pg/ml†	5933±2581	5890±2501
Endometrial thickness on hCG trigger day — mm	10.6±2.2	10.6±2.2
No. of oocytes retrieved	20.3±7.9	19.4±6.7
No. of good-quality embryos on day 3	9.6±4.5	9.2±4.1
No. of good-quality embryos on day 5 or 6	7.3±3.1	7.0±2.8
Result on preimplantation genetic testing — no./total no. (%)		
Balanced euploid	1262/1809 (69.8)	—
Monosomy	80/1809 (4.4)	—
Trisomy	81/1809 (4.5)	—
Subsegmental aneuploid	86/1809 (4.8)	—
Chromosomal mosaic	211/1809 (11.7)	—
Complex‡	64/1809 (3.5)	—
Questionable	25/1809 (1.4)	—
Absence of normal embryo	17/603 (2.8)	—

* Plus–minus values are means ±SD. The term hCG denotes human chorionic gonadotropin.
† Data were missing regarding the estradiol level in 33 women in the PGT-A group and in 38 in the conventional-IVF group.
‡ A complex result was defined as a combination of more than one of the following features: monosomy, trisomy, subsegmental aneuploid, or chromosomal mosaic.

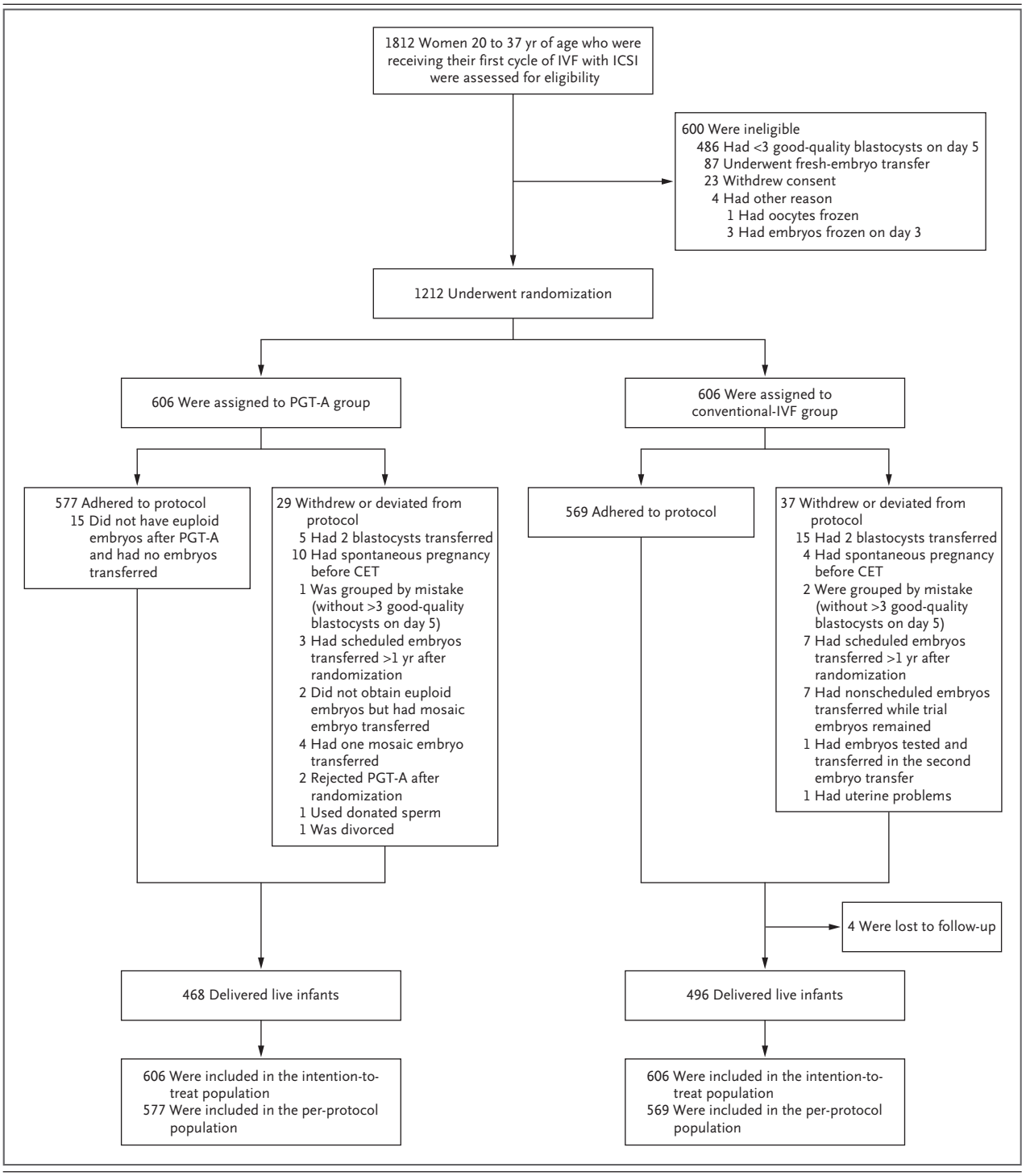
compared with the use of the Wilcoxon rank-sum test owing to the non-normality of the variables. Categorical variables are reported as frequencies and percentages and compared by means of the chi-square test. Patients with missing covariates were excluded from analyses of the affected variables. Women who were lost to follow-up were considered not to have had a live birth. We also conducted a secondary per-protocol analysis, along with a tertiary analysis of outcomes after the initial embryo transfer, post hoc analyses according to subsequent individual embryo-transfer cycles, and prespecified subgroup analyses according to the stimulation protocol, endometrial preparation for frozen-embryo transfer, and age group.

For the primary outcome, a two-sided P value of less than 0.05 was considered to indicate statistical significance. No adjustment was performed for multiplicity of secondary or subgroup analyses. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

Initially, a total of 1812 subfertile women were screened. Of these women, 1212 who met the inclusion criteria underwent randomization (with 606 women assigned to each group); 1146 women (94.6%) adhered to the protocol. The baseline characteristics and outcomes of ovarian stimulation were similar in the two groups (Tables 1 and 2). Of the 1809 embryos that were analyzed by PGT-A, 1262 (69.8%) were euploid, 311 (17.2%) were aneuploid, 211 (11.7%) were mosaic, and 25 (1.4%) were questionable; 17 women in the PGT-A group (2.8%) had only abnormal embryos. The results of next-generation sequencing were similar among the various platforms that were used (Table S1 in the Supplementary Appendix). Of the 606 women in each group, 29 (4.8%) in the PGT-A group and 37 (6.1%) in the conventional-IVF group withdrew from the trial or had a deviation from the protocol (Fig. 1).



PRIMARY AND SECONDARY OUTCOMES

In the intention-to-treat analysis, the primary outcome of cumulative live birth occurred in 468 of 606 women (77.2%) in the PGT-A group and in 496 of 606 (81.8%) in the conventional-IVF group (absolute difference, −4.6 percentage points; 95% confidence interval [CI], −9.2 to −0.0; P<0.001), which met the criteria for noninferiority for conventional IVF (Table 3, and Figs. S1 and S2).

The time until a live birth was similar in the

Figure 1 (facing page). Trial Enrollment and Outcomes.
In the group that was assigned to receive preimplantation genetic testing for aneuploidy (PGT-A), 5 women underwent the transfer of two blastocysts; of these women, 1 underwent the transfer of two nonscheduled embryos (i.e., embryos that were not included in the first three selected blastocysts for testing in the PGT-A group). Also in the PGT-A group, 2 women declined to undergo embryo biopsy and sequencing; of these women, 1 underwent the transfer of two frozen embryos that had been obtained on day 3 of embryo culture. In the group assigned to receive conventional in vitro fertilization (IVF), 7 women underwent the transfer of nonscheduled embryos (i.e., embryos that were not included in the first three selected blastocysts for priority transfer); of these women, 5 had two nonscheduled embryos transferred. CET denotes cryopreserved embryo transfer, and ICSI intracytoplasmic sperm injection.

two groups. The mean number of embryos that were transferred to result in a live birth was 1.2±0.4 in the PGT-A group and 1.3±0.6 in the conventional-IVF group. The frequencies of cumulative clinical pregnancy loss were 8.7% in the PGT-A group and 12.6% in the conventional-IVF group (rate ratio, 0.69; 95% CI, 0.49 to 0.98). The proportion of couples with a good birth outcome was similar in the two groups. In between-group comparisons of pregnancy outcomes performed separately for each embryo transfer, the proportions of women having a live birth, biochemical pregnancy, clinical pregnancy, ongoing pregnancy, and pregnancy loss were similar in the two groups for each outcome (Tables S2 through S5). More women in the conventional-IVF group underwent a second or third embryo-transfer cycle: 192 women in the conventional-IVF group and 119 in the PGT-A group for a second cycle and 49 and 5, respectively, for a third cycle.

The incidences of moderate or severe ovarian hyperstimulation syndrome, ectopic pregnancy, obstetrical or perinatal complications, and congenital anomalies were also similar in the two groups (Table 4 and Table S6).

The results of the per-protocol analysis were generally consistent with those of the primary analysis: a live birth in 452 of 577 women (78.3%) in the PGT-A group and in 478 of 569 (84.0%) in the conventional-IVF group (absolute difference, –5.7 percentage points; 95% CI, –10.3 to –1.1) (Table S7). The results of subgroup analyses are shown in Table S8.

In addition, we performed post hoc analyses regarding the pregnancy outcomes in the two groups from all embryo transfers and other conceptions that occurred within 1 year after randomization. Live-birth rates were similar in the two groups, with an incidence of 85.3% in the PGT-A group and 82.5% in the conventional-IVF group (rate ratio, 1.03; 95% CI, 0.98 to 1.09) (Table S9).

DISCUSSION

In this large randomized, controlled trial involving 1212 subfertile women with a good prognosis for a live birth, conventional IVF resulted in a cumulative live birth rate that was noninferior to that with PGT-A. Although the frequency of pregnancy loss among clinical pregnancies appeared to be lower in the PGT-A group, this differential did not translate into a higher cumulative live-birth rate or shorter mean time until a live birth. Birth weights and the incidence of maternal or neonatal complications and congenital anomalies were similar in the two groups.

The live-birth rate has been recommended as the most relevant patient-centered outcome in clinical trials of infertility treatment.[21] The cumulative live-birth rate for a given oocyte-retrieval cycle is a logical extension of this recommendation, since it captures the results of a given IVF treatment cycle. In previous trials involving women with a good prognosis for a live birth, the implantation or ongoing pregnancy rate after the first embryo transfer during a PGT-A cycle was superior or similar to that in a conventional-IVF cycle.[9-11] However, our results showed that the cumulative live-birth rate after conventional IVF alone was not only noninferior to the rate with PGT-A but was numerically higher (81.8% vs. 77.2%).

There are two possible explanations for the inferior outcome after PGT-A. First, the decision not to transfer mosaic embryos and the possibility of false positive or negative results for all embryos may compromise the effectiveness of PGT-A. The incidence of embryo mosaicism as assessed by trophectoderm biopsy is estimated to be 3 to 20%.[22] Several studies have shown that mosaic embryos may develop into viable euploid newborns, with a live-birth rate varying from 30 to 47%.[23-25] For safety reasons, our protocol did not include the transfer of mosaic embryos, which were transferred in only 6 cases on the

Table 3. Cumulative Live-Birth Rate and Secondary Outcomes.*

Outcome	PGT-A Group (N=606)	Conventional-IVF Group (N=606)	Absolute Difference (95% CI)	Rate Ratio (95% CI)
Primary outcome				
Cumulative live-birth rate — no. (%)†	468 (77.2)	496 (81.8)	−4.6 (−9.2 to −0.0)	0.94 (0.89 to 1.00)
Singleton	462 (76.2)	478 (78.9)	−2.6 (−7.3 to 2.1)	0.97 (0.91 to 1.03)
Twin	6 (1.0)	18 (3.0)	−2.0 (−3.5 to −0.4)	0.33 (0.13 to 0.83)
Secondary outcomes				
Cumulative biochemical pregnancy — no. (%)	526 (86.8)	571 (94.2)	−7.4 (−10.7 to −4.2)	0.92 (0.89 to 0.96)
Cumulative clinical pregnancy — no. (%)	505 (83.3)	556 (91.7)	−8.4 (−12.1 to −4.7)	0.91 (0.87 to 0.95)
Cumulative ongoing pregnancy — no. (%)	479 (79.0)	514 (84.8)	−5.8 (−10.1 to −1.5)	0.93 (0.88 to 0.98)
Birth weight				
Singleton				
No. of observations	462	478		
Mean weight — g	3417±488	3449±488	−32 (−95 to 30)	
Twin				
No. of observations	12	36		
Mean weight — g	2500±714	2605±420	−105 (−444 to 235)	
Cumulative pregnancy loss — no./total no. (%)				
Biochemical	31/526 (5.9)	41/571 (7.2)	−1.3 (−4.2 to 1.6)	0.82 (0.52 to 1.29)
Clinical	46/526 (8.7)	72/571 (12.6)	−3.9 (−7.5 to −0.2)	0.69 (0.49 to 0.98)
First trimester	37/526 (7.0)	60/571 (10.5)	−3.5 (−6.8 to −0.1)	0.67 (0.45 to 0.99)
Second trimester	9/526 (1.7)	12/571 (2.1)	−0.4 (−2.0 to 1.2)	0.81 (0.35 to 1.92)
Good birth outcome — no. (%)‡	378 (62.4)	385 (63.5)	−1.2 (−6.6 to 4.3)	0.98 (0.90 to 1.07)
Features of live births				
Duration of pregnancy — wk	39.2±1.7	39.1±1.6	0.0 (−0.2 to 0.2)	
No. of embryos transferred	1.2±0.4	1.3±0.6	−0.2 (−0.2 to −0.1)	
No. of embryo-transfer procedures	1.1±0.4	1.3±0.5	−0.1 (−0.2 to −0.1)	
Interval since randomization — mo	12.5±2.0	12.4±2.3	0.1 (−0.2 to 0.4)	
Frozen embryos				
No. of unused embryos	5.2±3.2	5.5±2.9	−0.3 (−0.6 to 0.1)	
No. of unused embryos in women without a live birth	4.4±2.8	4.9±2.9	−0.4 (−1.2 to 0.3)	

* Plus–minus values are means ±SD. All comparisons were calculated with the conventional-IVF group as the reference except that the statistical inference for the primary hypothesis was conducted under the noninferiority framework of comparing the conventional-IVF group with the PGT-A group. No adjustment was performed for multiplicity of secondary analyses, so 95% confidence intervals for these risk estimates should not be used to infer definitive treatment outcomes.

† P<0.001 for noninferiority. The number of patients who would need to be treated to achieve a live birth was 21.7 (95% CI, 10.9 to 1250).

‡ A good birth outcome was defined as a live birth at 37 weeks or more of gestation, with a birth weight between 2500 and 4000 g and without a major congenital anomaly.

request of the trial patients. In addition, the results of trophectoderm biopsy may not totally represent the genetic composition of the inner cell mass of the blastocyst that is the precursor to the embryo,[26,27] and subsequent cell division may also eliminate a genetically abnormal cell line.[28,29] This uncertainty — along with technical limitations, such as contamination and preferential amplification (because the copy number of short DNA fragments is always more than

Table 4. Adverse Events.

Adverse Event	PGT-A Group (N = 606)	Conventional-IVF Group (N = 606)	Absolute Difference (95% CI)	Rate Ratio (95% CI)
	no./total no. (%)		*percentage points*	
Maternal				
Before biochemical pregnancy				
Moderate or severe ovarian hyperstimulation syndrome	13/606 (2.1)	11/606 (1.8)	3.3 (–1.2 to 1.9)	1.18 (0.53 to 2.62)
After biochemical pregnancy				
First trimester				
Ectopic pregnancy	2/526 (0.4)	4/571 (0.7)	–0.3 (–1.2 to 0.5)	0.54 (0.10 to 2.95)
Vaginal bleeding*	11/505 (2.2)	6/556 (1.1)	1.1 (–0.4 to 2.6)	2.02 (0.75 to 5.42)
Second or third trimester				
Gestational diabetes mellitus*	47/505 (9.3)	56/556 (10.1)	–0.8 (–4.3 to 2.8)	0.92 (0.64 to 1.34)
Preeclampsia or eclampsia*	16/505 (3.2)	31/556 (5.6)	–2.4 (–4.9 to 0.0)	0.57 (0.31 to 1.03)
Gestational hypertension*	10/505 (2.0)	10/556 (1.8)	0.2 (–1.5 to 1.8)	1.10 (0.46 to 2.62)
Premature rupture of membranes*	36/505 (7.1)	34/556 (6.1)	1.0 (–2.0 to 4.0)	1.17 (0.74 to 1.83)
Preterm delivery*	30/505 (5.9)	36/556 (6.5)	–0.5 (–3.4 to 2.4)	0.92 (0.57 to 1.47)
Placenta previa*	4/505 (0.8)	7/556 (1.3)	–0.5 (–1.7 to 0.7)	0.63 (0.19 to 2.14)
Placental abruption*	2/505 (0.4)	1/556 (0.2)	0.2 (–0.4 to 0.9)	2.20 (0.20 to 24.21)
Cervical incompetence*	3/505 (0.6)	6/556 (1.1)	–0.5 (–1.6 to 0.6)	0.55 (0.14 to 2.19)
Anemia*	22/505 (4.4)	24/556 (4.3)	0.0 (–2.4 to 2.5)	1.01 (0.57 to 1.78)
After delivery				
Postpartum hemorrhage†	17/469 (3.6)	18/497 (3.6)	0.0 (–2.4 to 2.4)	1.00 (0.52 to 1.92)
Puerperal infection†	1/469 (0.2)	1/497 (0.2)	0.0 (–0.6 to 0.6)	1.06 (0.07 to 16.89)
Postpartum anemia†	1/469 (0.2)	4/497 (0.8)	–0.6 (–1.5 to 0.3)	0.26 (0.03 to 2.36)
Fetal, after 12 wk through neonatal period				
Therapeutic abortion or fetal reduction due to fetal congenital anomalies during 12 to 28 wk of gestation	1/505 (0.2)	6/556 (1.1)	–0.9 (–1.8 to 0.1)	0.18 (0.02 to 1.52)
Stillbirth†	1/469 (0.2)	1/497 (0.2)	0.0 (–0.6 to 0.6)	1.06 (0.07 to 16.89)
Neonatal hospitalization of >3 days‡	58/474 (12.2)	66/514 (12.8)	–0.6 (–4.7 to 3.5)	0.95 (0.69 to 1.33)
Neonatal respiratory distress syndrome‡	3/474 (0.6)	6/514 (1.2)	–0.5 (–1.7 to 0.6)	0.54 (0.14 to 2.16)
Neonatal jaundice‡	115/474 (24.3)	113/514 (22.0)	2.3 (–3.0 to 7.5)	1.10 (0.88 to 1.39)
Neonatal infection‡	16/474 (3.4)	19/514 (3.7)	–0.3 (–2.6 to 2.0)	0.91 (0.48 to 1.75)
Congenital anomaly‡	9/474 (1.9)	12/514 (2.3)	0.4 (–1.4 to 2.2)	1.00 (0.99 to 1.02)
Low birth weight‡§	21/474 (4.4)	30/514 (5.8)	–1.4 (–4.2 to 1.3)	0.76 (0.44 to 1.31)
Very low birth weight‡¶	4/474 (0.8)	0		
Macrosomia‡‖	34/474 (7.2)	42/514 (8.2)	–1.0 (–4.3 to 2.3)	0.88 (0.57 to 1.36)
Birth weight lower than 5th percentile in singleton‡	8/461 (1.7)	11/478 (2.3)	–0.6 (–2.4 to 1.2)	0.75 (0.31 to 1.86)
Birth weight higher than 90th percentile in singleton‡	79/461 (17.1)	81/478 (16.9)	–0.2 (–5.0 to 4.6)	1.00 (0.94 to 1.06)

* Evaluation was performed in all clinical pregnancies.
† Evaluation was performed during or after all deliveries.
‡ Evaluation was performed in all live newborns.
§ Low birth weight was defined as a value of less than 2500 g.
¶ Very low birth weight was defined as a value of less than 1500 g.
‖ Macrosomia was defined as a birth weight of more than 4000 g.

that of long fragments) — will unavoidably cause false positive or negative results, resulting in embryo waste or false embryo transfer. Second, trophectoderm biopsy was conducted only in women in the PGT-A group rather than in both groups, and such biopsy procedures may be harmful, as was shown for preimplantation genetic screening on cleavage-stage embryos.[30]

Two trials,[6,31] which specifically included women who were older than 36 years of age, showed no improvement in the cumulative live-birth rate after PGT-A. Similarly, we found no benefit for PGT-A regardless of maternal age (≤35 years or >35 years). In addition, another two trials involving women who had a good prognosis (one of which included patients who were recruited from 34 clinics and included testing in nine laboratories across different countries) showed no improvements in ongoing pregnancy and live-birth rates with PGT-A after a first frozen-embryo transfer.[11,12] We likewise found no significant differences between groups in the rates of ongoing pregnancy and live birth after the first frozen-embryo transfer. We also noted that the pregnancy outcomes after each of three transfers were all similar between the two groups when analyzed separately, whereas the cumulative pregnancy outcome was lower with PGT-A. These findings support the importance of the cumulative live-birth rate as the primary end point in clinical trials.

The aim of PGT-A is to help achieve a healthy child and reduce the related burden of implantation failures and miscarriages.[32] In our trial, the results of a prespecified intention-to-treat analysis showed a lower rate of early pregnancy loss with PGT-A, which is consistent with the findings in the two trials involving women of advanced maternal age.[6,31] The frequency of biochemical loss was similar in the two trial groups, which suggests that embryos that are selected by morphologic criteria may be as likely as those selected by PGT-A to begin implantation but PGT-A does a better job of selecting embryos that continue through the first trimester.

Our trial has some limitations. We included only women who had a good prognosis for a live birth, among whom only three embryos were tested in the PGT-A group, and only up to three transfers in 1 year were included in the trial. Thus, the results may not be generalizable to women who do not have a good prognosis (e.g., those with recurrent miscarriage or recurrent implantation failure) or to situations in which more embryos are available for testing and transfer. Also, we performed intracytoplasmic sperm injection in all patients, which may not reflect the practice of many IVF programs and could potentially limit the generalizability of our results. In addition, approximately 5 to 6% of the patients in each group deviated from the protocol, most commonly owing to natural conception before frozen-embryo transfer or having two blastocysts transferred. However, results of per-protocol analyses were generally consistent with those of the intention-to-treat analysis, although the per-protocol analyses were limited by not reflecting a comparison of randomized groups.

We found that conventional IVF treatment was noninferior to PGT-A and resulted in a higher cumulative live-birth rate in women with a good prognosis for a live birth.

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APPENDIX

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