F&S: 26837R3: Decline and resubmit

RUNNING TITLE: **Cost-effectiveness of PGT-A**

TITLE: Cost-effectiveness of preimplantation genetic testing for aneuploidies

Edgardo SOMIGLIANA, MD-PhD [a,b,*], Andrea BUSNELLI, MD [a], Alessio PAFFONI MSc-PhD [c], Paola VIGANO, MSc-PhD [d] , Alessandra RICCABONI, MD [b], Carmen RUBIO MSc [e], Antonio CAPALBO, MSc [f]

[a] Dept of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy

[b] Obstet-Gynecol Dept, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[c] ART Unit, Azienda Socio Sanitaria Territoriale Lariana, Cantù, Come, Italy

[d] Obstet-Gynecol Dept, San Raffaele Scientific Institute, Milan, Italy

[e] Igenomix, Molecular Genetics Laboratory, Valencia, Spain

[f] Igenomix, Molecular Genetics Laboratory, Marostica, and La Sapienza Università di Roma, Italy.

* To whom correspondence should be addressed

Edgardo SOMIGLIANA

Infertility Unit, Fondazione Ca' Granda, Ospedale Maggiore Policlinico

Phone: +39-02-55034304

Via M. Fanti, 6 - 20122 - Milan - Italy

E-mail: dadosomigliana @yahoo.it

Capsule

The use of preimplantation genetic testing for aneuploidies is highly debated. This theoretical study suggests that the procedure can be economically advantageous when employed in specific settings and patients groups.

Abstract

Objective: To evaluate the economical benefit of preimplantation genetic testing of aneuploidies (PGT-A) when applied in an extended culture and stringent elective Single Embryo Transfer (eSET) framework.

Design: Theoretical cost-effectiveness study

Setting: Center with established expertise in trophectoderm biopsy for preimplantation genetic testing of monogenic disorders.

Patients/Animals: None

Intervention: Comparison of the cost-effectiveness between two IVF treatment strategies: i) serial transfer of all available blastocysts without genetic testing (first fresh transfer and subsequent frozen-thawed transfer) and ii) systematic use of genetic testing (trophectoderm biopsy, freeze all and frozen-thawed transfers of euploid blastocysts). The costs considered for this analysis are based on regional public health system provider.

Main Outcome Measure: Costs per live birth

Results: Cost-effectiveness profile of PGT-A improves with female age and number of available blastocysts. Sensitivity analyses varying the costs of embryo transfer, the costs of genetic analyses, the magnitude of the detrimental impact of PGT-A on live birth rate and the crude live birth rates change to some extent the thresholds for effectiveness but generally confirm the notion that PGT-A can be economically advantageous in some specific subgroups.

Conclusions: PGT-A can be cost-effective in specific clinical settings and population groups. Economical considerations deserve attention in the debate regarding the clinical utility of PGT-A.

Key words: preimplantation genetic testing / elective single embryo transfer / effectiveness / blastocyst

Introduction

Since its first success in 1978, *in vitro* fertilization (IVF) has undergone enormous improvements and subsequent widespread application (1). Some of the most recent achievements in the field include prevention of Ovarian Hyperstimulation Syndrome (OHSS) (2) and the drastic reduction of multiple pregnancy through extensive adoption of elective single embryo transfer (eSET) strategy (3). This latter approach has been facilitated by the implementation of extended embryo culture (up to the blastocyst stage), allowing the selection of embryos with higher reproductive potential.

In a similar way, preimplantation genetic testing of aneuploidies (PGT-A), a methodology that allows comprehensive testing of embryonic cells chromosomal complement, strives to de-select aneuploid embryos and could prove an important step forward for improving the effectiveness of eSET. However, the utility of this technology is currently debated (4-9). On one hand, PGT-A improves embryo selection (10) and is more patient friendly (women have to undergo fewer embryo transfers and face a lower risk of miscarriage) (11). On the other hand, this approach increases the costs of the procedure and could lead to the erroneous discarding of healthy embryos, thus reducing the cumulative chances of live birth per oocytes retrieval. Indeed, although rare, PGT-A can provide false positive results (12) and the biopsy of the trophectoderm cells may impact embryo's viability, hence its implantation potential, particularly if the procedure is not performed properly (13).

Surprisingly, the burning debate on the role of PGT-A has given limited attention to cost-effectiveness considerations (14,15). This is in contrast with the current strong global commitment for equity and sustainability (16). Optimized cost-effectiveness of treatments is a main priority in modern medicine. A relevant point in destabilizing the equilibrium of this debate is the continuous decrease in diagnostic costs since the adoption of Next Generation Sequencing (NGS) platforms for PGT-A. Despite inevitably increasing procedural complexity and IVF costs, PGT-A can still result in higher cost-effectiveness when applied in specific clinical contexts.

Current strategies for the management of infertile women undergoing IVF vary broadly and are influenced by national legislations and regulations, cultural environments, payment modalities (public funded, insurance based or pure private) and local expertise and equipment. As a consequence, performing cost-effectiveness analyses with the purpose of drawing conclusions that could be valid worldwide is unrealistic. For this reason and with the aim of providing an unbiased assessment study on the potential economical benefit of PGT-A, we focused our proof of concept study on a highly specialized clinical setting (a referral Center with established expertise on trophectoderm biopsy and a stringent policy of eSET) and treating a highly selected population (patients retrieving a sufficient number of good quality oocytes to allow the extended culture strategy). Specifically, we compared the cost-effectiveness profile of two strategies: i) serial transfer of all available blastocysts without genetic testing (first fresh transfer and subsequent frozen-thawed transfers) and ii) systematic use of genetic testing (trophectoderm biopsy, freeze all and frozen-thawed transfers of euploid blastocysts). The analyses were performed varying the female age and the number of available blastocysts.

Materials and methods

This study evaluated economical differences a conventional approach without genetic testing and an approach with the systematic use of PGT-A. The two strategies are outlined in Figure 1. The primary aim of the study was to identify thresholds for female age and number of available blastocysts that determines a high cost-effectiveness of PGT-A compared to the conventional approach. The study was based on a theoretical model and was thus exempted from acceptance of Institutional Review Board.

The model applies to women who have viable blastocysts ($n \geq 1$) for transfer in the context of a rigid and systematic policy of eSET policy. In order to generalize the results of the analysis, we considered a scenario where the health provider covered all procedures charges and costs, thus excluding more complex and financially heterogeneous schemes (i.e. insurances). The assumptions made for developing the model are reported in details in Supplemental Table 1. The most relevant ones were the following: 1) PGT-A is associated with a 5% relative reduction in live birth rate due to the theoretical biopsy-related damage to the embryo and to the false positive results that may derive from the inherent technical error of chromosomal diagnostics (12,17-20). In fact, there are no definitive and precise estimates for this rate. Nonetheless, a conservative 5% rate was assumed despite recent evidence demonstrating no major effect of the biopsy on embryo viability (12) and indicating a false positive rate lower than 5% (17;19;20); 2) miscarriage rate following PGT-A is constant at 8% per eSET regardless of female age (21), 3) local technical expertise and trophectoderm biopsy equipment is in place (i.e. an active program for preimplantation genetic testing for monogenic disorders was assumed), 4) although the proportion of pregnant women undergoing first trimester testing for aneuploidy identification (i.e., amniocentesis) may be lower in the PGT-A group, this variable was excluded due to lack of scientific data.

Costs involved in the two alternative models are summarized in Supplemental Table 2. When available, final charges rather than pure costs were included. Specifically, most treatment/procedures costs were retrieved from the local Diagnosis-Related Group (DRG) reimbursements (http://www.e-drg.it/drg24/Codici.htm) whilst costs of the drugs were obtained from the local medical agency (AIFA: Agenzia Italiana del Farmaco, http://www.agenziafarmaco.gov.it). However, the local DRGs for IVF did not include PGT-A. For this reason, specific costs for PGT-A were calculated independently and added to the DRG. They included costs associated to freezing surplus embryos, embryo biopsies and genetic analyses.

Pregnancy supplements were considered independent costs because they were not part of the DRG-related reimbursement for IVF.

The formulae used to calculate the costs of the two strategies were as follows:

Conventional approach

$$TotK_{Conv} = (N._{Blasto} * K_{ET}) + (P_{miscConv} * K_{misc}) + [(P_{miscConv} + LBR_{Conv}) * K_{drugsPreg}] - [If\ N._{Blasto} > 1, (N._{Blasto} / 2) * LBR_{Conv} * K_{ET}]$$

PGT-A approach

$$TotK_{PGTA} = K_{PGTA} + [P_{euploidy} * N._{Blasto} * K_{ET}) + (P_{miscPGTA} * K_{misc}) + [(P_{miscPGTA} + LBR_{PGTA}) * K_{drugsPreg}] - [If\ N._{Blasto} > 1, (P_{euploidy} * N._{Blasto} / 2) * LBR_{PGTA} * K_{ET}]$$

K is used for costs. Specifically: "$TotK_{Conv}$" stands for total costs of the conventional approach / "$TotK_{PGTA}$" stands for total costs of the PGT-A approach / "K_{ET}" stands for costs of fresh or frozen embryo transfer / "K_{PGTA}" stands for costs of the PGT-A (that varies with the number of available blastocysts) / "K_{misc}" stands for costs of miscarriage management / "$K_{drugsPregnant}$" stands for drug costs for supplementation when pregnancy starts. The letter P is used for probability. Specifically: "$P_{miscConv}$" and "$P_{miscPGTA}$" stand for the absolute rates of miscarriage in the conventional and PGT-A approaches, respectively / $P_{euploidy}$ indicates the probability of euploidy. LBR_{Conv} and LBR_{PGTA} are also probabilities as they indicate the Live Birth Rate in the conventional and PGT-A groups, respectively. As shown in the two formulae, there is a subtraction (only for women with > 1 blastocyst) because we assumed that, in women achieving pregnancy, only half of the blastocysts had to be transferred.

The chances of pregnancy and live birth were obtained from the ART Italian Register (http://old.iss.it/rpma). Since data was not presented per year but per age group, a linear regression

was performed to calculate the live birth and miscarriage rates for every single age category. Specifically, the following regression curves were used for these calculations:

Cumulative Live birth rate per retrieval: $Y = (- 0.022 * X) + 1.036$ (X is age)

Miscarriage rate: $Y = (0.024 * X) – 0.584$ (X is age)

Similarly, to obtain homogeneous data on the risk of aneuploidy, we used a database of PGT-A results including >10,000 cases kindly provided by Igenomix and performed a regression curve to produce standardized rates. The regression curve was as follows:

Euploide rate: $Y = (-0.057 * X) + 2.669$ (X is age)

The clinical pregnancy rates, live birth rates, miscarriage rates and aneuploidy rates estimated using these calculations are shown in Supplemental Table 3.

The data are presented as cost-effectiveness ratios between the cost per live birth for the PGT-A strategy and the cost per live birth for the conventional approach. Ratios > 1 indicate that PGT-A is more cost-effective while ratios < 1 indicate that the conventional approach is more cost-effective.

Primary sensitivity analyses were done for age and number of available blastocysts. Specifically, age was moved over an 11 points axis, starting with the group of women aged ≤34 years of age and then providing point estimates for every year up to age 44. Precise year estimates for women under 35 were not provided because the chances of pregnancy, miscarriage and aneuploidy do not vary significantly across this population. Moreover, the model was discontinued after age 44 because pregnancies ≥45 years are exceptional events. The maximum number of blastocysts was 4 because trends were clear. The inclusion of analyses for younger women and cases with ≥ 5 blastocysts would not have brought additional meaningful insights, though complicating the presentation of the results. Additional sensitivity analyses were performed by halving the costs of the embryo transfer procedures (from € 2194 to € 1097), increasing the detrimental impact of the PGT-A on the live birth rate (from 5% to 10-15%), modifying the costs of PGT-A (from +25% to -25%) and varying the live birth rates (applying a relative increase and decrease of 25%). The decision of applying a

higher variability for the charges of the embryo transfer procedure (-50%) was based on a recent local debate on the magnitude of the DRG-related reimbursement (some stakeholders estimate € 2,194 to excessive). Drug costs were not included since they are expected to be similar for the two strategies.

Calculations were performed using Microsoft Excel. For readers interested in replicating the analyses by adapting individual costs to their contexts, this file is available as an additional material (appendix) for those interested in replicating the analyses in different contexts by adapting the items of costs. In addition to the results presented in the paper, the file includes analyses up to 6 blastocysts and the raw costs saved per newborn.

Results

Cost-effectiveness ratios between the two strategies calculated per age and number of available blastocysts are shown in Figure 2 (*upper panel*). In general, the PGT-A strategy becomes more cost-effective with an increase of age. Specifically, it is superior to the conventional approach for women aged ≥36 years and for those aged 35 with at least three blastocysts. Taking into account the aforementioned ongoing discussion among stakeholders surrounding the magnitude of the local reimbursement for the fresh or frozen embryo transfer procedures, we also performed sensitivity analysis considering half of the currently reimbursed cost (e.g. reducing it from € 2,194 and € 1,097 (Figure 2, *lower panel*). In this scenario, the threshold ages favoring the PGT-A strategy are 42, 40, 39 and 38 years for one, two, three and four blastocysts, respectively.

Sensitivity analyses modulating the detrimental impact of PGT-A on live birth rate, the costs of genetic analyses and the live birth rate are presented in Table 1. Data is presented separately for the two main scenarios of embryo transfer costs (€ 2,194 and € 1,097, respectively).

Discussion

In this study, we showed that, in a referral center for preimplantation detection of monogenic diseases performing extended embryo culture and eSET, the PGT-A approach could be cost-effective. In our specific economical setting, the procedure is actually not advantageous up to at least age 35-36. Afterwards, PGT-A overcomes the conventional approach at different age thresholds depending on the number of available blastocysts. When halving the costs of embryo transfer (as this might better reflects general worldwide contexts), the PGT-A remains financially advantageous, although it becomes more cost-effective at older ages (38-42 years according to the number of available blastocysts). Moreover, the sensitivity analyses showed that the model is minimally influenced by the live birth rates and by the magnitude of the theoretical detrimental impact of the PGT-A strategy on the cumulative chances of pregnancy. Conversely, the costs of the PGT-A may be more relevant. More prominent differences emerged when varying these costs from +25% to -25%. The context of a 25% reduction of PGT-A costs deserves attention considering that analytical costs may continue to reduce in the near future.

Hot topics fuelling current debate on PGT-A include additional costs of the genetic analyses, possible biopsy-related injury to the blastocysts, potential psychological benefits of preventing miscarriages, possible increased iatrogenic rate of aneuploidy due to an excessive ovarian hyper-stimulation, effects of blastocysts versus cleavage stage transfers and inherent biological errors in chromosomal diagnosis (4-9). In this study, we aimed to provide an evaluation from a different viewpoint that has been often disregarded: the evaluation of PGT-A from a mere cost-effectiveness perspective. With this purpose, we focused on a particular setting and we tried to take balanced assumptions that could be acceptable for both those in favor and against the use of PGT-A. For the most debated arguments, we decided to favor the conventional approach for precautionary reasons as prudence is always preferred when discussing the possible adoption of a new expensive approach

in clinical practice. For instance, we have included in the calculations an overall reduction in live birth rates due to possible biopsy-associated embryonic damage or the incomplete accuracy of the genetic analysis (5% in the baseline scenario, increased to 10-15% in the sensitivity analyses). However, we did not consider the potential beneficial effects of PGT-A on the drop-out rates and we assumed that the frequency of prenatal genetic investigations would be similar in the two groups.

The two previously published economical studies on PGT-A reported contrasting results. Indeed, Collins *et al*. focused on women older than 37 years and concluded that the PGT-A strategy could be more cost-effective (14). However, this study did not focus on eSET and did not take into consideration the potential additional benefits of transferring supernumerary frozen blastocysts, thus providing only a partial evaluation of the two approaches. Moreover, no attempts to identify effectiveness thresholds for age and number of blastocysts were made. Scriven investigated the cost-effectiveness profile of PGT-A using a complex and intricate model and failed to show any benefit (15). However, the virtual population tested was young (median age of 33, range 22-39) and no strata analyses were performed. This is a crucial point because, as shown in our model, the age of the women is fundamental and the negative conclusions emerging from this study cannot be inferred to the whole population of women undergoing IVF.

Some limitations of our study should be recognized. Firstly, the study is based on a theoretical model rather than on a RCT. On the other hand, it has to be considered that an exceptionally large and possibly unachievable RCT would be required to provide a reliable answer to the specific query of our study (e.g. from which thresholds of age and number of blastocysts a strategy of PGT-A becomes more cost-effective). In fact, some of the assumptions listed in Supplemental Table 1 lack robust scientific support and may be questioned (in particular points N. 2, 3, 5, 12, 13, 14 and 15). Some of these uncertainties were addressed with the sensitivity analyses (N. 2 and 3). Notably, although the statement that the number of available blastocysts does not influence the chance of

success (point N. 3) is obviously debatable, the sensitivity analysis highlighted the limited relevance of this approximation: the model was not influenced by modifying the chances of pregnancy (Table 1). Other assumptions were also estimated (as available evidence is yet insufficient) but were generally conservative. They included a similar rate of obstetrics complications (point N. 12) across strategy groups, a similar attendance to first trimester screenings (point N. 13), the irrelevance of miscarriage on quality of life (point N. 14) and a similar rate of drop-out (point N. 15). All these assumptions were actually expected to partly favor the conventional approach, thus protecting our conclusions from criticism.

Secondly, we started from a very specific scenario. The specific thresholds for cost-effectiveness emerging from our study may actually be valid only for a situation similar to the one described (e.g. high biopsy competence, extended embryo culture and extensive eSET application). Inferences to other settings could not be extrapolated and thresholds should be recalculated based on local conditions. Moreover, one could argue against the policy of stringent and systematic eSET regardless of age. The scenario can indeed significantly change if more than one blastocyst is transferred. Specific cost-effectiveness analyses (including the additional costs of twin pregnancies) would be required to address this issue. These analyses are however beyond the scope of the present study which strictly adheres to the modern plea for a drastic prevention of multiple pregnancies. Finally, we did not include time to pregnancy analyses in our model. Such analysis may ultimately favor PGT-A, in particular for older women with several blastocysts. Indeed, PGT-A could be expected to reduce the rate of patients' drop-out since the burden of treatment is lowered (less transfers to perform) and may shorten time to pregnancy. This issue was not addressed because reliable real-life data on the impact of PGT-A on the rate of drop-out is not available.

Thirdly, the use of the local health provider perspective partly limits the generalization of our findings. Of relevance here is the elevated reimbursement associated to the embryo transfer procedure (€ 2,194 for either fresh and frozen embryo transfer), a decision that was presumably

taken by stakeholders to indirectly favor eSET in order to shrink multiple pregnancies (no specific legislation on the number of embryos to be transferred exists in Italy). It should be noted that our analyses were mainly based on charges rather than pure costs. We evaluated pure costs only for the few items that are not currently considered by the local health provider. To prevent criticisms on the generalization of our findings, we thus decided to perform a primary sensitivity analysis that halved the charges for embryo transfer. Moreover, we performed other secondary sensitivity analyses varying the most relevant items. All these analyses generally support the conclusion that PGT-A could be cost-effective in the different scenarios. Nonetheless, we believe that evaluations using local data should be performed to recommend stringent thresholds for the use of PGT-A in clinical practice. To facilitate this objective, we have included in the supplementary material the Excel matrix used to elaborate the cost-effectiveness model for the present study (see Appendix in the Supplementary material). This template can assist the readers in developing their own cost-effectiveness models based on internal data and specific costs and socio-economical settings. Finally, it is interesting to note that the model is not sensitive to patient's prognosis: varying live birth rates from -25% to +25% did not show any impact on the analysis outcome. As a consequence, one may infer that cost-effectiveness of PGT-A may not be influenced by specific diagnostic or prognostic subgroups.

In conclusion, cost-effectiveness analyses deserve utmost consideration in the debate on the clinical utility of PGT-A. Our study shows that the PGT-A can be cost-effective after age 35 in referral centers with expertise in trophectoderm biopsy and that follow a policy of extended embryo culture and stringent eSET. However, we could not infer universal thresholds of age and number of blastocysts for recommending PGT-A as these thresholds can vary depending on local clinical settings. Recommendations should be established based on local conditions of expertise, costs and reimbursements programs.

Acknowledgements

None

References

1. Cohen J, Trounson A, Dawson K, Jones H, Hazekamp J, Nygren KG, Hamberger L. The early days of IVF outside the UK. Hum Reprod Update 2005;11:439-59.

2. Nelson SM. Prevention and management of ovarian hyperstimulation syndrome. Thromb Res 2017;151 Suppl 1:S61-S64.

3. Practice Committee of Society for Assisted Reproductive Technology; Practice Committee of American Society for Reproductive Medicine. Elective single-embryo transfer. Fertil Steril 2012;97:835-42.

4. Mastenbroek S, Repping S. Preimplantation genetic screening: back to the future. Hum Reprod 2014;29:1846-50.

5. Gleicher N, Orvieto R. Is the hypothesis of preimplantation genetic screening (PGS) still supportable? A review. J Ovarian Res 2017;10:21.

6. Kaser D. The Status of Genetic Screening in Recurrent Pregnancy Loss. Obstet Gynecol Clin North Am 2018;45:143-54.

7. Morin SJ, Kaser DJ, Franasiak JM. The dilemma of aneuploidy screening on low responders. Curr Opin Obstet Gynecol 2018;30:179-84.

8. Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology. The use of preimplantation genetic testing for aneuploidy (PGT-A): a committee opinion. Fertil Steril 2018;109:429-36.

9. Sullivan-Pyke C, Dokras A. Preimplantation Genetic Screening and Preimplantation Genetic Diagnosis. Obstet Gynecol Clin North Am 2018;45:113-25.

10. Dahdouh EM, Balayla J, García-Velasco JA. Comprehensive chromosome screening improves embryo selection: a meta-analysis. Fertil Steril 2015;104:1503-12.

11. Rubio C, Bellver J, Rodrigo L, Castillón G, Guillén 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.

12. Scott RT Jr, Upham KM, Forman EJ, Zhao T, Treff NR. Cleavage-stage biopsy significantly impairs human embryonic implantation potential while blastocyst biopsy does not: a randomized and paired clinical trial. Fertil Steril 2013;100:624-30.

13. Neal SA, Franasiak JM, Forman EJ, Werner MD, Morin SJ, Tao X, et al. High relative deoxyribonucleic acid content of trophectoderm biopsy adversely affects pregnancy outcomes. Fertil Steril 2017;107:731-6.e1.

14. Collins SC, Xu X, Mak W. Cost-effectiveness of preimplantation genetic screening for women older than 37 undergoing in vitro fertilization. J Assist Reprod Genet 2017;34:1515-22.

15. Scriven PN. Towards a better understanding of preimplantation genetic screening for aneuploidy: insights from a virtual trial for women under the age of 40 when transferring embryos one at a time. Reprod Biol Endocrinol 2017;15:49.

16. GBD 2015 SDG Collaborators. Measuring the health-related Sustainable Development Goals in 188 countries: a baseline analysis from the Global Burden of Disease Study 2015. Lancet 20168;388:1813-50.

17. Capalbo A, Treff NR, Cimadomo D, Tao X, Upham K, Ubaldi FM, et al. Comparison of array comparative genomic hybridization and quantitative real-time PCR-based aneuploidy screening of blastocyst biopsies. Eur J Hum Genet 2015;23:901-6.

18. Werner MD, Hong KH, Franasiak JM, Forman EJ, Reda CV, Molinaro TA, et al. Sequential versus Monophasic Media Impact Trial (SuMMIT): a paired randomized controlled trial comparing a sequential media system to a monophasic medium. Fertil Steril 2016;105:1215-21.

19. Scott RT Jr, Ferry K, Su J, Tao X, Scott K, Treff NR. Comprehensive chromosome screening is highly predictive of the reproductive potential of human embryos: a prospective, blinded, nonselection study. Fertil Steril. 2012;97:870-5.

20. Werner, M.D. J.M. Franasiak, K.H. Hong, C.R. Juneau, X. Tao, J. Landis, K.M. Upham, N.R. Treff, R.T. Scott. A prospective, blinded, non-selection study to determine the predictive value of ploidy results using a novel method of targeted amplification based Next generation sequencing (NGS) for comprehensive chromosome screening (CCS). Fertil Steril. 2015;104: e12-e13

21. Chen M, Wei S, Hu J, Quan S. Can Comprehensive Chromosome Screening Technology Improve IVF/ICSI Outcomes? A Meta-Analysis. PLoS One 2015;10:e0140779.

22. Annual report of the Society for Assisted Reproductive Techniques (SART), 2016. https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?reportingYear=2015 Assessed on December 10th, 2018.

23. Cobo A, de los Santos MJ, Castellò D, Gámiz P, Campos P, Remohí J. Outcomes of vitrified early cleavage-stage and blastocyst-stage embryos in a cryopreservation program: evaluation of 3,150 warming cycles. Fertil Steril 2012;98:1138-46.e1.

24. Zhang J, Gilles JM, Barnhart K, Creinin MD, Westhoff C, Frederick MM; National Institute of Child Health Human Development (NICHD) Management of Early Pregnancy Failure Trial. A comparison of medical management with misoprostol and surgical management for early pregnancy failure. N Engl J Med 2005;353:761-9.

25. Mizrachi Y, Dekalo A, Gluck O, Miremberg H, Dafna L, Feldstein O, et al. Single versus repeat doses of misoprostol for treatment of early pregnancy loss-a randomized clinical trial. Hum Reprod 2017;32:1202-07.

Figure legend

Figure 1: Strategies for the clinical management of women with viable blastocysts. The conventional approach (serial transfer of all the available blastocysts) is shown in the left side. The approach with systematic preimplantation genetic testing for aneuploidie (PGT-A) is shown in the right side. In PGT-A strategy, fresh embryo transfer is never performed and the total number of transfers is lower (aneuploid blastocysts are discarded).

Figure 2: Costs ratios between PGT-A and conventional approaches according to age and number of available blastocysts. Ratios > 1 indicate that PGT-A is more cost-effective while ratios < 1 indicate that the conventional approach is more cost-effective. The original model is shown in the upper panel. The lower panel shows results when a 50% reduction in the cost of the embryo transfer procedure was applied.