



Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Case Report

Healthy live births after mosaic blastocyst transfers with the use of next-generation sequencing

Yung-Liang Liu^{a, b, 1}, Tzu-Ning Yu^{b, 1}, Ching-Hui Chen^{b, c}, Peng-Hui Wang^{d, e, f},
Chi-Huang Chen^{b, c, *}, Chii-Ruey Tzeng^{b, c, **}^a Department of Obstetrics and Gynecology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan^b Division of Infertility, Department of Obstetrics and Gynecology, Taipei Medical University Hospital, Taipei, Taiwan^c Department of Obstetrics and Gynecology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan^d Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan^e Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan^f Department of Medical Research, China Medical University Hospital, Taichung, Taiwan

ARTICLE INFO

Article history:

Accepted 2 July 2019

Keywords:

Aneuploidy

Euploidy

Preimplantation genetic testing for

aneuploidy

Mosaicism

Next-generation sequencing

ABSTRACT

Objective: To determine whether transfer of high-mosaicism ($\geq 50\%$) embryos can result in healthy newborns.**Case report:** Two embryos resulting from controlled ovarian stimulation (COS) in Patient one, 41 years of age (y/o), underwent preimplantation genetic testing for aneuploidy (PGT-A), which demonstrated that one was mosaic (68%) and the other aneuploid; the mosaic embryo was transferred. Amniocentesis at 18 weeks of gestational age (GA) revealed a normal 46, XY karyotype. A phenotypically normal boy was delivered at 39 and 5/7 weeks of GA. For Patient two, 39 (y/o), nine embryos obtained after COS underwent PGT-A, indicating one euploid, four mosaic, and four aneuploid embryos. One euploid and one mosaic (50%) embryo were transferred, resulting in a twin pregnancy. Amniocentesis at 18 weeks of GA showed both fetuses had normal 46, XY karyotypes. Two phenotypically normal boys were delivered at 37 2/7 weeks of GA.**Conclusion:** Transfer of high-mosaicism embryos selected using current techniques can result in healthy euploid newborns. Amniocentesis suggested that mosaic embryos can be self-corrected before 18 weeks of GA.© 2019 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Many molecular techniques including array-comparative genomic hybridization (aCGH) and next-generation sequencing (NGS) have been developed to investigate embryo ploidy during *in vitro* fertilization (IVF) [1,2]. A day 3, single-blastomere biopsy for preimplantation genetic testing for aneuploidy (PGT-A) analyzes all

24 chromosomes to allow identification and transfer of euploid embryos. PGT-A has been reported to improve live-birth rates per cycle in women aged 38–41 years [3]. However, it is not clear whether PGT-A should be implemented as a general screening test in routine IVF practice [1,4,5].

Embryonic mosaicism is defined as the occurrence of two or more genetically different cell lineages within the same embryo [6,7]. Mosaicism at a ratio of 20–80% normal to abnormal cells can be identified in a 5- to 10-cell trophectoderm biopsy of a blastocyst using high-resolution NGS [8]. This raises the question of whether embryos with a high rate of a mosaicism (>40–80% ratio) should be transferred if they are the only ones available. Despite encouraging studies reporting the delivery of healthy babies after transfer of mosaic embryos identified either by NGS or aCGH methodologies [9,10], an ongoing concern in our clinical practice is whether the currently available platforms yield reproducible results.

* Corresponding author. Division of Infertility, Department of Obstetrics and Gynecology, Taipei Medical University Hospital, No. 252, Wuxing St., Xinyi Dist., Taipei 11031, Taiwan.

** Corresponding author. Division of Infertility, Department of Obstetrics and Gynecology, Taipei Medical University Hospital, No. 252, Wuxing St., Xinyi Dist., Taipei 11031, Taiwan.

E-mail addresses: d102095012@gmail.com (C.-H. Chen), tzengcr@tmu.edu.tw (C.-R. Tzeng).

¹ The first two authors contributed equally to this article.

Herein we report two cases of live births following transfer of high-mosaicism embryos and review the literature, focusing on chromosomal mosaicism and the clinical outcomes of IVF treatment.

Case presentation

The study was approved by the joint Institutional Review Board of Taipei Medical University (TMU-JIRB number: No. 201711084).

Patient one

A 41-year-old woman consulted our infertility center in 2017 during a 5-year period of secondary infertility. She had three children with her former husband. She had a past history of tubal pregnancy, right status post-laparoscopic salpingectomy, and left tubal ligation in 2000. No other specific history was reported. There was no other obvious cause of infertility. Semen analysis of her present husband was normal.

She received the first cycle of controlled ovarian stimulation (COS) using the ultra-long-acting GnRH agonist (leuprolide acetate) protocol. Four mature metaphase-II (M–II) oocytes were aspirated and inseminated by intracytoplasmic sperm injection (ICSI). Three embryos were cultured to the cleavage stage and transferred. However, she did not become pregnant. One month later, she underwent a second COS with an antagonist protocol. PGT-A was suggested because of her previous implantation failure and her age.

Ovarian stimulation was commenced by daily injections of 150 U human menopausal gonadotropin (hMG) (Menopur; Ferring), 150 U follicle-stimulating hormone (FSH) (Gonal-F; Merck Serono) and 4 IU (0.665 mg) of recombinant human growth hormone (rhGH, Saizen; Merck Serono) for 5 days from day 2 of the patient's menstrual cycle (MC2). Follicular monitoring started on MC7 and was performed every 2–3 days using transvaginal ultrasound (TVS) to record the number of developing follicles. Blood concentrations of serum luteinizing hormone (LH), estrogen (E2), and progesterone (P4) were measured on the same days as the TVS. Gonadotropin-releasing hormone antagonist (GnRH antagonist) (Cetrotide; Merck Serono) was administered subcutaneously at 0.125 mg/day from MC7 when the lead follicle reached 14 mm in

diameter and was continued until the day of triggering. Daily injections of 150 U hMG and 150 U FSH (Gonal-F) were added on MC7 and MC8 to promote adequate follicle growth. On MC9, there were at least three dominant follicles with mean diameter ≥ 18 mm and the E2 level was 1717 pg/ml. The final stage of oocyte maturation was triggered using 1 mg leuprolide acetate (Lupro; Nang Kuang) and 6500 IU recombinant human chorionic gonadotropin (hCG) (rhCG, Ovidrel; Merck Serono). TVS-guided oocyte retrieval was performed 36 h after the trigger.

Seven oocytes, including five M–II, one metaphase-I (M–I) and one germinal vesicle (GV) oocytes, were retrieved and inseminated by ICSI. Two embryos were cultured to the blastocyst stage and trophectoderm biopsies for PGT-A were performed. Samples were then tested by a commercial provider of PGT-A using 24-chromosome screening by NGS (VeriSeq PGS with BlueFuse Multi Software; Illumina, Inc.) according to the manufacturer's instructions. The results indicated that one embryo was mosaic (68%) for partial trisomy 1 and the other embryo was aneuploid; no euploid embryos were available (Fig. 1a). After counseling, the patient elected to receive the mosaic embryo. She achieved pregnancy after frozen-thawed embryo transfer (FET) and hormone replacement therapy (HRT). She underwent amniocentesis at 18 weeks of gestation age (GA) which identified no chromosome abnormality and a karyotype of 46, XY (Fig. 1b). The pregnancy was carried to 39 5/7 weeks of GA, and a 2995 g phenotypically normal male baby was delivered.

Patient two

The patient was a 39-year-old woman with a 3-year history of secondary infertility of unexplained etiology. She had regular menstrual cycles with an interval of 28–30 days. Semen analysis of her husband was normal. Her past medical history was unremarkable. Her obstetric history included one spontaneous pregnancy with delivery of a 2818 g female baby in 2014.

She received two cycles of COS, two fresh embryo transfers, and one FET but did not become pregnant. She underwent a third COS with a progestin-primed ovarian stimulation (PPOS) protocol. PGT-A was suggested because of her age and repeated implantation failure.

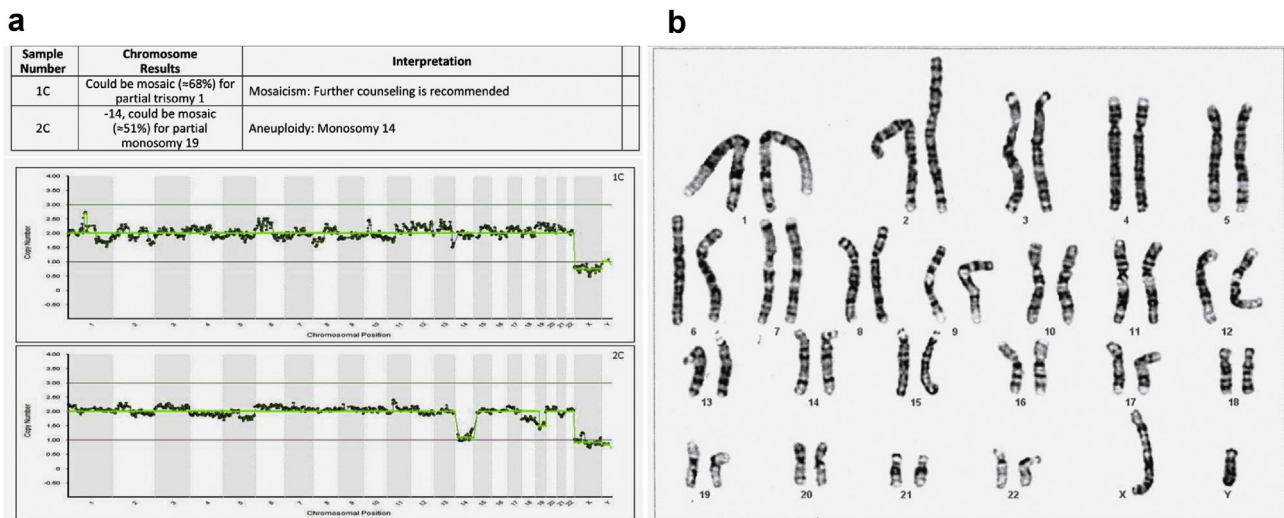
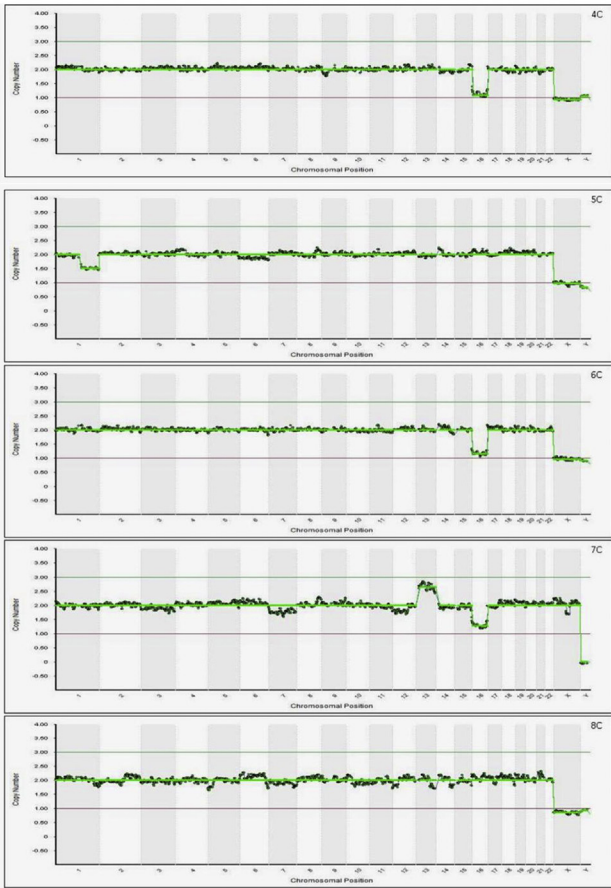
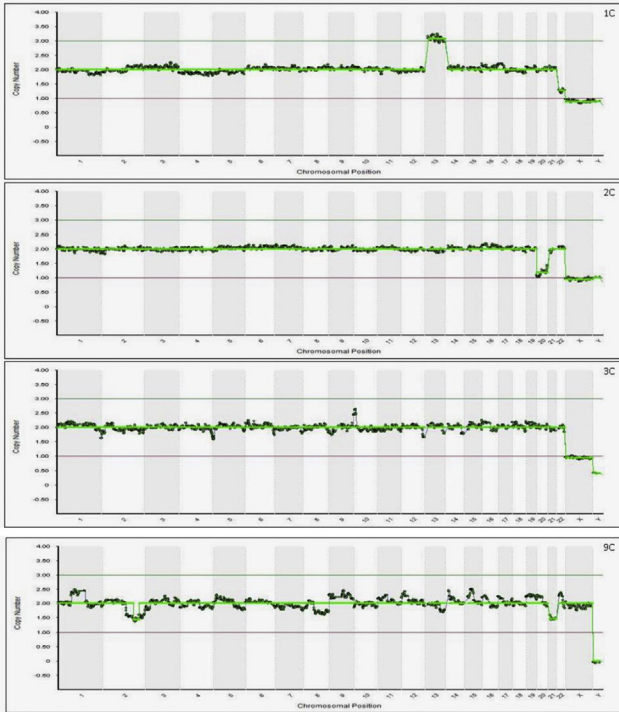


Fig. 1. The results of preimplantation genetic testing for aneuploidy (PGT-A) and amniocentesis for patient one. (a) PGT-A showed that blastocyst 1C could be mosaic (approx. 68%) for partial trisomy 1 and the blastocyst 2C was aneuploid. (b) The amniocentesis demonstrated a normal karyotype of 46, XY.

a

Sample Number	Chromosome Results	Interpretation
1C	+13, could be mosaic (=72%) for monosomy 22	Aneuploidy: Trisomy 13
2C	-20	Aneuploidy: Monosomy 20
3C	Could be mosaic (=59%) for sex chromosome aneuploidy	Mosaicism: Further counseling is recommended
4C	-16	Aneuploidy: Monosomy 16
5C	Could be mosaic (=50%) for partial monosomy 1	Mosaicism: Further counseling is recommended
6C	-16	Aneuploidy: Monosomy 16
7C	Could be mosaic (=65%) for trisomy 13, could be mosaic (=72%) for monosomy 16	Mosaicism: Further counseling is recommended
8C	No gene dosage variation was detected	Euploidy
9C	Could be mosaic (=57%) for partial monosomy 2, could be mosaic (=54%) for monosomy 21	Mosaicism: Further counseling is recommended



b

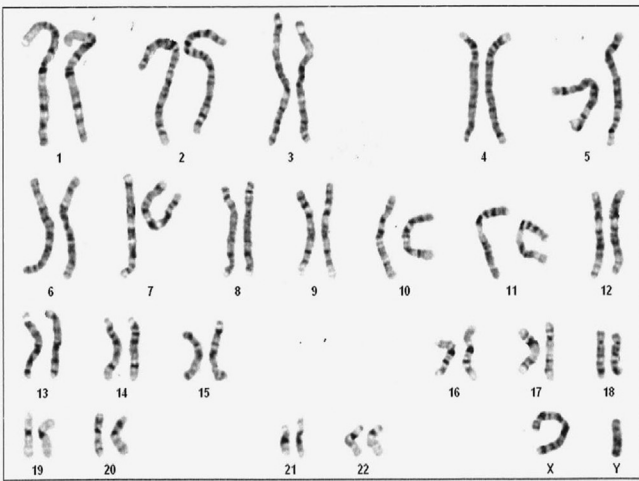
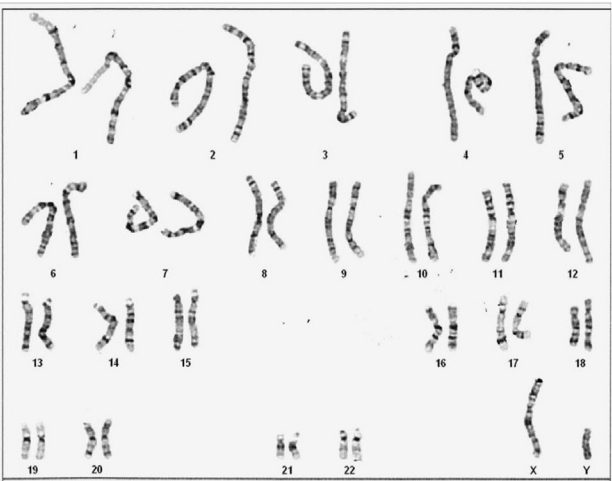


Fig. 2. The results of preimplantation genetic testing for aneuploidy (PGT-A) and amniocentesis for patient two. (a) PGT-A showed that blastocyst 8C was euploid, blastocysts 3C, 5C, 7C, and 9C were mosaic and blastocysts 1C, 2C, 4C, and 5C were aneuploid. Blastocysts 8C and 5C were transferred. (b) The amniocentesis results for both twin A (left panel) and twin B (right panel) demonstrated a normal karyotype of 46, XY.

Ovarian stimulation was commenced by giving two vials of recombinant FSH + recombinant LH (Pergoveris 150 IU/75 IU) and 8 IU (1.33 mg) of rHGH for 1 day, followed by 1 vial of Pergoveris and 6 IU (1 mg) of rHGH for another 2 days starting at MC2. Medroxyprogesterone acetate (10 mg/day) was administered from MC2 onward. Follicular monitoring started on MC5 and was performed every 2–3 days using TVS to record the number of developing follicles. Serum LH, E2, and P4 concentrations were measured on the same days as the TVS. In addition, she received two vials of Pergoveris on MC5 and one vial of Pergoveris on MC6–MC9 to ensure adequate follicle growth. On MC10, the level of E2 was 5046 pg/ml, and there were more than three follicles with mean diameter ≥ 18 mm. The final stage of oocyte maturation was triggered using 0.1 mg triptorelin (Decapeptyl, Ferring) and 1000 IU rhCG. TVS-guided oocyte retrieval was performed 36 h after the trigger.

Twenty-four oocytes including sixteen M–II, one M–I, and seven GV were retrieved and inseminated by ICSI. Nine embryos were cultured to the blastocyst stage and trophectoderm biopsies for PGT-A were performed. The results demonstrated one euploid, four mosaic, and four aneuploid embryos (Fig. 2a). Because of her history of repeated implantation failure, after counseling she elected to receive one euploid and one mosaic (about 50% for partial monosomy 1) embryos. She achieved a twin pregnancy after FET with HRT. She underwent amniocentesis at 18 weeks of GA and both fetuses were karyotyped as 46, XY (Fig. 2b). The pregnancy was carried to 37 2/7 weeks of GA, and two phenotypically normal male babies with body weights of 2176 g and 2642 g were delivered.

Discussion

We report two cases of healthy live births after transfer of high-mosaicism blastocysts ($\geq 50\%$) identified by NGS, which indicates that reproducible results can be obtained in our clinical practice using the currently available platforms. Both patients were classified as advanced maternal age (AMA) and had a history of implantation failure [11–15]. The most likely cause of failure in assisted reproductive technology is embryonic aneuploidy, a major type of chromosome abnormality in which cells contain an abnormal number of chromosomes [16,17]. PGT-A has been utilized to improve clinical pregnancy and live birth rates in IVF patients of AMA [3,18,19] and with repeated implantation failure (RIF) [20–22] because these patients have a high prevalence of aneuploid embryos. In one recent study that included 1389 blastocysts derived from 296 cycles and evaluated by aCGH or PGT-A demonstrated comparable live birth rates in IVF patients of AMA, with RIF or recurrent miscarriage or oocyte donors [23], further supporting the application of PGT-A in patients with an increased risk of aneuploid embryos. Hence, we suggested that our patients utilize PGT-A as a tool to increase their live birth rate.

Mechanisms of embryo mosaicism include chromosome nondisjunction, anaphase lagging, mitotic nondisjunction, inadvertent chromosome destruction, and premature cell division before DNA duplication [7,24–27]. The incidence of embryonic mosaicism is higher in cleavage-stage embryos (15–90%) than in blastocysts (30–40%) [6,7,28–30]. Greco et al. were the first to report healthy live births after transfer of mosaic aneuploid blastocysts identified by means of aCGH [9]. Eighteen women who underwent IVF but had no euploid embryos received a mosaic embryo after counseling. Eight pregnancies, of which six resulted in the birth of a singleton infant at term, were reported [9]. This group published a subsequent report comparing the clinical outcomes of euploid embryos with those of mosaic embryos containing low ($<50\%$) and high ($\geq 50\%$) percentages of aneuploidy [10]. Low-

mosaicism embryos had similar clinical outcomes to euploid embryos with respect to clinical pregnancy, implantation, and live births per embryo, while high-mosaicism embryos had inferior clinical outcomes. The embryos transferred in our two patients were classified as high-mosaicism embryos. Although our study is preliminary, our results support the findings of Greco et al. that transfer of high-mosaicism blastocysts can result in the birth of a healthy infant at term.

The influence of the type of mosaicism on clinical outcomes in IVF treatment has also been investigated. Munne et al. reported pregnancy outcomes after transfer of mosaic embryos identified by NGS [8], and identified a lower ongoing implantation rate (10%) for transfer of complex-mosaic blastocysts (aneuploid, double aneuploid, and segmental mosaic) than other types of mosaic embryos. Moreover, embryos containing $>40\%$ aneuploidy and those with chaotic mosaics (multiple mosaic abnormalities) probably also have lower ongoing implantation rates [8].

When IVF patients have no euploid embryos available for transfer, we follow the suggested guidelines published by the Preimplantation Genetic Diagnosis International Society (PGDIS) newsletter of 2016 [31]. Our first patient had no euploid embryos but had one mosaic embryo (68% for partial trisomy 1). According to the PGDIS guidelines, this mosaic embryo belonged in a favorable transfer category. Our second patient had one euploid embryo and four mosaic embryos but elected to receive two embryos because of her repeated implantation failure. Hence, we selected the mosaic embryo (about 50% mosaic for partial monosomy 1) based on the suggested guidelines that “embryos revealing mosaic euploid/monosomy are preferable to euploid/trisomy, given that monosomic embryos (excepting 45, X) are not viable”. Both our patients produced healthy live babies. Thus, when there is no euploid embryo for transfer in IVF patients who undergo PGT-A, we can prioritize mosaic embryos for transfer based on the guidelines of the 2016 PGDIS newsletter [31].

An increased frequency of aneuploid oocytes and embryos is associated with advancing maternal age [32,33]. In contrast, Nakhuda et al. suggested that the incidence of mosaicism per embryo did not increase with advancing maternal age [34]. Therefore, advancing maternal age may lead to an increased incidence of aneuploid rather than mosaic embryos.

Amniocentesis at 18 weeks gestation revealed that the fetuses in both our patients had a normal karyotype of 46, XY, suggesting that the two mosaic embryos self-corrected before 18 weeks gestation. The potential mechanisms of self-correction of mosaic and aneuploid embryos include superior growth of the euploid cells or favorable allocation of the normal cells to the inner cell mass, postzygotic chromosome gain or chromosome loss, mitotic nondisjunction, and trisomic rescue [7,29,35–38]. However, these mechanisms require further investigation.

In conclusion, our two cases confirm that selected high-mosaicism embryos can produce healthy euploid newborns and that reproducible results can be obtained in clinical practice using currently available technologies. The normal karyotype observed at amniocentesis suggested that mosaic embryos could potentially self-correct before 18 weeks gestation.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgments

This work was supported by the Ministry of Science and Technology, Taiwan, ROC (MOST 106-2314-B-016-004, MOST 107-2314-B-016-065-MY2, and MOST 106-2314-B-075-061-MY3), Tri-Service

General Hospital (TSGH-C106-081, TSGH-C107-082, TSGH-C108-116), and Tri-Service General Hospital, Penghu Branch (TSGH-PH-105-4).

References

- [1] The use of preimplantation genetic testing for aneuploidy (PGT-A): a committee opinion. *Fertil Steril* 2018;109:429–36.
- [2] Niederberger C, Pellicer A, Cohen J, Gardner DK, Palermo GD, O'Neill CL, et al. Forty years of IVF. *Fertil Steril* 2018;110:185–324 e5.
- [3] Rubio C, Bellver J, Rodrigo L, Castillon G, Guillen A, Vidal C, et al. In vitro fertilization with preimplantation genetic diagnosis for aneuploidies in advanced maternal age: a randomized, controlled study. *Fertil Steril* 2017;107:1122–9.
- [4] Orvieto R. Preimplantation genetic screening- the required RCT that has not yet been carried out. *Reprod Biol Endocrinol* 2016;14:35.
- [5] Orvieto R, Gleicher N. Should preimplantation genetic screening (PGS) be implemented to routine IVF practice? *J Assist Reprod Genet* 2016;33:1445–8.
- [6] Munne S, Weier HU, Grifo J, Cohen J. Chromosome mosaicism in human embryos. *Biol Reprod* 1994;51:373–9.
- [7] Taylor TH, Gitlin SA, Patrick JL, Crain JL, Wilson JM, Griffin DK. The origin, mechanisms, incidence and clinical consequences of chromosomal mosaicism in humans. *Hum Reprod Update* 2014;20:571–81.
- [8] Munne S, Blazek J, Large M, Martinez-Ortiz PA, Nisson H, Liu E, et al. Detailed investigation into the cytogenetic constitution and pregnancy outcome of replacing mosaic blastocysts detected with the use of high-resolution next-generation sequencing. *Fertil Steril* 2017;108:62. 71.e8.
- [9] Greco E, Minasi MG, Fiorentino F. Healthy babies after intrauterine transfer of mosaic aneuploid blastocysts. *N Engl J Med* 2015;373:2089–90.
- [10] Spinella F, Fiorentino F, Biricik A, Bono S, Ruberti A, Cotroneo E, et al. Extent of chromosomal mosaicism influences the clinical outcome of in vitro fertilization treatments. *Fertil Steril* 2018;109:77–83.
- [11] Yin H, Jiang H, He R, Wang C, Zhu J, Cao Z. Cumulative live birth rate of advanced-age women more than 40 with or without poor ovarian response. *Taiwan J Obstet Gynecol* 2019;58:201–5.
- [12] Pan M, Huang LY, Zhen L, Li DZ. A cost-effectiveness analysis comparing two different strategies in advanced maternal age: combined first-trimester screening and maternal blood cell-free DNA testing. *Taiwan J Obstet Gynecol* 2018;57:536–40.
- [13] Lin CJ, Chen SW, Chen CP, Lee CC, Town DD, Chen WL, et al. Higher male prevalence of chromosomal mosaicism detected by amniocentesis. *Taiwan J Obstet Gynecol* 2018;57:370–3.
- [14] Zhu C, Wang M, Niu G, Yang J, Wang Z. Obstetric outcomes of twin pregnancies at advanced maternal age: a retrospective study. *Taiwan J Obstet Gynecol* 2018;57:64–7.
- [15] Chang YW, Chen LC, Chen CY, Yeh CC, Cheng LY, Lai YL, et al. Robertsonian translocations: an overview of a 30-year experience in a single tertiary medical center in Taiwan. *J Chin Med Assoc* 2013;76:335–9.
- [16] Santaguida S, Amon A. Short- and long-term effects of chromosome mis-segregation and aneuploidy. *Nat Rev Mol Cell Biol* 2015;16:473–85.
- [17] Rodrigo L, Mateu E, Mercader A, Cobo AC, Peinado V, Milan M, et al. New tools for embryo selection: comprehensive chromosome screening by array comparative genomic hybridization. *BioMed Res Int* 2014;2014:517125.
- [18] Rubio C, Bellver J, Rodrigo L, Bosch E, Mercader A, Vidal C, et al. Preimplantation genetic screening using fluorescence in situ hybridization in patients with repetitive implantation failure and advanced maternal age: two randomized trials. *Fertil Steril* 2013;99:1400–7.
- [19] Schoolcraft WB, Katz-Jaffe MG. Comprehensive chromosome screening of trophectoderm with vitrification facilitates elective single-embryo transfer for infertile women with advanced maternal age. *Fertil Steril* 2013;100:615–9.
- [20] Greco E, Bono S, Ruberti A, Lobascio AM, Greco P, Biricik A, et al. Comparative genomic hybridization selection of blastocysts for repeated implantation failure treatment: a pilot study. *BioMed Res Int* 2014;2014:457913.
- [21] Fragouli E, Katz-Jaffe M, Alfarawati S, Stevens J, Colls P, Goodall NN, et al. Comprehensive chromosome screening of polar bodies and blastocysts from couples experiencing repeated implantation failure. *Fertil Steril* 2010;94:875–87.
- [22] Blockeel C, Schutyser V, De Vos A, Verpoest W, De Vos M, Staessen C, et al. Prospectively randomized controlled trial of PGS in IVF/ICSI patients with poor implantation. *Reprod Biomed Online* 2008;17:848–54.
- [23] Lee CI, Wu CH, Pai YP, Chang YJ, Chen CI, Lee TH, et al. Performance of pre-implantation genetic testing for aneuploidy in IVF cycles for patients with advanced maternal age, repeat implantation failure, and idiopathic recurrent miscarriage. *Taiwan J Obstet Gynecol* 2019;58:239–43.
- [24] Munne S, Velilla E, Colls P, Garcia Bermudez M, Vemuri MC, Steuerwald N, et al. Self-correction of chromosomally abnormal embryos in culture and implications for stem cell production. *Fertil Steril* 2005;84:1328–34.
- [25] Mantzouratou A, Delhanty JD. Aneuploidy in the human cleavage stage embryo. *Cytogenet Genome Res* 2011;133:141–8.
- [26] Mantikou E, Wong KM, Reppling S, Mastenbroek S. Molecular origin of mitotic aneuploidies in preimplantation embryos. *Biochim Biophys Acta* 2012;1822:1921–30.
- [27] Sachdev NM, Maxwell SM, Besser AG, Grifo JA. Diagnosis and clinical management of embryonic mosaicism. *Fertil Steril* 2017;107:6–11.
- [28] Baart EB, Martini E, van den Berg I, Macklon NS, Galjaard RJ, Fauser BC, et al. Preimplantation genetic screening reveals a high incidence of aneuploidy and mosaicism in embryos from young women undergoing IVF. *Hum Reprod* 2006;21:223–33.
- [29] Fragouli E, Lenzi M, Ross R, Katz-Jaffe M, Schoolcraft WB, Wells D. Comprehensive molecular cytogenetic analysis of the human blastocyst stage. *Hum Reprod* 2008;23:2596–608.
- [30] Fragouli E, Alfarawati S, Daphnis DD, Goodall NN, Mania A, Griffiths T, et al. Cytogenetic analysis of human blastocysts with the use of FISH, CGH and aCGH: scientific data and technical evaluation. *Hum Reprod* 2011;26:480–90.
- [31] PGDIS position statement on chromosome mosaicism and preimplantation aneuploidy testing at the blastocyst stage: preimplantation Genetic Diagnosis International Society. 2016 [cited 2019 April 05]. Available from: http://www.pgdis.org/docs/newsletter_071816.html.
- [32] Ata B, Kaplan B, Danzer H, Glassner M, Opsahl M, Tan SL, et al. Array CGH analysis shows that aneuploidy is not related to the number of embryos generated. *Reprod Biomed Online* 2012;24:614–20.
- [33] Franasiak JM, Forman EJ, Hong KH, Werner MD, Upham KM, Treff NR, et al. The nature of aneuploidy with increasing age of the female partner: a review of 15,169 consecutive trophectoderm biopsies evaluated with comprehensive chromosomal screening. *Fertil Steril* 2014;101:656. 663.e1.
- [34] Nakhuda G, Jing C, Butler R, Guimond C, Hitkari J, Taylor E, et al. Frequencies of chromosome-specific mosaics in trophectoderm biopsies detected by next-generation sequencing. *Fertil Steril* 2018;109:857–65.
- [35] Wells D, Delhanty JD. Comprehensive chromosomal analysis of human pre-implantation embryos using whole genome amplification and single cell comparative genomic hybridization. *Mol Hum Reprod* 2000;6:1055–62.
- [36] Barbash-Hazan S, Frumkin T, Malcov M, Yaron Y, Cohen T, Azem F, et al. Preimplantation aneuploid embryos undergo self-correction in correlation with their developmental potential. *Fertil Steril* 2009;92:890–6.
- [37] Bazrgar M, Gourabi H, Valojerdi MR, Yazdi PE, Baharvand H. Self-correction of chromosomal abnormalities in human preimplantation embryos and embryonic stem cells. *Stem Cells Dev* 2013;22:2449–56.
- [38] Fragouli E, Munne S, Wells D. The cytogenetic constitution of human blastocysts: insights from comprehensive chromosome screening strategies. *Hum Reprod Update* 2019;25:15–33.