In Vitro Fertilization with Preimplantation Genetic Screening

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ABSTRACT

BACKGROUND

Pregnancy rates in women of advanced maternal age undergoing in vitro fertilization (IVF) are disappointingly low. It has been suggested that the use of preimplantation genetic screening of cleavage-stage embryos for aneuploidies may improve the effectiveness of IVF in these women.

METHODS

We conducted a multicenter, randomized, double-blind, controlled trial comparing three cycles of IVF with and without preimplantation genetic screening in women 35 through 41 years of age. The primary outcome measure was ongoing pregnancy at 12 weeks of gestation. The secondary outcome measures were biochemical pregnancy, clinical pregnancy, miscarriage, and live birth.

RESULTS

Four hundred eight women (206 assigned to preimplantation genetic screening and 202 assigned to the control group) underwent 836 cycles of IVF (434 cycles with and 402 cycles without preimplantation genetic screening). The ongoing-pregnancy rate was significantly lower in the women assigned to preimplantation genetic screening (52 of 206 women [25%]) than in those not assigned to preimplantation genetic screening (74 of 202 women [37%]; rate ratio, 0.69; 95% confidence interval [CI], 0.51 to 0.93). The women assigned to preimplantation genetic screening also had a significantly lower live-birth rate (49 of 206 women [24%] vs. 71 of 202 women [35%]; rate ratio, 0.68; 95% CI, 0.50 to 0.92).

CONCLUSIONS

Preimplantation genetic screening did not increase but instead significantly reduced the rates of ongoing pregnancies and live births after IVF in women of advanced maternal age. (Current Controlled Trials number, ISRCTN76355836.)

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THE USE OF IN VITRO FERTILIZATION (IVF) has steadily increased over the past decade. The American and European registries of assisted reproductive technology reported a total of 352,769 initiated IVF cycles in the year 2002.[1,2] In about half of these cycles, the woman was 35 years of age or older,[1,2] reflecting the demographic trend toward postponement of the time to start a family.[3] Unfortunately, IVF by itself cannot compensate for the lower fecundity associated with increasing age.[3]

A potential cause of the low pregnancy rates in women of advanced maternal age undergoing IVF is the increased incidence of numerical chromosomal abnormalities in embryos from these women.[4] It is thought that most of these chromosomally abnormal embryos do not develop to term. Consequently, transfer of embryos shown to be euploid by preimplantation genetic screening has been proposed as a way to increase live-birth rates in these women.[4] In preimplantation genetic screening, a single blastomere is aspirated from each embryo, and the copy number of a set of chromosomes is determined. Embryos that are identified as abnormal are then discarded, and embryos with a normal genetic constitution are selected for transfer.

The use of preimplantation genetic screening is increasingly common, in particular among women of advanced maternal age.[5,6] It has even been suggested that preimplantation genetic screening will become a standard procedure for women undergoing IVF.[6] Evidence supporting the use of preimplantation genetic screening, however, is limited. Observational studies comparing IVF with and without preimplantation genetic screening have shown that the use of preimplantation genetic screening is associated with higher implantation rates for transferred embryos but not with an increase in the rate of ongoing pregnancies per initiated cycle or per follicular aspiration.[7-11] A recent Cochrane review of preimplantation genetic screening included only two trials (one available only in abstract form), and it reported no significant difference in ongoing-pregnancy rates between women undergoing IVF with and those undergoing IVF without preimplantation genetic screening.[12] We conducted a multicenter, randomized, double-blind, controlled trial comparing ongoing-pregnancy rates after IVF with and without preimplantation genetic screening in women of advanced maternal age.

METHODS

STUDY POPULATION

Women from 35 through 41 years of age who were scheduled for IVF in the Academic Medical Center in Amsterdam or the University Medical Center Groningen, or in one of the clinics of these centers (the Onze Lieve Vrouwe Gasthuis in Amsterdam and the Medical Center Leeuwarden in Leeuwarden), who had no previous failed IVF cycles and who did not object to a possible double-embryo transfer, were eligible to participate in the study. The study protocol was approved by the institutional review boards of all participating hospitals and by the Central Committee on Research Involving Human Subjects in the Netherlands.

After providing written informed consent, the women were randomly assigned to undergo three cycles of IVF, with embryo selection based either on preimplantation genetic screening or on morphologic features of the embryo; the latter is standard care in the Netherlands. A cycle was defined as an ovarian stimulation procedure that resulted in a follicular aspiration.
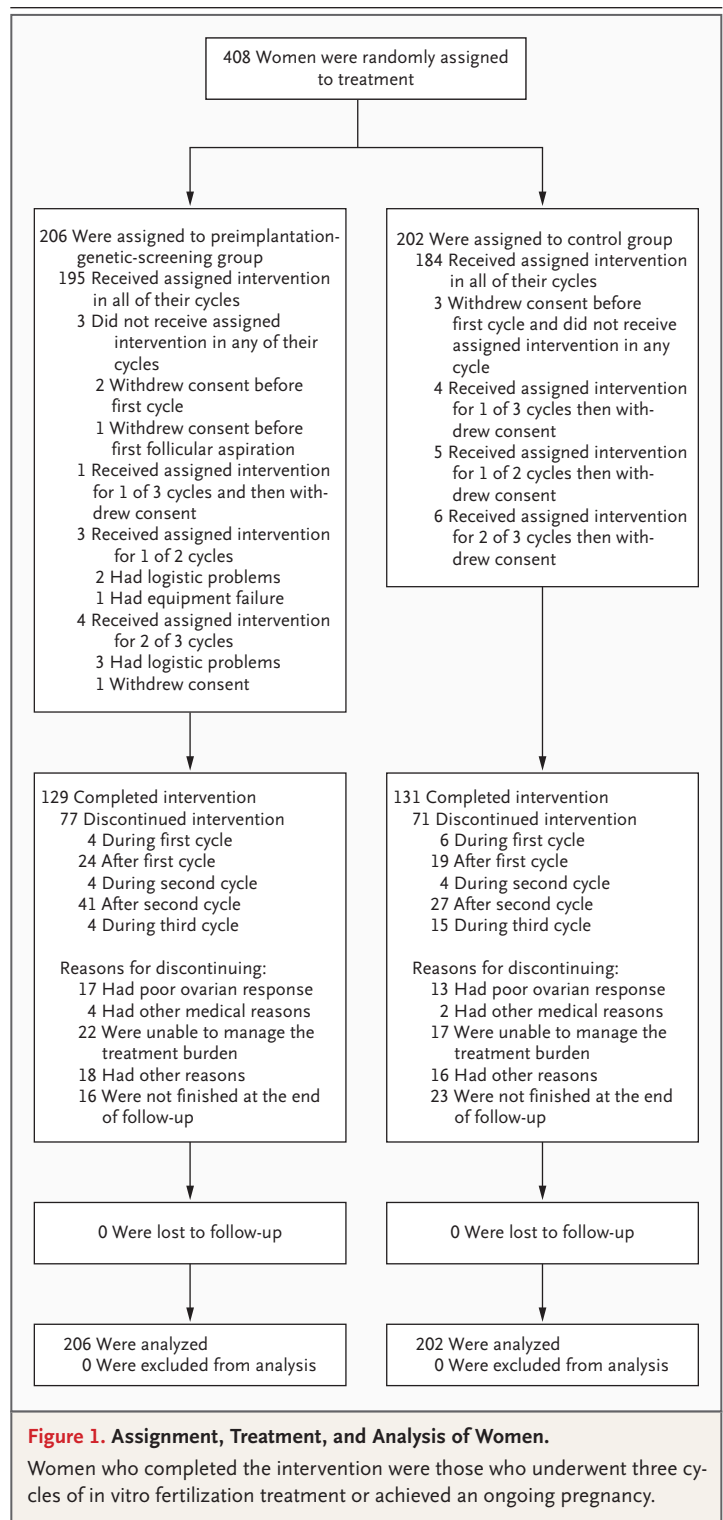
Randomization was performed centrally, before the first follicular aspiration, by a computer program with a minimization procedure for age (35 through 37 years and 38 through 41 years) and reproductive technique (IVF and intracytoplasmic sperm injection), with stratification according to study center. The women and their doctors were unaware of treatment allocation; to maintain blinding, they were not allowed to enter the laboratories and were given no information about the number and quality of the embryos to be transferred.

The stimulation protocol included ovarian down-regulation with a gonadotropin-releasing hormone agonist (triptorelin, Decapeptyl, Ferring) starting in the midluteal phase. Ovarian hyperstimulation was conducted with recombinant follicle-stimulating hormone (follitropin, Gonal-F, Serono) starting on cycle day 5, at an initial dose of 150 IU in the first cycle. Follicular aspiration was performed under transvaginal ultrasound guidance 36 hours after ovulation induction with 10,000 U of human chorionic gonadotropin (Pregnyl, Organon). The oocytes were inseminated with 10,000 progressively motile spermatozoa (in vitro fertilization) or injected with a single spermatozoon (intracytoplasmic sperm injection) approximately 4 hours after follicular aspiration.

For women assigned to preimplantation genetic screening, the screening procedure started 3 days after follicular aspiration during each cycle. Laser-assisted (Zilos, Hamilton Thorne Biosciences) biopsy of a single blastomere was performed on all available embryos containing at least four blastomeres. Individual blastomeres were fixed on glass slides with polyoxy-ethylene(20)sorbitan monolaurate (Tween 20) (0.1% in 0.01 N hydrochloric acid) and a methanol–acetic acid mixture (in a 3:1 ratio).[13,14] A biopsy of a second blastomere was performed only if no nucleus suitable for fluorescence in situ hybridization (FISH) was available after fixation of the first blastomere and only if the remaining embryo contained at least four blastomeres. FISH analysis was performed in two rounds for a total of eight chromosomes. On the day of embryo biopsy, all available nuclei were analyzed for chromosomes 1, 16, and 17 with chromosome enumeration probes (Vysis); the next day (after overnight hybridization), the same nuclei were analyzed for chromosomes 13, 18, 21, X, and Y with MultiVysion PGT probes (Vysis). Embryo biopsy, blastomere fixation, and FISH analysis were all performed by experienced embryologists and technicians.

On the basis of the results of FISH analysis, embryos were categorized as normal if two copies of each autosome were present and the sex chromosomes were either XX or XY, abnormal if a different chromosomal constitution was found, and undetermined if no determination of chromosomal constitution could be made because of a failed biopsy, the absence of a nucleus after fixation of the blastomere, the presence of an incomplete nucleus after fixation, or failure of the FISH procedure. Embryos on which no biopsy was performed because they contained fewer than four blastomeres were also categorized as undetermined.

The two chromosomally normal embryos with the best morphologic features[15] were selected for transfer on day 4. Embryos were given a score daily according to their morphologic features, with a focus on the number and regularity of blastomeres and the percentage of fragmentation.[15] Chromosomally abnormal embryos were never selected for transfer. If no chromosomally normal embryos with good morphologic features were available for transfer, undetermined embryos with good morphologic features were selected for transfer. In the control group, the selection of embryos for transfer was based solely on morphologic features according to the scoring procedure described above. A maximum of two embryos were transferred 4 days after insemination. In both study groups, if more than two embryos were suitable for transfer, supplementary good-quality em-

Figure 1. Assignment, Treatment, and Analysis of Women.
Women who completed the intervention were those who underwent three cycles of in vitro fertilization treatment or achieved an ongoing pregnancy.

bryos were cryopreserved. In cases of failed IVF cycles, these cryopreserved embryos were thawed and transferred to the woman's uterus before a new cycle was initiated.

OUTCOME MEASURES

The primary outcome was ongoing pregnancy, which was defined as a viable intrauterine pregnancy after 12 weeks of gestation. Secondary outcomes included biochemical pregnancy, clinical pregnancy, miscarriage, and live birth. Biochemical pregnancy was defined as a serum β human chorionic gonadotropin level of at least 2 IU per liter 2 weeks after embryo transfer. Clinical pregnancy was defined as the presence of a gestational sac confirmed by transvaginal ultrasound examination at a gestational age of 7 weeks.

SAMPLE-SIZE CALCULATION

In the 3 years preceding the trial, the cumulative pregnancy rate among women of advanced maternal age in the participating centers after three cycles of IVF was 40%. An increase of at least 15% was considered to be clinically relevant. We calculated that a sample size of 372 women would be needed to detect an increase in the cumulative ongoing-pregnancy rate from 40 to 55% (rate ratio, 1.38) after three cycles of IVF with preimplantation genetic screening, with a power of at least 80% at a significance level of 0.05.

STATISTICAL ANALYSIS

We calculated the rates of pregnancy and live birth in each group and the corresponding rate ratios with 95% confidence intervals. We used chi-square statistics to test for significance. Data were analyzed according to the intention-to-treat principle.

Two months after initiation of the trial, one interim analysis by a data safety and monitoring committee unaware of treatment assignment was planned. The O'Brien–Fleming procedure for a two-stage design was applied, in which the significance level for the final analysis of the primary outcome was 0.045 or less. An automatically generated, blinded overview, which was available only to the data safety and monitoring committee, was used for this interim analysis.

RESULTS

Between May 2003 and November 2005, a total of 408 women were randomly assigned to undergo IVF with (206 women) or without (202 women) preimplantation genetic screening. One hundred ninety-five women in the preimplantation-genetic-screening group and 184 in the control group underwent the assigned intervention in all their cycles (Fig. 1); the primary reason for failure to consistently undergo the assigned intervention was withdrawal of consent, in most cases because of unwillingness to accept the blinding. These women were informed of their treatment assignment and received standard IVF with embryo transfer on day 3 of their remaining cycle or cycles. In the few cases in which preimplantation genetic screening could not be performed because of logistic problems or failure of the laser equipment, the women were not informed of their treatment assignment and were treated according to protocol in their remaining cycles.

Seventy-seven of the 206 women assigned to preimplantation genetic screening and 71 of the 202 control women did not complete three cycles of IVF nor did they achieve ongoing pregnancy

Table 1. Characteristics of the Women.*		
Characteristic	Women Who Underwent Preimplantation Genetic Screening (N=206)	Controls (N=202)
Age — yr	38.0±1.7	37.9±1.6
Nulligravid — no. (%)	98 (48)	90 (45)
Nulliparous — no. (%)	139 (67)	123 (61)
Duration of infertility — yr	4.1±3.1	3.8±2.5
Body-mass index†	24.6±4.4	24.0±3.7
Cause of infertility — no. (%)‡		
Poor semen quality	78 (38)	78 (39)
Unexplained	77 (37)	74 (37)
Tubal	48 (23)	44 (22)
Anovulation	14 (7)	11 (5)
Endometriosis	12 (6)	7 (3)
Cervical	8 (4)	9 (4)
Ovarian failure§	2 (1)	1 (<1)

* Plus–minus values are means ±SD.
† The body-mass index is the weight in kilograms divided by the square of the height in meters. Complete data were available for 348 women (85%).
‡ More than one diagnosis per couple was possible; 353 couples had one diagnosis, and 55 couples had two diagnoses.
§ Donated oocytes from women of advanced maternal age were used in these cases.

within the study period. The reasons for not completing three cycles were similar between groups and were primarily due to poor ovarian response or the burden of treatment (Fig. 1).

Treatment was continued until June 2006, and follow-up ended in January 2007. No women were lost to follow-up. The baseline characteristics were similar in the two study groups (Table 1).

As compared with women in the control group, women in the preimplantation-genetic-screening group had a significantly lower rate of ongoing pregnancy (25% [52 of 206] vs. 37% [74 of 202]; rate ratio, 0.69; 95% confidence interval [CI], 0.51 to 0.93) and a significantly lower live-birth rate (24% [49 of 206] vs. 35% [71 of 202]; rate ratio, 0.68; 95% CI, 0.50 to 0.92). The biochemical and clinical pregnancy rates were also significantly lower in the preimplantation-genetic-screening group than in the control group. The miscarriage rates did not differ significantly between the groups (Table 2).

Clinical characteristics according to treatment cycle are shown in Table 3. A total of 836 cycles of IVF with follicular aspiration were performed (434 cycles with and 402 cycles without preimplantation genetic screening). The ongoing-pregnancy rates and the rates of biochemical and clinical pregnancy in the two groups were not significantly different when data were analyzed for first cycles only, for second cycles only, or for third cycles only.

The embryologic characteristics of treatment are shown in Table 4. In the preimplantation-genetic-screening group, 75 of 642 transferred embryos (11.7%) implanted (as determined by the presence of a gestational sac according to transvaginal ultrasound at a gestational age of 7 weeks). In the control group, 99 of 673 transferred embryos (14.7%) implanted. Post hoc analyses of the results from the preimplantation-genetic-screening group showed that in cycles in which two embryos with normal FISH results were transferred, the implantation rate was 16.8% (53 of 316), and that in cycles in which two undetermined embryos were transferred, the implantation rate was 6.0% (6 of 100).

In the preimplantation-genetic-screening group, one woman underwent elective termination of a pregnancy that was spontaneously conceived after prenatal diagnosis showed a trisomy 18. There was one intrauterine death (due to abruptio placentae) and one premature delivery of twins at 24 weeks of gestation, resulting in the postpartum death of both children. In the control group, two women underwent elective termination of pregnancy because of prenatally detected

Table 2. Outcomes in Women Who Underwent Preimplantation Genetic Screening and in Controls.

Outcome	Women Who Underwent Preimplantation Genetic Screening (N=206)	Controls (N=202)	Rate Ratio (95% CI)*	P Value
Women with an ongoing pregnancy — no. (%)	52 (25)	74 (37)	0.69 (0.51–0.93)	0.01
Women with ≥1 biochemical pregnancy — no. (%)	81 (39)	106 (52)	0.75 (0.60–0.93)	0.008
Total no. of biochemical pregnancies	94	118		
Women with ≥1 clinical pregnancy — no. (%)	61 (30)	88 (44)	0.68 (0.52–0.88)	0.003
Total no. of clinical pregnancies	67	92		
Women with ≥1 miscarriage — no. (%)	37 (18)	36 (18)	1.01 (0.67–1.53)	0.97
Total no. of miscarriages	43†	44‡		
Women with ≥1 live birth — no. (%)	49 (24)	71 (35)	0.68 (0.50–0.92)	0.01
Total no. of live births	59§	85¶		

* CI denotes confidence interval.
† One miscarriage occurred at 18 weeks of gestation; all other miscarriages occurred before 12 weeks of gestation.
‡ All miscarriages occurred before 12 weeks of gestation.
§ There were 39 singleton and 10 twin births; one woman underwent elective termination of pregnancy, one pregnancy ended in an intrauterine death, and one premature delivery resulted in the postpartum death of a twin.
¶ There were 57 singleton and 14 twin births; two women underwent elective termination of pregnancy, and one pregnancy ended in an intrauterine death.

Table 3. Clinical Characteristics According to Treatment Cycle.*

Characteristic	Women Who Underwent Preimplantation Genetic Screening (N = 206)	Controls (N = 202)	P Value
No. of women who started a cycle			
Cycle 1	206	202	
Cycle 2	150	134	
Cycle 3	89	81	
No. of stimulation procedures initiated			
Cycle 1	232	226	0.83
Cycle 2	153	143	0.06
Cycle 3	90	85	0.24
Duration of stimulation — days†			
Cycle 1	13.2±3.1	13.2±2.7	0.89
Cycle 2	12.3±2.4	12.0±2.1	0.20
Cycle 3	11.9±2.2	12.6±4.5	0.19
Total dose of gonadotropin — IU†			
Cycle 1	2736±1318	2801±1321	0.63
Cycle 2	3307±1643	3067±1483	0.21
Cycle 3	3334±1626	3426±1812	0.73
Follicular aspirations — no. (%)			
Cycle 1	200 (97)	195 (97)	0.75
Cycle 2	146 (97)	130 (97)	0.87
Cycle 3	88 (99)	77 (95)	0.14
Embryo transfers — no. (%)			
Cycle 1	166 (81)	176 (87)	0.07
Cycle 2	125 (83)	120 (90)	0.13
Cycle 3	76 (85)	68 (84)	0.79
Biochemical pregnancies — no. (%)			
Cycle 1	46 (22)	56 (28)	0.21
Cycle 2	23 (15)	33 (25)	0.05
Cycle 3	20 (22)	18 (22)	0.97
Clinical pregnancies — no. (%)			
Cycle 1	34 (17)	46 (23)	0.11
Cycle 2	18 (12)	21 (16)	0.37
Cycle 3	10 (11)	17 (21)	0.08
Ongoing pregnancies — no. (%)			
Cycle 1	25 (12)	39 (19)	0.05
Cycle 2	15 (10)	16 (12)	0.60
Cycle 3	8 (9)	11 (14)	0.34
Women with ≥1 transfer of cryopreserved embryos — no. (%)			
Cycle 1	13 (6)	14 (7)	0.80
Cycle 2	7 (5)	15 (11)	0.04
Cycle 3	2 (2)	9 (11)	0.02

Table 3. (Continued.)			
Characteristic	Women Who Underwent Preimplantation Genetic Screening (N=206)	Controls (N=202)	P Value
Ongoing pregnancies after transfer of cryopreserved embryos — no. (%)			
Cycle 1	0	2 (1)	
Cycle 2	0	2 (1)	
Cycle 3	0	0	
Spontaneous ongoing pregnancies — no. (%)			
Cycle 1	3 (1)	2 (1)	
Cycle 2	1 (<1)	2 (1)	

* Plus–minus values are means ±SD.
† Results are given per cycle with follicular aspiration.

fetal conditions, trisomy 18 in one case and a cleft lip and palate in the other. There was one intrauterine death of a fetus, which was delivered at 24 weeks of gestation.

DISCUSSION

In this large, randomized, double-blinded, controlled trial, we have shown that preimplantation genetic screening did not increase but instead significantly reduced the ongoing-pregnancy and live-birth rates after IVF in women of advanced maternal age.

Women were randomly assigned to three cycles of IVF with or without preimplantation genetic screening, the latter treatment mimicking usual IVF practice. Our power calculation was based on the assumption that all women would complete three IVF cycles and that the ongoing-pregnancy rate in the control group would be 40%. Although about one third of the women in our study did not complete three cycles of IVF, mainly because of poor ovarian response or the burden of IVF treatment, an ongoing-pregnancy rate of 37% was achieved in the control group.

The clinical pregnancy rate per follicular aspiration in the group undergoing preimplantation genetic screening (14%) is in line with published results from other centers. The European Society of Human Reproduction and Embryology Preimplantation Genetic Diagnosis Consortium, which retrospectively collects data on the outcomes of preimplantation genetic screening, reported a clinical pregnancy rate of 12% per follicular aspi-

ration among 478 IVF cycles of women of advanced maternal age undergoing preimplantation genetic screening in 2003.[5]

Our results are also in line with the outcomes of the only other large, randomized trial of preimplantation genetic screening published to date, although that trial was not powered for the outcomes of ongoing pregnancy or live birth.[16] In that trial, 389 women were randomly assigned to a single treatment cycle of IVF, with or without preimplantation genetic screening. Women assigned to preimplantation genetic screening had a relative ongoing-pregnancy rate of 0.72 (95% CI, 0.43 to 1.21) and a relative live-birth rate of 0.69 (95% CI, 0.41 to 1.17). The primary outcome of the study was implantation rate (and therefore embryos instead of women were used as the basis for the sample-size calculations), which was nonsignificantly higher in the preimplantation-genetic-screening group than in the control group (17.1% vs. 11.5%).

Secondary analyses in our trial found implantation rates of 11.7% in the preimplantation-genetic-screening group and 14.7% in the control group. The transfer of embryos that did not undergo biopsy or embryos without a FISH result (for which the implantation rate was 6.0%) contributed to a lower overall implantation rate associated with preimplantation genetic screening in our trial. Nonetheless, our policy of transferring such undetermined embryos, if no embryos with normal FISH results were available, led to additional ongoing pregnancies. The implantation rate in cycles in which two embryos

Table 4. Embryologic Characteristics of Treatment.*

Characteristic	Women Who Underwent Preimplantation Genetic Screening	Controls
Cumulus–oocyte complexes — no. (mean no. per cycle with follicular aspiration)	3540 (8.2)	3440 (8.6)
Fertilization procedures — no.		
IVF	273	261
Intracytoplasmic sperm injection	161	141
Oocytes inseminated — no. (mean no. per cycle with follicular aspiration)	3301 (7.6)	3222 (8.0)
Embryos — no. (mean no. per cycle with follicular aspiration)	2173 (5.4)	2046 (5.1)
Embryos that underwent biopsy — no. (mean no. per cycle)	1700 (4.8)	—
Results of fluorescence in situ hybridization — no. (% of all embryos that underwent biopsy)		
Normal	653 (38.4)	—
Abnormal	706 (41.5)	—
Undetermined	341 (20.1)	—
Failed biopsy	47 (2.8)	—
No nucleus	97 (5.7)	—
Incomplete nucleus	83 (4.9)	—
Failed fluorescence in situ hybridization	114 (6.7)	—
Embryos transferred — no. (mean no. per transfer)	642 (1.8)	673 (1.9)
Implanted embryos — no. (% of embryos transferred)	75 (11.7)	99 (14.7)
Embryos cryopreserved — no. (mean no. per cycle with follicular aspiration)	132 (0.3)	326 (0.8)
Cryopreserved embryos transferred — no. (mean no. per transfer)	44 (1.5)	83 (1.7)
Implanted cryopreserved embryos — no. (% of cryopreserved embryos transferred)	1 (2.3)	5 (6.0)

* Dashes denote not applicable.

with normal FISH results were transferred (16.8%) was similar to the rates previously reported with preimplantation genetic screening.[10,16]

The implantation rate, however, is not an appropriate outcome measure for describing the effectiveness of preimplantation genetic screening. It introduces a unit-of-analysis error, since women rather than embryos are randomly assigned to treatment, and an analysis of implantation rates fails to account for the nonindependence of outcomes between different embryos from the same cycle and from the same woman.[17] The primary outcome in fertility studies should ideally be live birth, since this is the main goal of fertility treatment. Although our trial was designed with ongoing pregnancy as the primary outcome, live-birth rates mirrored ongoing-pregnancy rates and were also significantly lower in the preimplantation-genetic-screening group than in the control group.

Several mechanisms may be responsible for the failure of preimplantation genetic screening to improve the outcomes of IVF in women of advanced maternal age. It is possible that biopsy of a blastomere on day 3 of embryonic development hampers the potential of an embryo to successfully implant[18]; however, the effect of biopsy alone on pregnancy rates has not been studied. Furthermore, the limitation in the number of chromosomes that can be analyzed with FISH could lead to the transfer of embryos labeled as normal that are in fact aneuploid for one or more chromosomes not tested. This problem may be overcome in the future by the use of new techniques, such as array comparative genomic hybridization, in which the complete ploidy status can be given for a blastomere after biopsy.[19] Finally, many human embryos resulting from IVF may be mosaic,[16,20,21] so that the chromosomal constitution revealed by analysis of the blastomere may not be representative of the entire embryo.

Our study was limited to women undergoing preimplantation genetic screening for the indication of advanced maternal age. Whether the results

would be different for women with other indications for preimplantation genetic screening is uncertain. In addition, we do not have information on birth defects in the live-born infants, although we are currently collecting such data.

Our study demonstrated that preimplantation genetic screening significantly reduced, rather than increased, the likelihood of an ongoing pregnancy and live birth in women of advanced maternal age. These results argue strongly against routinely performing preimplantation genetic screening as an adjunct to IVF in this group of women.

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