What are patients doing with their mosaic embryos? Decision making after genetic counseling

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Objective: To assess patient decisions regarding mosaic embryos and their impact on clinical outcomes.
Design: Review of patients who had genetic counseling regarding mosaic embryos.
Setting: Academic department.
Patient(s): Ninety-eight patients who had mosaic embryos but no euploid embryos.
Intervention(s): Genetic counseling to discuss mosaic-embryo transfer (MET) after preimplantation genetic testing for aneuploidy.
Main Outcome Measure(s): Patient decisions regarding MET. Outcomes for patients who pursued MET were compared with those for patients who pursued additional in vitro fertilization or intrauterine insemination cycles. Decisions regarding prenatal testing after MET were assessed.
Result(s): Initially, 29.6% of patients pursued MET and 41.8% attempted a new treatment cycle. Only 6.1% of patients discarded their mosaic embryos without further treatment. Of the remaining patients, 2.0% transported their mosaic embryos to a different facility and 20.5% had not taken further action while their embryos remain stored. Patients who pursued additional cycles were more likely to have an ongoing pregnancy compared with those who pursued MET (51.2% vs. 27.6%; $P<.05$); however, there was no statistically significant difference in the percentage of patients who had at least one biochemical pregnancy or spontaneous abortion. Ultimately, 32.7% of patients underwent MET, and 54.5% of pregnant patients pursued amniocentesis.
Conclusion(s): MET is desired by a substantial proportion of patients who do not have euploid embryos. Patients who opt for additional treatment cycles have a greater chance of achieving an ongoing pregnancy compared with those who pursue MET; however, future studies are needed to compare the cost-effectiveness for both options. (Fertil Steril® 2019;111:132–7. ©2018 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Preimplantation genetic testing, PGT-A, mosaicism, genetic counseling, next-generation sequencing

Preimplantation genetic testing for aneuploidy (PGT-A) is increasingly performed in conjunction with in vitro fertilization (IVF). Several studies have demonstrated that by enabling selection of a single euploid blastocyst, PGT-A is associated with fewer multiple gestations and reduced miscarriage rates (1–4). Although embryonic mosaicism has been described for more than two decades (5), the evolution of PGT-A from analysis of a single blastomere by means of fluorescence in situ hybridization (FISH) to analysis of several trophectoderm cells by means of array comparative genomic hybridization (aCGH) and later next-generation sequencing (NGS) has increased its detection. Previously, results were reported simply as normal (euploid) or abnormal (aneuploid) and embryo selection was usually a simple decision. Now, with the reporting of mosaic results, selecting the best embryo for transfer has become a more complicated process.

Greco et al. (6) were the first to report on a small number of babies born from embryos diagnosed as chromosomally mosaic. Subsequently, several other centers have now reported on apparently healthy deliveries from these embryos, albeit at a lower rate than euploid embryos and with a higher chance of miscarriage (7, 8). Therefore, it is becoming increasingly apparent that mosaic embryos represent a distinct category of PGT-A results (9), with their reproductive potential lying somewhere between those of aneuploid and euploid embryos.

Received July 25, 2018; revised October 1, 2018; accepted October 2, 2018; published online November 10, 2018.
A.G.B. has nothing to disclose. D.H.M. is the Laboratory Director at Biogenetics Corporation, Mountainside, New Jersey; Laboratory Director at Sperm and Embryo Bank of New York, New York; and Director of Clinical Science at REPROART: Georgian American Center for Reproductive Medicine in Tbilisi, Georgia. J.A.G. has nothing to disclose.
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Fertility and Sterility® Vol. 111, No. 1, January 2019 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2018.10.001

There are several different explanations for mosaic PGT-A results. Mosaicism is diagnosed when the data for a given chromosome or chromosomal segment falls within an intermediate range between the designated euploid and aneuploid thresholds (10). Studies have shown that mixing different proportions of euploid and aneuploid cells results in a linear change of copy number status, indicating that mosaicism present in a trophectoderm biopsy can be detected by some NGS platforms (11–13). However, technical factors, such as amplification bias and contamination, can also generate intermediate copy number profiles resembling the presence of mosaicism (14). Therefore, although a mosaic diagnosis may reflect a mixed euploid/aneuploid composition of the trophectoderm sample, it may also reflect technical variation.

Counseling patients about mosaic PGT-A results remains a considerable challenge. Although the babies born from mosaic-embryo transfer (MET) appear to be healthy, long-term outcomes are not yet known. In addition, given that live births with persisting mosaicism of nearly every chromosome have occurred and often have severe phenotypes, it can not be overlooked that abnormal outcomes remain a possibility. Other potential risks include uniparental disomy (UPD) syndromes, which may result if mosaicism is the result of a trisomy or monosomy rescue event (15), as well as intrauterine growth restriction and fetal demise due to persisting placental mosaicism. Therefore, although the chance of an adverse outcome following MET appears to be low, it is not yet well defined.

Given the potential risks, genetic counseling is essential for any patient who is considering MET. The goal of genetic counseling is to ensure that patients have adequate comprehension of mosaic results and can make autonomous decisions about whether to proceed with MET, maintain these embryos in cryostorage pending better characterization of outcomes in the future, or discard them. For patients who proceed with MET, it is essential to stress the recommendation for prenatal genetic counseling in the event of a pregnancy, the differences between the various screening and diagnostic tests that are currently available, and the limitations of these tests (16).

Currently, there is a lack of research addressing the decisions patients make following genetic counseling about mosaic results. The purpose of the present study was to assess those decisions and their impact on clinical outcomes.

MATERIALS AND METHODS

All patients who completed at least one cycle of IVF with PGT-A as well as genetic counseling from January 2016 to May 2018 for the primary indication of discussing the option of MET were reviewed. Patients who had at least one blastocyst that was euploid, untested, or undiagnosed (due to failed amplification or inconclusive PGT-A results) were not included in the analysis. Approval was obtained from the Institutional Review Board of the New York University School of Medicine (study number S13-00389).

For most embryos discussed during genetic counseling, PGT-A was performed at Coopergenomics by means of whole-genome amplification and NGS on a Miseq (Veriseq protocol; Illumina), and mosaicism was reported in the range of 20%–80%; biopsies with <20% aneuploidy were reported as euploid, and biopsies with >80% aneuploidy were reported as aneuploid (11). One mosaic embryo was diagnosed at the Foundation for Embryonic Competence by targeted amplification and NGS on an Ion Torrent Proton sequencer (17), and mosaicism was reported according to the laboratory's internal protocols.

Topics covered during genetic counseling included the possible interpretations of a mosaic result, risks and potential outcomes following MET, prenatal testing options, embryo selection, and current data about mosaicism, in accordance with previously published recommendations (16, 18, 19). Given the limited data available, specific recommendations regarding whether or not to pursue MET were not provided; however, prenatal diagnosis was recommended and patients were informed that amniocentesis is more representative of fetal tissues than chorionic villus sampling (CVS). The appointment occurred either in person or by telephone, depending on patient preference.

We assessed whether, in the absence of euploid or untested/undiagnosed embryos, patients opted to transfer their mosaic embryos, discard them, or maintain them in cryostorage while pursuing additional treatment cycles. Multiple logistic regression was used to determine predictors of patient decisions to pursue MET. We also evaluated the rate at which patients who had genetic counseling decided to pursue MET over the course of the study period. Outcomes for patients who initially elected to pursue MET were compared by means of chi-square analysis with cumulative outcomes for patients who pursued at least one additional IVF or intrauterine insemination (IUI) cycle. For ongoing pregnancies after MET, patient decisions regarding prenatal testing were assessed.

RESULTS

Mosaicism Rate at Our Center

The overall rate of chromosomal mosaicism per biopsied embryo observed at our center during the study period was 28.4%; 19.1% of all NGS-tested embryos had only mosaic aneuploidies (i.e., without any additional nonmosaic aneuploidies) and were considered for MET.

Patient Characteristics

One hundred twenty-nine patients completed genetic counseling with an on-site genetic counselor to discuss the option of MET. Twelve patients (9.3%) opted for an in-person appointment and the remainder (90.7%) of the appointments were conducted by telephone. Thirty-one patients (24.0%) had at least one euploid or untested/undiagnosed embryo and were excluded from the analysis. The mean age of the remaining 98 patients was 39.8 years at the time of counseling. Most of the embryos discussed were created with autologous gametes, and 14 patients had mosaic embryos that were created with donor gametes (4 with donor oocytes and 10 with donor sperm). Two patients had mosaic embryos that had also undergone preimplantation genetic testing for a monogenic disorder (both cystic fibrosis) with unaffected (normal or carrier) results.

Patient Decisions

After genetic counseling, 29/98 patients (29.6%) initially elected to proceed with MET (Fig. 1). Another 41/98 patients (41.8%) opted to attempt a new IVF or IUI cycle; the majority used the same oocyte source as with their previous cycles, and 3 patients who previously cycled with autologous oocytes elected to use donor oocytes. Six patients (6.1%) elected to discard their mosaic embryos and did not pursue any additional treatment with our clinic.

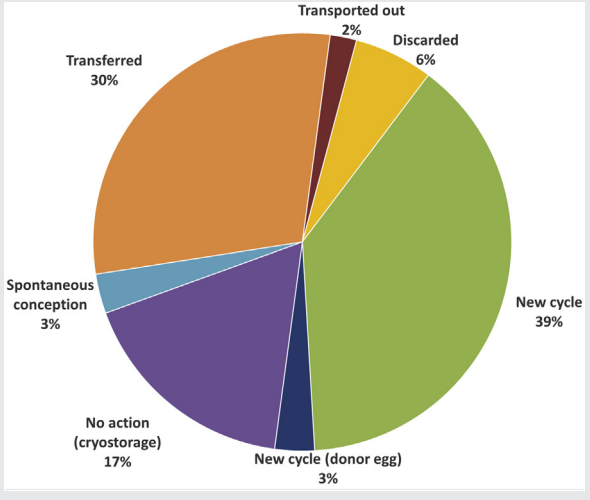
Three of the 41 patients (7.3%) who initially attempted additional treatment cycles but were unsuccessful eventually elected to pursue MET. Therefore, a total of 32/98 patients (32.7%) ultimately transferred at least one mosaic embryo in 35 MET cycles. Five cycles (14.3%) involved the transfer of more than one embryo. The remaining 30/35 cycles (85.7%) involved single MET.

Increased values of both patient age and number of previous egg retrievals were found to be significant positive contributors to the decision to pursue MET, according to multiple logistic regression (ln odds ratio [OR] 6.5; $P<.0025$; Fig. 2).

Supplemental Figure 1 (available online at www.fertstert.org) illustrates the rate at which patients were counseled and elected MET over the study period. From March to May 2016, a higher proportion of patients opted for MET (10/16, 62.5%). Toward the end of the study period, from January to May 2018, a smaller proportion of patients opted for MET (2/16, 12.5%). During the majority of the study period, however, from June 2016 to December 2017, the rate at which patients elected to pursue MET was relatively stable (17/65, 26.2%).

At the time of writing, 17/98 patients (17.3%) had not pursued any action regarding their mosaic embryos and had not completed any further treatments with our clinic. It is unknown whether they may have pursued treatment in other IVF programs. The mosaic embryos for these patients remain in cryostorage.

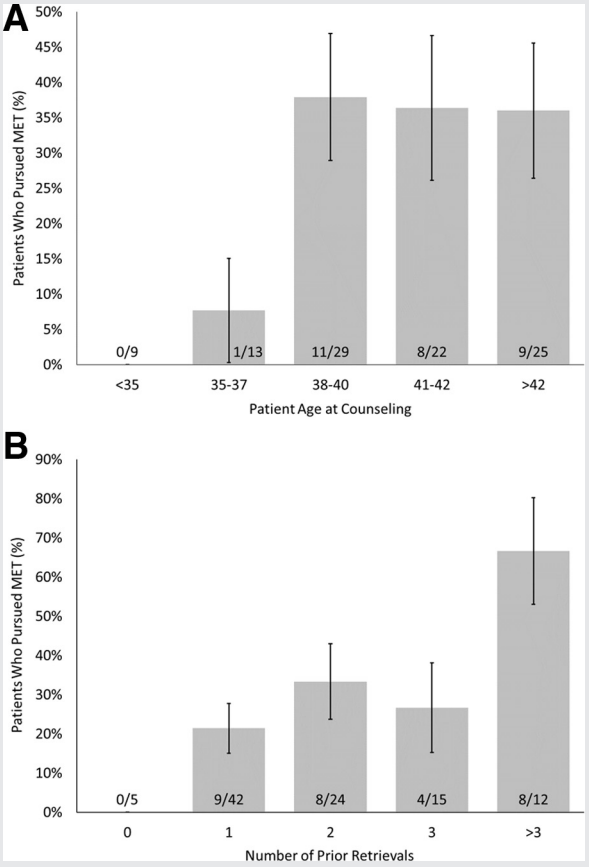
FIGURE 1



Initial decisions of patients following genetic counseling about the option of mosaic-embryo transfer.

Besser. Patient decisions about mosaic embryos. Fertil Steril 2018.

FIGURE 2



Factors affecting the percentage of patients who elected to pursue mosaic-embryo transfer (MET). (**A**) Age of patient at the time of counseling. (**B**) Number of previous egg retrievals.

Besser. Patient decisions about mosaic embryos. Fertil Steril 2018.

Outcomes

Of the patients who attempted one or more additional IVF or IUI cycles, 21/41 (51.2%) eventually had a successful pregnancy and 5/41 (12.2%) had at least one spontaneous abortion (SAB) or biochemical pregnancy (Table 1). Three other patients conceived spontaneously through intercourse while their mosaic embryos remained in cryostorage; one had a live birth, another had an ectopic pregnancy, and the outcome of the third is unknown.

Of the patients who initially pursued at least one MET cycle, 8/29 had a successful pregnancy (27.6%). Seven patients (24.1%) had at least one SAB or biochemical pregnancy.

Prenatal Diagnosis

Of the patients who had a successful pregnancy after MET, 6/11 (54.5%) were confirmed to have undergone prenatal diagnosis with the use of amniocentesis (Table 2). Two of these patients elected to pursue prenatal chromosomal microarray (CMA) in addition to routine karyotyping. All karyotype and CMA results were normal. No patients were known to pursue CVS or prenatal UPD testing. None of the babies born were reported to have any congenital anomalies at delivery.

TABLE 1

Patients who initially opted for MET vs. those who pursued additional IVF or IUI cycles.

Outcome (per patient)	MET (n = 29)	Additional IVF/IUI cycles (n = 37)	*P* value
Ongoing pregnancy (%)	8/29 (27.6%)	21/41 (51.2%)	.048[a]
≥1 spontaneous abortion/ biochemical pregnancy (%)	7/29 (24.1%)	5/41 (12.2%)	.192

Note: MET = mosaic-embryo transfer; IUI = intrauterine insemination; IVF = in vitro fertilization.
[a] Statistically significant at $P<.05$.

Besser. Patient decisions about mosaic embryos. Fertil Steril 2018.

DISCUSSION

In the present study population, more than one-fourth of patients elected to pursue MET instead of additional treatment cycles, despite the potential risks enumerated during genetic counseling. Specific reasons for patient decisions were not obtained as part of this analysis, but it is likely that some information discussed during pre-test counseling was reassuring, such as the possibility that a mosaic diagnosis may not signify true embryonic mosaicism (10, 14), or the possibility that aneuploid cells, if truly present, may be limited to the trophectoderm.

Older patients were more inclined to pursue MET, likely owing to the reduced potential for a new treatment cycle to produce a euploid embryo. Patients who had more previous egg retrievals were also more likely to choose MET, possibly owing to the physical and psychologic burden of pursuing additional treatment, as well as exhausted financial resources.

Although patients who had euploid or untested/undiagnosed embryos available were not included in the data analysis, it can be noted that six patients in that group also elected to pursue MET. For four of those patients, the reason provided was sex selection. One patient transferred both mosaic and undiagnosed embryos together, and one wanted to "save" her euploid embryos, to minimize uncertainty about reproductive options for future potential offspring. Thus, there are some situations in which patients may elect to pursue MET even when euploid or untested/undiagnosed embryos are available.

We found that most patients who do not immediately pursue MET elect to maintain these embryos in cryostorage. Despite an annual storage fee at our clinic, few patients elected to discard their mosaic embryos. In contrast, patients in our program rarely elect to store embryos with fully aneuploid (nonmosaic) results. This highlights the importance of counseling patients about the distinction between mosaic and nonmosaic aneuploid PGT-A results, because decision making may depend on this distinction.

The rate at which patients chose MET was relatively stable throughout the study period. This result was unexpected, given that attitudes about embryonic mosaicism and MET have likely evolved over time. The rate at which patients chose MET was higher toward the beginning of the study period and lower toward the end, which likely reflects the time that had elapsed between the genetic counseling appointment and the point at which decision making was assessed; that is, patients who were counseled early in the study period had more time to make decisions, and patients who were counseled late in the study period likely had not completed their decision making at the time of data analysis. In addition, this difference may reflect inconsistencies in referral practices, because patients were initially more likely to be referred for genetic counseling only if they inquired about MET (and therefore may have already decided to pursue it), and over time the referral threshold decreased.

Patients who pursued additional IVF or IUI cycles had more successful pregnancies than those who pursued MET. However, given the financial, physical, and psychologic burden associated with additional IVF cycles, MET may be a preferred option for some patients. Furthermore, there are some patients for whom additional cycles may not be an

TABLE 2

Prenatal testing decisions among patients who became pregnant following MET.

Patient	CVS	AF	CMA	UPD	Outcome
1	N	N	N	N	LB of singleton (apparently healthy)
2	N	N	N	N	LB of singleton (apparently healthy)
3	N	Y	N	N	LB of singleton (apparently healthy)
4	N	Y	N	N	LB of singleton (apparently healthy)
5	N	Y	Y	N	Ongoing singleton pregnancy
6	N	N	N	N	LB of singleton (premature due to cervical insufficiency)
7	U	U	U	U	LB of singleton (apparently healthy)
8	U	U	U	U	Ongoing twin pregnancy
9	N	Y	N	N	LB of singleton (apparently healthy)
10	N	Y	Y	N	Ongoing singleton pregnancy
11	N	Y	N	N	Ongoing singleton pregnancy

Note: AF = amniocentesis; CMA = chromosomal microarray; CVS = chorionic villus sampling; LB = live birth; N = no; UPD = uniparental disomy studies; U = unknown; Y = yes.

Besser. Patient decisions about mosaic embryos. Fertil Steril 2018.

option, such as those who only had a limited number of cryopreserved oocytes that underwent fertilization and PGT-A and are now past reproductive age.

More than one-half of our patients who became pregnant following MET pursued prenatal diagnosis with the use of amniocentesis, which was recommended during the initial genetic consultation. However, despite all pregnancies resulting from embryos that were identified as mosaic for a partial aneuploidy, only two patients elected to pursue prenatal CMA; the reasons for this are unclear but may include the high cost or lack of insurance coverage for this test, the possibility of identifying a copy number variant of unknown significance or other incidental finding, or reassurance that the large deletions/duplications detected by PGT-A are often visible by routine G-band karyotyping. No patients pursued CVS, likely because they were counseled about the possibility of false positive or false negative results when sampling placental tissue. One patient who declined prenatal diagnosis entirely reported that she was less concerned about the possibility of an abnormal outcome after a nuchal translucency measurement within normal limits. Because patients were not interviewed as part of this study, it is unclear whether that patient had adequate understanding of the limitations of ultrasound evaluation in the diagnosis of a mosaic aneuploidy.

A limitation of this study is that decision making was assessed for patients at only a single center. Although the goal of genetic counseling is to provide nondirective education and support, it is likely that patient decisions were influenced by clinic-specific policies and provider attitudes regarding MET. Therefore, clinics with different policies and perspectives about MET may see a different distribution of decisions made by their patient populations. Furthermore, this study was limited by the outcome information that was known to our clinic; therefore, it may not include data about cycles or pregnancies that occurred if patients sought additional treatment elsewhere. Future research is needed to determine whether patient decisions and associated outcomes may vary depending on the type of mosaicism or PGT-A platform used, because the reproductive potential of these embryos may differ (7, 8, 13). Finally, this study did not assess the reasoning behind patient decisions, nor did it evaluate patient understanding after genetic counseling. Additional research in these areas is essential to establish best practices for genetic counseling about mosaic PGT-A results.

CONCLUSION

This is the first study to assess the decisions made by patients after genetic counseling about mosaic PGT-A results. Our data suggest, despite the limited outcome data available and potential risks, that MET is desired by a substantial proportion of patients who do not have euploid embryos, particularly by patients of advanced age or who have undergone multiple IVF cycles. Prenatal diagnosis appears to be desired by the majority of patients who become pregnant following MET. Patients who opt to cycle again and create additional embryos have a greater chance of eventually achieving a successful pregnancy; however, future studies are needed to compare the cost-effectiveness, time to live birth, and risks associated with both options.

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¿Qué están haciendo los pacientes con sus embriones mosaicos? Toma de decisiones tras el asesoramiento genético.

Objetivo: Evaluar la decisión de los pacientes con respecto a embriones mosaicos y su impacto en los resultados clínicos.

Diseño: Revisión de pacientes que obtuvieron asesoramiento genético con respecto a embriones mosaicos.

Escenario: Departamento académico.

Paciente(s): Noventa y ocho pacientes que tuvieron embriones mosaicos y ningún embrión euploide.

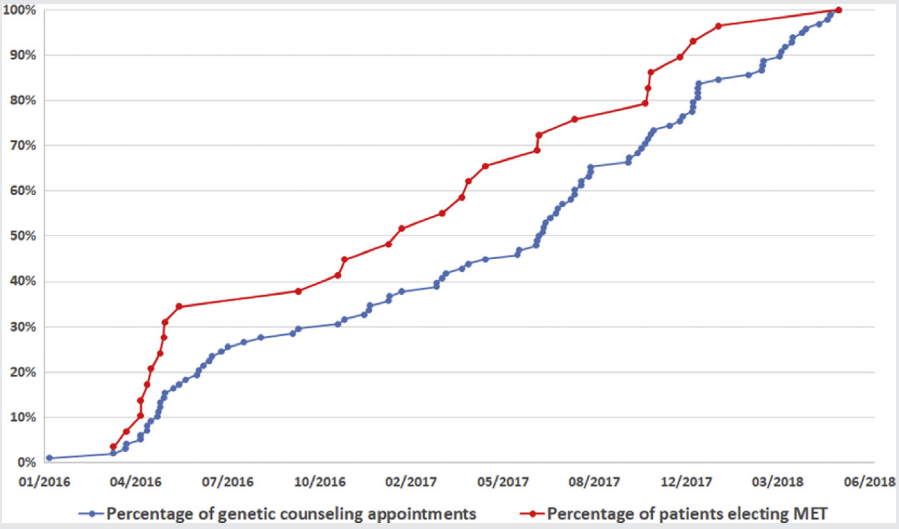
Intervenciones: Asesoramiento genético para debatir la transferencia de embriones mosaicos (TEM) una vez realizado el estudio genético preimplantacional por aneuplodías.

Medida de los resultados principales: Decisiones de los pacientes con respecto a la TEM. Los resultados de los pacientes que llevaron a cabo la TEM fueron comparados con aquellos resultados de pacientes que llevaron a cabo ciclos adicionales de fecundación in vitro o inseminaciones intrauterinas. Las decisiones con respecto al diagnóstico prenatal después de la TEM fueron evaluadas.

Resultado(s): En principio, un 26.9% de los pacientes llevaron a cabo la TEM y un 41.8% optaron por un nuevo ciclo de tratamiento. Sólo un 6.1% de los pacientes descartaron sus embriones mosaicos sin tratamientos adicionales. Del resto de pacientes, el 2.0% trasladaron sus embriones mosaicos a un centro diferente y un 20% no ha realizado nada al respecto mientras que sus embriones se mantienen almacenados. Los pacientes que se sometieron a ciclos adicionales consiguieron un embarazo viable con mayor probabilidad que los que realizaron la TEM (51.2% vs. 27.6%; $P<.05$); sin embargo, no hubo diferencias estadísticamente significativas en el porcentaje de pacientes que tuvieron al menos un embarazo bioquímico o aborto espontaneo. Finalmente, el 32.7% de los pacientes se sometieron a la TEM y 54.5% de las pacientes embarazadas se realizaron la amniocentesis.

Conclusión(es): la TEM es elegida por una proporción substancial de pacientes que no tienen embriones euploides. Los pacientes que optan por ciclos de tratamientos adicionales tienen una mayor oportunidad de lograr un embarazo viable en comparación con aquellos que prefieren la TEM; sin embargo, es necesario realizar estudios adicionales para comparar la rentabilidad de ambas opciones.

SUPPLEMENTAL FIGURE 1



Cumulative temporal distributions for patients who had genetic counseling and those who decided to pursue mosaic-embryo transfer (MET) over the study period. These curves indicate the date of counseling for all patients who completed counseling (*blue*) and for patients who subsequently elected MET (*red*). If the percentage of counseled patients who opted for MET was the same throughout the study period, these two curves would be superimposed. From March to May 2016, the rate of rise for patients who elected MET was greater than the rate of rise for patients undergoing counseling, indicating that a higher proportion of counseled patients opted for MET (10/16, 62.5%) during this period. From June 2016 to December 2017, the two curves are relatively parallel, indicating that the percentage of patients who pursued MET following counseling was relatively constant (17/65, 26.2%) during this period. From January to May 2018, the rate of rise for patients who elected MET was less than the rate of rise for patients undergoing genetic counseling, indicating that a smaller percentage of the counseled patients (2/16, 12.5%) pursued MET during this period.

Besser. Patient decisions about mosaic embryos. Fertil Steril 2018.