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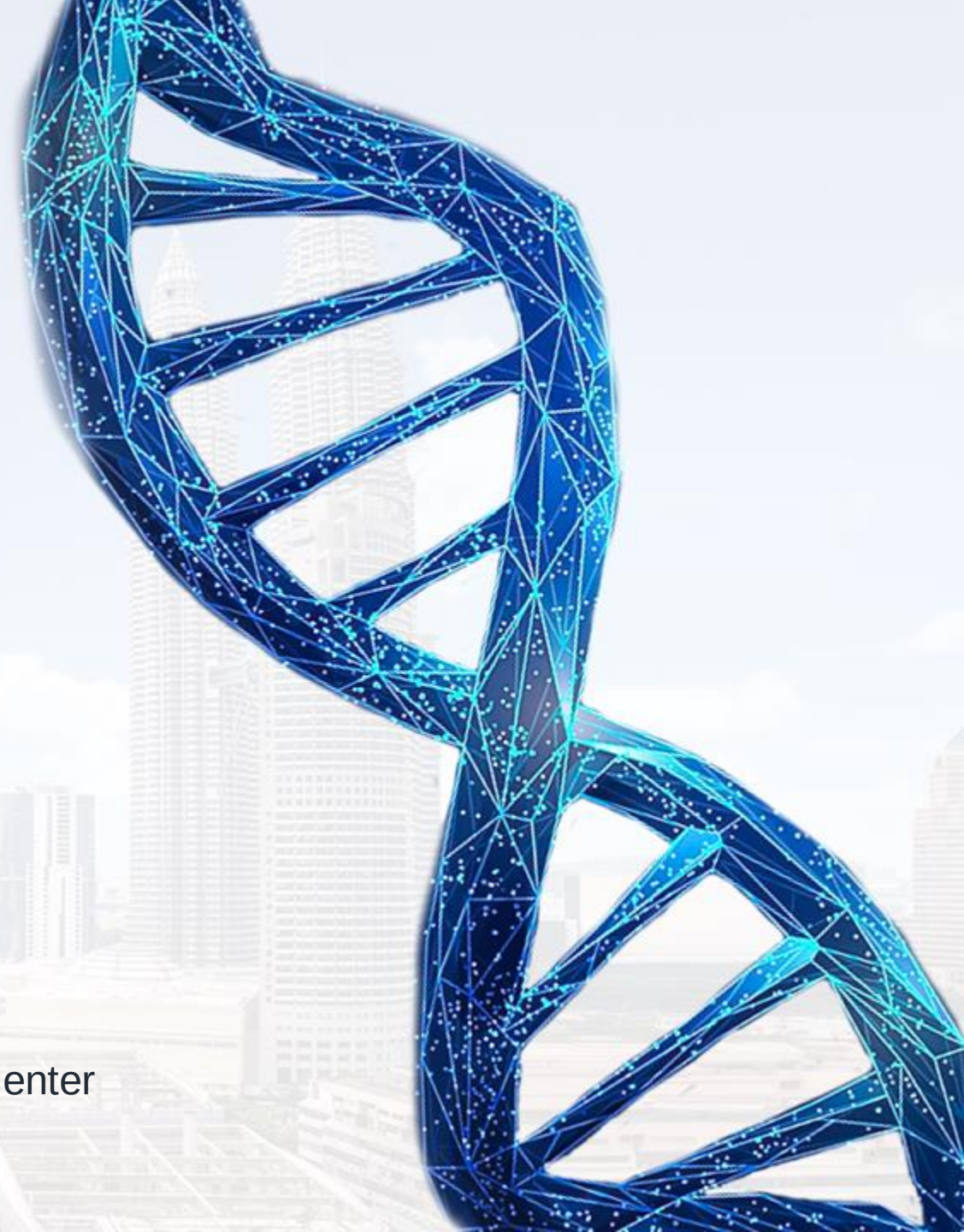
PGT and BEYOND...

Only one embryo: should it be tested?



Semra Kahraman M.D.
Istanbul Memorial Hospital, ART and Reproductive Genetics Center

REVIEW

The dilemma of aneuploidy screening on low responders

Scott J. Morin[a,b], Daniel J. Kaser[a,b], and Jason M. Franasiak[a,b]

Purpose of review
Preimplantation genetic testing for aneuploidy (PGT-A) has been demonstrated to improve implantation and pregnancy rates and decrease miscarriage rates over standard morphology-based embryo selection. However, there are limited data on its efficacy in patients with diminished ovarian reserve or a poor response to stimulation who may have fewer embryos to select amongst.

Recent findings
Early findings demonstrate that PGT-A reduces the miscarriage rate and decreases the time to delivery in

Diminished ovarian reserve is associated with reduced euploid rates via preimplantation genetic testing for aneuploidy independently from age: evidence for concomitant reduction in oocyte quality with quantity

Eleni Greenwood Jaswa, M.D., M.Sc.,[a] Charles E. McCulloch, Ph.D.,[b] Rhodel Simbulan, M.S.,[a] Marcelle I. Cedars, M.D.,[a] and Mitchell P. Rosen, M.D., H.C.L.D.[a]

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Objective(s): To determine whether women with diminished ovarian reserve (DOR) (quantitatively) had lower rates of euploid blastocysts, as a proxy for oocyte quality.
Design: Retrospective cohort study.
Setting: University reproductive health clinic.
Patient(s): A total of 1,152 women aged 19–42 years underwent 1,675 IVF cycles yielding 8,073 blastocysts for biopsy from 2010 to 2019.
Interventions(s): Preimplantation genetic testing for aneuploidy.
Main Outcome Measure(s): Euploid rates, defined as the number of euploid blastocysts divided by the number of biopsied blastocysts per cycle.
Result(s): A total of 225 women (20%) had DOR as infertility diagnosis per the Bologna criteria. Age was higher among the women with DOR (39.5 y vs. 37.0 y). Euploid rates were lower among women with vs. without DOR (29.0% vs. 44.9%). In generalized linear models controlling for age, women with DOR had 24% reduced odds of a biopsied blastocyst being euploid versus women without DOR. In a secondary analysis assigning DOR status to women producing the lowest quartile of age-adjusted mature oocyte yield, this relationship remained. No differences were identified in live birth rates between women with and without DOR after euploid single-embryo transfer independently from age (n = 944 transfers; 56.8% vs. 54.8%, respectively).
Conclusion(s): Blastocysts from women with DOR are less likely to be euploid than those from women without DOR after adjustment for age. Given the concomitant reduction in euploid rates with quantity of oocytes observed in this study, quantitative ovarian reserve assessments (i.e., follicular machinery) may yield insight into relative ovarian aging. (Fertil Steril® 2021;115:966–73. ©2020 by American Society for Reproductive Medicine.)

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ASSISTED REPRODUCTION TECHNOLOGIES

Preimplantation genetic testing for aneuploidy in poor ovarian responders with four or fewer oocytes retrieved

Jie Deng[1] · Helena Y. Hong[2] · Qianying Zhao[1] · Ashni Nadgauda[3] · Sogol Ashrafian[4] · Barry Behr[1] · Ruth B. Lathi[1]

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Abstract
Purpose To assess whether preimplantation genetic testing for aneuploidies (PGT-A) at the blastocyst stage improves clinical outcomes compared with transfer of embryos without PGT-A in poor ovarian response (POR) patients.
Methods Retrospective cohort study of IVF cycles from 2016 to 2019 at a single academic fertility center. IVF cycles with POR and four or fewer oocytes retrieved were stratified into PGT-A (*n* = 241) and non-PGT (*n* = 112) groups. In PGT-A cycles, trophectoderm biopsy, next generation sequencing with 24 chromosome screening, and single euploid frozen embryo transfer were perfo
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A diagnosis of diminished ovarian reserve does not impact embryo aneuploidy or live birth rates compared to patients with normal ovarian reserve

Yuval Fouks, M.D.,[a,b] Alan Penzias, M.D.,[a,c,d] Werner Neuhausser, M.D., Ph.D.,[c] Denis Vaughan, M.D.,[a,c,d] and Denny Sakkas, Ph.D.[a]

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Objective: To estimate the aneuploidy rates in young women with diminished ovarian reserve (DOR) before treatment and poor ovarian response (POR) postretrieval.
Design: Retrospective cohort study.
Setting: A single academically-affiliated fertility clinic.
Patient(s): Autologous frozen embryo transfer cycles from December 2014 to June 2020 were reviewed. Demographic and clinical factors that impact outcomes were used for propensity score matching (PSM) in a ratio of 2:1 and 4:1 for preimplantation genetic testing for aneuploidy pre-cycle DOR and POR after stimulation, respectively.
Intervention(s): None.
Main Outcome Measure(s): Aneuploid rates, defined as the number of aneuploid blastocysts divided by the number of biopsied blastocysts per cycle. No euploid embryos to transfer, defined as all cohorts of embryos being aneuploid.
Result(s): A total of 383 women diagnosed with DOR were compared with matched controls. Aneuploid rates did not differ significantly between the two groups (42.2% vs. 41.7%; RR = 1.06; 95% CI, 0.95–1.06). No differences were identified in live birth rates per transfer between women with and without DOR after euploid single-embryo transfers (56.0% and 60.5%, respectively). An additional PSM analysis to assess aneuploidy rates for patients with POR (<5 oocytes) vs. those without it, resulted in similar rates of aneuploidy between the two comparison groups (41.1% vs. 44%, R = 1.02; 95% CI, 0.91–1.14). The prevalence of cycles with "no euploid embryos" in the POR cohort was higher (26% vs. 13%); however, rates of cases with a single embryo available for biopsy were lower in the DOR group, relative to controls (11% vs. 31%).
Conclusion(s): Young women diagnosed with DOR or POR exhibited equivalent aneuploidy rates and live birth rates per euploid embryo transfer in a large matched population, based on age, body mass index, and IVF cycle initiation. The lower percentage of cycles with no euploid embryo available for transfer in DOR and POR patients is because of the decreased total number of oocytes/developing embryos and not because of increased aneuploidy rates in these groups. (Fertil Steril® 2022;118:504–12. ©2022 by American Society for Reproductive Medicine.)

AIMS

- To gather data which might lead to more informed choices of treatment: PGT-A or non-PGT-A in cases with low ovarian reserve
- To discuss the conundrum faced by clinicians in managing patients with limited embryo availability
- To establish how best to advise patients with low ovarian reserve

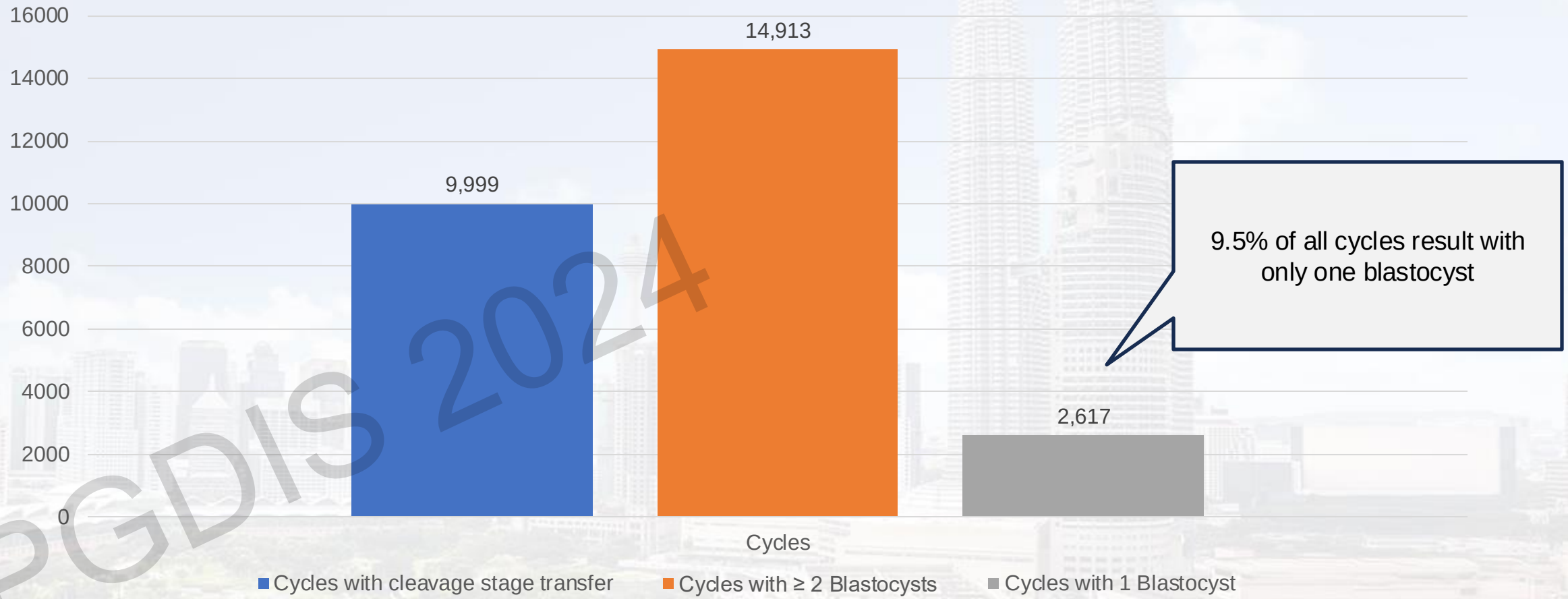
Retrospective analysis of 2653 ART cases…

- PGT group was considered vulnerable since many had experienced recurrent miscarriages or a history of recurrent implantation failure
- After non-directive counselling, patients decided to either transfer the embryo without any intervention or to utilize biopsy and comprehensive chromosome screening
- All of these patients had diminished ovarian reserve, hence the low blastocyst recovery rate.
- Just over half (57%) of these patients elected to proceed with embryo screening

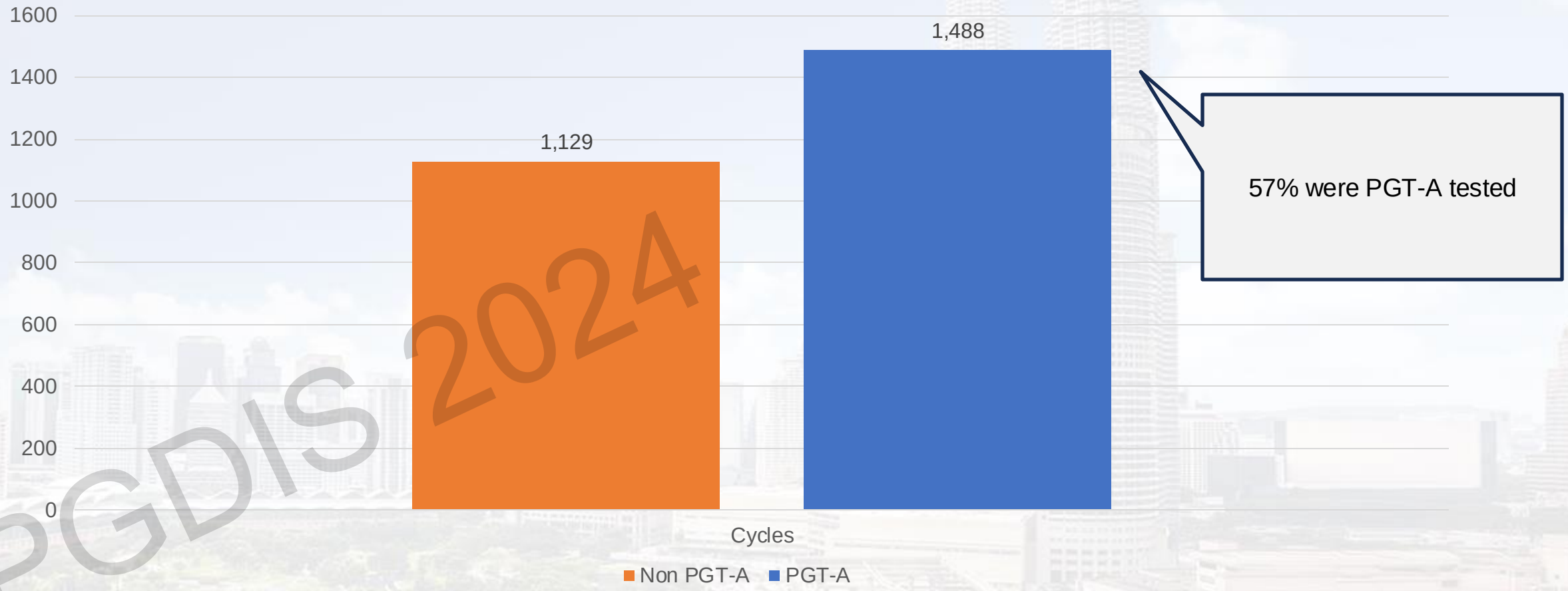
Study Design

- ✓ Retrospective study
- ✓ Istanbul Memorial Hospital, ART and Reproductive Genetics Center, 27,529 OPU cycles from August 2011 to March 2024
- ✓ Single, transferable, good or top-quality blastocysts in women between 20 and 44 years of age
- ✓ 2617 ART cycles (1488 PGT-A cycles and 1129 non-PGT-A cycles)
- ✓ aCGH in 21.7% of the cases between 2011-2016 and NGS in 78.3% between 2017-2024
- ✓ **Exclusion criteria**; PGT-SR and PGT-M cycles, endometrial factor, uterine factor adenomyozis, Mullerian anomalies

27,529 OPU Cycles



2617 cycles with one blastocyst



Cycle Characteristics

	Single blastocyst with PGT-A (1488)	Single blastocyst without PGT-A (1129)	p
Age	**39.57 ± 3.92**	35.6 ± 5.15	**p< 0.0001***
AMH	**0.99 ± 1.14**	1.25 ± 1.63	**p< 0.0001***
COC	**3.84 ± 3.27**	5.30 ± 4.48	**p< 0.0001***
MII	**3.18 ± 2.58**	4.29 ± 3.42	**p< 0.0001***
2PN	**2.39 ± 1.82**	3.23 ± 2.46	**p< 0.0001***
Maturation rate	82.8 %	80.9 %	p = 0.19 **
Fertilization rate	75.1 %	75.3 %	p = 0.13 * *

PGT-A group

- More advanced maternal age patients
  - Lower AMH
  - Lower number of
    - COC
    - MII
    - 2PN obtained

* Mann-Whitney U Test
**Chi-Square test

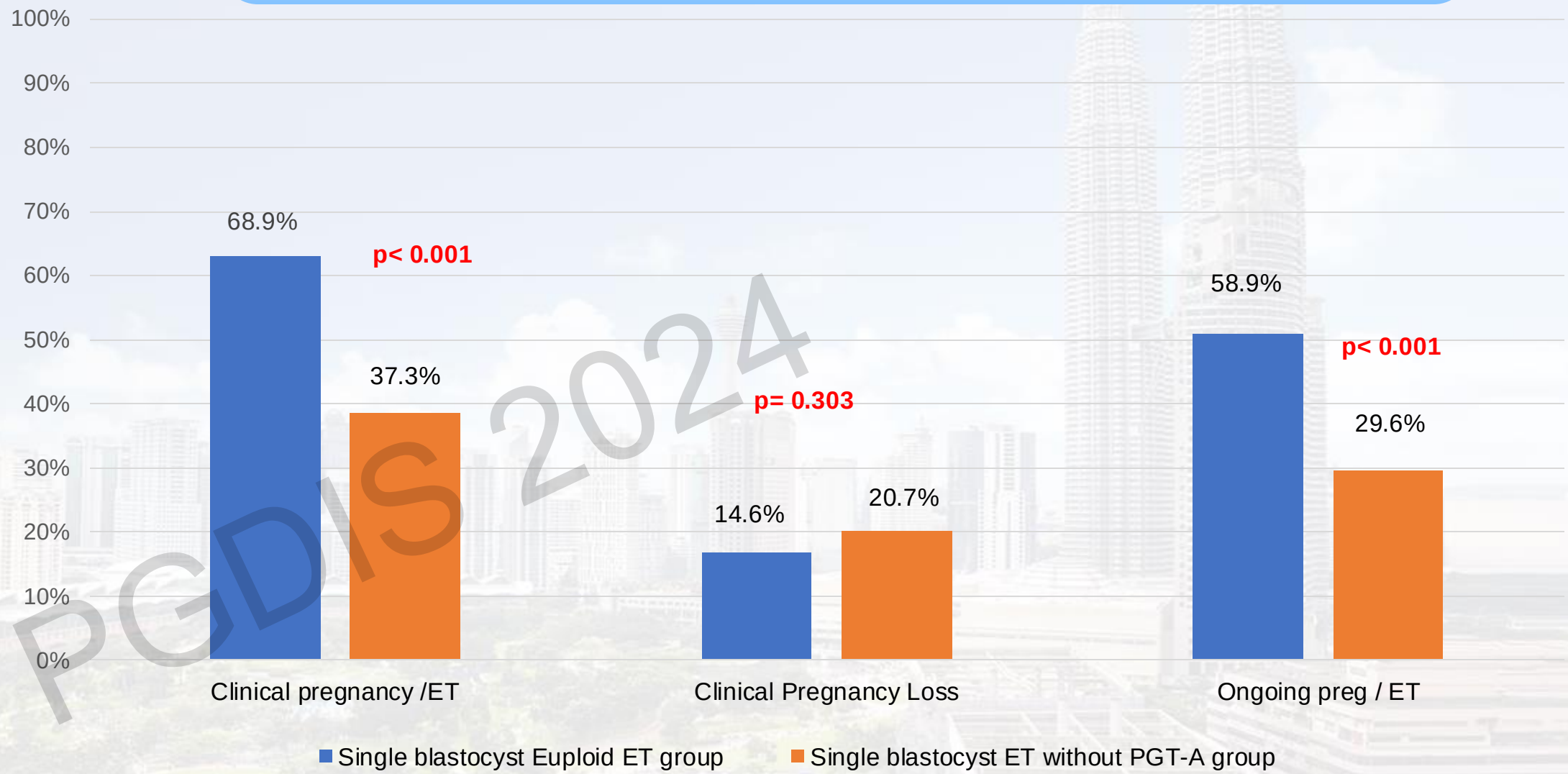
PGT-A euploid transfer vs no PGT-A

	PGT-A	Non-PGT-A	p
	Euploid	**Fresh ET+FET**	
OPU Cycles	289	1129	
Transfer cycles	248	1052	
Biochemical Pregnancy	76.2%	44.6%	<0.0001
Biochemical Miscarriage	9.5%	16.3%	0.0249
Clinical Pregnancy	68.9%	37.3%	<0.0001
Clinical Miscarriage	14.6%	20.7%	0.0895
Ongoing Pregnancy	58.9%	29.6%	<0.0001
Total Pregnancy Loss	22.7%	33.7%	0.0059

PGT-A vs fresh transfers

	Frozen Embryo Transfer following PGT-A	No PGT-A	p
	Euploid	Fresh ET	
OPU Cycles	289	901	
Transfer cycles	248	901	
Biochemical Pregnancy	76.2%	43.8%	<0.0001
Biochemical Miscarriage	9.5%	17.1%	0.0152
Clinical Pregnancy	68.9%	36.2%	<0.0001
Clinical Miscarriage	14.6%	20.3%	0.1202
Ongoing Pregnancy	58.9%	28.9%	<0.0001
Total Pregnancy Losses	22.7%	34.1%	0.0057

pregnancy outcomes for patients with a single blastocyst



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ASSISTED REPRODUCTION TECHNOLOGIES

What to advise to patients with only one good quality blastocyst, PGT-A or not? Outcomes of 2064 cycles

Semra Kahraman[1] · Ipek Nur Balin Duzguner[1] · Yucel Sahin[1] · Tulay Irez[2]

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Abstract

Purpose To evaluate whether preimplantation genetic testing for aneuploidy (PGT-A) is beneficial for patients who have only one blastocyst available for biopsy or transfer.

Methods This retrospective study was based on 1126 single blastocyst PGT-A and 938 non-PGT-A cycles, a total of 2064 ART cycles which resulted in a single good quality blastocyst in women between 20 and 45 years old. The PGT-A group had 225 single euploid embryo transfer cycles and the non-PGT-A group had 938 single blastocyst embryo transfer cycles.

Results In the generalized linear mixed model (GLMM), female age and PGT-A variables were found to be significant variables on pregnancy outcomes. In the PGT-A cases, regardless of the effect of other variables, the probabilities of clinical pregnancy and live birth were found to be 3.907 and 3.448 fold higher respectively than in the non-PGT-A cases ($p < 0.001$). In non PGT-A cases, the probability of a total pregnancy loss was found to be 1.943 fold higher ($p = 0.013$).

Conclusion PGT-A in the presence of a single blastocyst significantly increases clinical pregnancy and live birth rates and decreases total pregnancy losses regardless of age. In addition, aneuploid embryo transfer cancelations prevent ineffective and potentially risky transfers.

Keywords Single blastocyst · PGT-A · Clinical pregnancy · Live birth

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LETTER TO EDITOR

What to advise to patients with only one good quality blastocyst, PGT-A or not? Outcomes of 2064 cycles

Raoul Orvieto[1] · Norbert Gleicher[2,3,4] · Pasquale Patrizio[5]

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To the Editor,

We perceive a need to comment on the study by Kahraman et al., [1] who retrospectively compared the IVF outcomes of patients who had only a single good-quality blastocyst and underwent transfer either with ($n=1126$) or without preimplantation genetic testing for aneuploidy (PGT-A) ($n=938$). The PGT-A group had 225 and the non-PGT-A group had 938 single euploid embryo transfer cycles.

Using a generalized linear mixed model (GLMM), the authors concluded that in PGT-A cases, regardless of other variables, the probabilities of clinical pregnancy and live birth were found to be, respectively, 3.907- and 3.443-fold higher than in non-PGT-A cases ($P<0.001$), with a 1.743-fold higher ($P=0.013$) probability of a total pregnancy loss in non PGT-A cases. They, therefore, concluded that in the presence of only a single blastocyst PGT-A significantly increased clinical pregnancy and live birth rates and, regardless of age, decreased total pregnancy losses.

Evidence for the clinical utility of PGT-A remains ambiguous [2–4], due to statistical biases from outcome reporting with reference to embryo transfer. Once their data set is reanalyzed with outcomes reported with reference to cycle start (i.e., intent to treat) quite different conclusions are reached.

It then becomes apparent that only 115 of their 1126 patients (10.2%) in the PGT-A group achieved a live-birth, compared to 278 out of 938 (29.6%) in the control group ($P<0.0001$). In practical terms this, furthermore, means that in 218 [(1126*29.6%)-115] cycles in the PGT-A group, embryos were discarded despite their potential ability to [illegible]

Viewed in this light the authors' claim of outcome benefits for PGT-A utilization in patients with only a single blastocyst are much less apparent and possibly even compromising to IVF cycle outcome chances, especially in patients with small embryo numbers.

Finally, it would have been better to calculate on a per cycle rather than a per-transfer basis. Even one blastocyst reflects favorable patient selection in comparison to infertile women with not even one transferrable embryo at blastocyst-stage.

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1. Kahraman S, Duzguner INB, Sahin Y, Irez T. What to advise to patients with only one good quality blastocyst, PGT-A or not? Outcomes of 2064 cycles. J Assist Reprod Genet. 2022;39(11):2555–62.
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These authors failed to recognize the false extrapolation they were attempting! It was not a randomized trial, it was patient self selection study.
Are they seriously proposing that aneuploid analysis was that wrong?
Are they seriously suggesting that aneuploid embryos have clinically meaningful implantation potential??

Are Orvietto and Gleicher being serious?
The embryos not transferred were aneuploid (mosaic embryos were outside of the original discussion)
How are they suggesting that transfer of an aneuploid embryo is in a patient's best interests?
Lost potential is only by very poor analysis or poor technique

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COMMENTARY

What to do with one good quality blastocyst and where do we place the emphasis?

Zachary W. Walker[1] · Elizabeth S. Ginsburg[1]

Received: 19 December 2022 / Accepted: 30 December 2022

Abstract
The use of preimplantation genetic testing for aneuploidy (PGT-A) in poor responders undergoing assisted reproductive technology has been a topic of debate with controversial results. It is critical to note the denominators used in data presented. Herein, we comment on the results found in the study by Kahraman et al. on the utility of PGT-A in poor responders with a single, good-quality blastocyst.

In this issue of *Journal of Assisted Reproduction and Genetics*, Kahraman et al. [1] report on a retrospective single-center cohort of 2064 cycles of single blastocyst transfers in poor responders who did and did not utilize preimplantation genetic testing for aneuploidy (PGT-A) with their only good quality blastocyst. Cycles utilizing PGT for structural rearrangements and monogenic disorders (PGT-SR and PGT-M) or had PGT-A results which returned as mosaic were excluded. All embryos that were 3BB or higher by Gardner's criteria were biopsied in the PGT-A group. Of the 2064 cycles that were included, 1126 cycles had single blastocysts biopsied for PGT-A compared to 938 cycles without PGT-A. Only 225 cycles (20%) within the PGT-A group had a euploid embryo eligible for transfer. There were numerous significant differences seen in the baseline demographics between the two groups including age (higher in the PGT-A group), body mass index (higher in the PGT-A group), infertility diagnosis (higher in the PGT-A group for recurrent pregnancy loss, recurrent implantation failure, diminished ovarian reserve, and advanced maternal age), number of aspirated oocytes (lower in PGT-A group), mature oocytes (lower in PGT-A group), and fertilized embryos (lower in PGT-A group). If one calculates the likelihood of live birth per initiated cycle, only 115/1126, or 10.2%, of patients who underwent PGT-A, as compared to 238/978, or 29.6%, of patients who did not, had a live birth. In our opinion, these data should have been included in the abstract of this paper.

However, the authors compared the PGT-A patients who had euploid embryos for transfer to the entire no PGT-A group, all of whom had a blastocyst transfer. The PGT-A euploid transfers had a higher biochemical pregnancy rate, clinical pregnancy rate (CPR), implantation rate, and live birth rate (LBR) per embryo transfer. However, there was no difference in total pregnancy loss rate between groups ($p = 0.493$). The authors concluded that patients with a single blastocyst should undergo PGT-A to increase CPR and LBR, decrease total pregnancy loss, and avoid "futile" transfers that would result in miscarriage or aneuploidy.

As previously noted, the baseline demographics between the two groups had significant clinically relevant differences, such as age and infertility diagnosis. Patients who underwent PGT-A were older and had a higher prevalence of recurrent pregnancy loss, recurrent implantation failure, diminished ovarian reserve, and lower mature eggs and 2PNs (two pronuclei). Therefore, it was scientifically inappropriate to compare the two groups.

The authors explain that their reason for omitting a "per cycle," or intent to treat, analysis is because it would "underestimate the role of PGT in reducing the number of futile transfers which would otherwise result in miscarriage, fetal aneuploidy, or implantation failure." However, this begs the question of how patients and physicians define *futility*. For example, one may say it is *futile* to perform PGT-A knowing that 80% of patients would not make a euploid embryo (based on the current method of testing a small sampling of trophectoderm cells) and thereby would not have the chance to undergo an embryo transfer. Gordon et al. found

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Published online: 13 January 2023

There is no per-intent-to-treat option even available.
Patients elected to test their single embryo and not transfer aneuploids
How can critics be so misunderstanding of the process and observation?
Aneuploids were not transferred
A futile transfer is one that has essentially no chance of success- suggesting that 20% is futile is at best naïve.
The process of PGT-A, at least done properly, does not create an aneuploid- the possibility of not having an embryo to transfer is very real but is not a function of PGT-A.
If patients want a transfer above all else, then don't test.
Walker and Ginsburg don't refute that transfer outcomes are better after PGT-A but confuse the concept of futile transfers and impact on a patient

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LETTER TO EDITOR

PGT-A in patients with a single blastocyst

Robert F. Casper[1]

Received: 5 April 2023 / Accepted: 5 April 2023 / Published online: 28 April 2023

I read the paper of Kahraman et al. [1], at first with interest, then surprise, and finally with distress for the patients who underwent the PGT-A procedure.

The conclusions of the authors of this paper were "PGT-A in the presence of a single blastocyst significantly increases clinical pregnancy and live birth rates and decreases total pregnancy losses regardless of age. In addition, aneuploid embryo transfer cancellations prevent ineffective and potentially risky transfers."

These conclusions are based on live birth rates per embryo transfer. They enrolled 2064 women with diminished ovarian reserve who had only a single good-quality blastocyst. PGT-A was performed in 1126 cycles and in 938 cycles an embryo transfer was done without PGT-A.

Of the PGT-A cycles, only 225 women (20%) had a transferrable, chromosomally normal embryo. There were 115 live births in these 225 women for a live birth rate of 50% per embryo transfer. In the 938 non-PGT cycles, all had an embryo transfer and there were 278 live births for a live birth rate of 30%. The author's conclusion of benefit from PGT-A was based on this difference in pregnancies per embryo transfer.

However, the relevant issue is how many women who started treatment actually took home a live baby or in other words, the intention to treat analysis. In that case, the live birth rate in the PGT-A group was 115 out of 1126 or 10% and the live birth rate in the non-PGT-A group was 278 of 938 cycles or 30%. This represents a threefold increase in live births in the non-tested group. In addition, total pregnancy losses were not significantly different (25% PGT-A vs 31%, $p = 0.493$).

Therefore, while the authors state unequivocally that PGT-A is beneficial in increasing pregnancy rates and reducing unnecessary miscarriages, in fact, the data would imply that PGT-A is harmful for live birth rate and is not associated with a reduction in spontaneous abortion rates.

From my calculations, based on the pregnancy rate in the non-PGT-A group, if the 1126 women in the treated group had not done PGT-A, there should have been an additional 223 live births.

PGT A in this study caused irreparable harm to patients with diminished ovarian reserve, many of whom lost their only chance to have a baby from their cycle of IVF. The author's interpretation of the study data is disingenuous and their conclusions are completely misleading.

Reference

1. Kahraman S, Duzguner INB, Sahin Y, Irez T. What to advise to patients with only one good quality blastocyst, PGT-A or not? Outcomes of 2064 cycles. J Assist Reprod Genet. 2022;39:2555–62.

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Casper suggests that the number of babies per procedure decision is correct.
Yet it is clear that the only transfer exclusions were aneuploid embryos- what is the logic behind this reasoning?
That massive mistakes were made in analysis? Casper has no evidence and doesn't even suggest such.
That aneuploid embryos can create clinical meaningful pregnancy outcomes? A brave suggestion and one that is contradictory to all evidence.
Disguising outcomes with expanded denominators in ITT proposal is naïve (or mischievous).
Irreparable harm??! It was a poor analysis that led to this conclusion. Assuming LB 0.511, then 394 aneuploids were transferred in the no PGT group- 394 futile transfers!
Clinical pregnancy losses were significantly higher for the no PGT group (23.2% vs 12.2% P=0.0071)

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LETTER TO EDITOR

The probability of detriment as well as benefit needs to be presented for PGT-A

Paul N. Scriven[1]

Received: 22 September 2022 / Accepted: 19 October 2022 / Published online: 25 October 2022

Sir,

The recent article by Kahraman and colleagues [1] reports the results of a study concerning the utility of preimplantation genetic testing for aneuploidy (PGT-A) for couples of poor prognosis who had only 1 blastocyst available. Their study demonstrated that PGT-A had efficacy to distinguish viable and non-viable embryos with various benefits.

It is generally accepted that in vitro fertilisation (IVF) is available to help people with fertility problems to have a baby. It is also recognised that the psychological burden of repeated implantation failure and spontaneous miscarriage of a much wanted pregnancy can be severe.

Albeit in a crude analysis, it seems that given 100 women with 1 embryo for transfer or testing, 10 women[1] benefit by avoiding a pregnancy loss; however, 19 fewer women[2] achieve the primary objective of having a baby. This is in the context of only transferring embryos with a uniform euploid test result, and where the women in the not tested group had a younger age demographic (35.3 vs. 38.6 years on average) and therefore likely represents an underestimate of the pregnancy loss benefit and an overestimate of the live birth detriment of PGT-A.

Quantifying the likely benefits and also the potential detriment to the goal of achieving a baby may help to better inform couples who might be considering having their embryo(s) tested. There is a continuing need for well-conducted experimental studies to obtain and present the probabilities of the various harms and benefits that may result before routinely offering PGT-A protocols as an adjunct to IVF.

Author contribution The author is responsible for the content and writing of the article.

Data availability Not applicable.

Code availability Not applicable.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The author declares no competing interests.

Reference

1. Kahraman S, Duzguner INB, Sahin Y, Irez T. What to advise to patients with only one good quality blastocyst, PGT-A or not? Outcomes of 2064 cycles. J Assist Reprod Genet. 2022. https://doi.org/10.1007/s10815-022-02617-7.

[1] [(131/938)−(40/1126)]×100=10
[2] [(278/938)−(115/1126)]×100=19

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A misunderstanding of the study leads to a mis analysis of outcomes
The groups were not equal in prognostic outcomes and yet the analysis continued as if they were.

Of the theoretical 100 women:

	PGT-A:	no PGT:
transfers	20	100
+ve BhCG	14	45
Implantation	13	39
Baby	10	23
Miscarriage	4	16
+BhCG-> baby	71%	51%

BUT
That's still 13 fewer babies! Yes, but only if the groups were equal and biopsy was 57% detrimental or results are 56% erroneous

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LETTER TO EDITOR

PGT-A for low responders: an authors' response

Semra Kahraman[1]

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Comments To The Editor

The authors welcome the opportunity to further discuss our recent paper.

This was a retrospective analysis of > 2000 ART cases performed over a decade in a single IVF unit. These patients were considered vulnerable since many had experienced recurrent miscarriages or a history of recurrent implantation failure. After non-directive counselling, patients decided to either transfer the embryo without any intervention or to utilise PGT-A before any transfer decision.

We clearly discussed the conundrum faced by clinicians in managing patients with limited embryo availability and the current view(s) on whether PGT-A was appropriate or untested transfer was a better way forward. The authors felt that a description of their outcomes may assist clinicians faced with similar low responder patients and to their knowledge, this is the first such study reporting on outcomes of patient decision-making and represented an important information nexus for both the field in general and clinicians in particular.

The suggestions by both Orvietto [1] and Walker [2] of outcomes being analysed as cycles started (i.e. intent-to-treat) are inappropriate. The two groups were very disparate in patient demographic and were not created as a randomised experiment. After exclusion of aneuploid embryos, which have an extremely small likelihood of success, embryo transfer is the correct reference point. Do critics of the study wish to argue that fully aneuploid embryos have clinically meaningful successful transfer outcomes? Unlike some of the studies in the literature where mosaic embryos were inappropriately categorised as abnormal, our study did not involve mosaic embryos. Similarly, any suggestion of lost potential within the PGT-A group is misguided or possibly even deceptive. In our study, patient decision-making was the key in group formation, not randomisation. The oversimplifications by both critics of our findings only display a misunderstanding of the group formation and also, unfortunately, of the value of generalised linear mixed models (GLMM) as used in this study.

The reference raised by Walker et al. (Gordon et al., 2022) regarding women ≥ 40 years undergoing PGT-A is actually a logical justification for performing PGT-A to identify euploid embryos and not a genuine rationalisation for not testing.

Any reference to Deng et al. 2020 [2] in regards to avoiding miscarriage is considered somewhat misplaced since miscarriage is only one failure point with our study supporting the idea that avoiding futile transfers was also a suitable intervention point for developing effective transfer strategies, even in low responders. Aneuploid embryos have reduced pregnancy initiation potential not just higher miscarriage potential.

A very recent paper by Scott et al. [3] further elaborated and exposed the faults in basic design and understandings of publications that confuse the purpose of PGT-A screening. Unfortunately, some critics persist in misdirecting the IVF field regarding PGT-A with their false categorisation of mosaic embryos as abnormal but subsequent transfer successes being evidence of PGT-A failure—a situation initially addressed over 6 years ago and reinforced recently with major society position statements (PGDIS and ESHRE).

Walker reminds us of the Hippocratic oath 'to do no harm' which is possibly better understood as 'do minimum harm in order to achieve a greater good'. The authors would argue that, given the true costs of a futile transfer (financial, medical, emotional for the patient and resources for the society), this is actually a strong justification for PGT-A testing.

We firmly support Walker et al. in recommending 'transparent counselling, shared decision-making and tailored recommendations based on the patient's goals'. Transparency would ensure that even opponents of PGT-A be neutral in discussions with patients. We suggest that patients will benefit as truer understandings are revealed.

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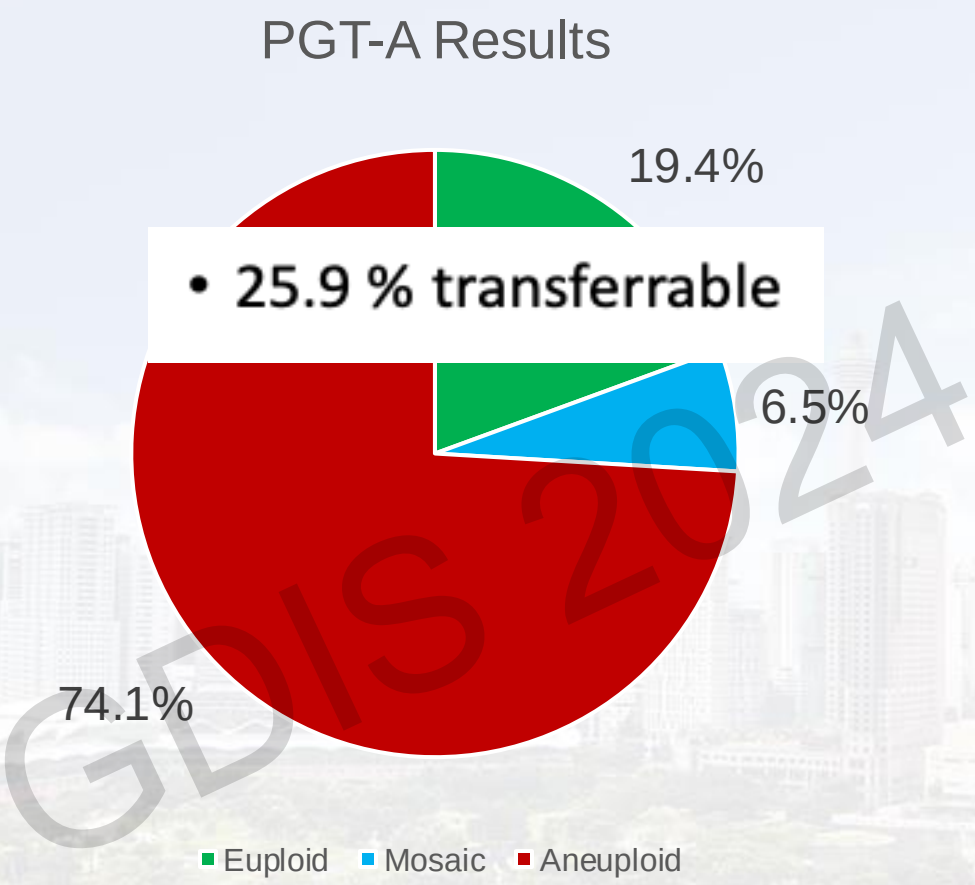
A comprehensive response showed that many erroneous assumptions were made by all critics.

The study was a patient choice, not a trial. Groups were substantially different in many parameters.

Underlying the decision was patients wanting to improve transfer outcomes and reduce the disappointment of a failed transfer or for some, the bigger disappointment of a positive start and a negative finish.

This is exactly what PGT-A provided!

More recent PGT-A results for Single Blastocyst Cases



- 1488 Blastocysts were tested with PGT-A
- 386 cycles with euploid or mosaic diagnosis (25.9% transferable embryos)

Comparison of different outcomes of cases with one blastocyst

	PGT-A transfers			No PGT-A transfers		
	Euploid	Mosaic	**Euploid + Mosaic**	Fresh ET	FET	**Fresh ET+FET**
OPU Cycles	289	97	386	901	228	1129
Transfer cycles	248	44	292	901	151	1052
Biochemical Pregnancy	76.2%	81.8%	77.1%	43.8%	49.7%	44.6%
Biochemical Miscarriage	9.5%	19.4%	11.1%	17.1%	12.0%	16.3%
Clinical Pregnancy	68.9%	65.9%	68.5%	36.2%	43.7%	37.3%
Clinical Miscarriage	14.6%	10.3%	14.0%	20.3%	22.7%	20.7%
Ongoing Pregnancy	**58.9%**	59.1%	**58.9%**	28.9%	33.8%	**29.6%**

PGT-A transfers vs no PGT-A transfers

	PGT-A	No PGT-A	p
	Euploid + Mosaic	Fresh ET+FET	
OPU Cycles	386	1129	
Transfer cycles	292	1052	
Biochemical Pregnancy	77.1%	44.6%	<0.0001
Biochemical Miscarriage	11.1%	16.3%	0.0701
Clinical Pregnancy	68.5%	37.3%	<0.0001
Clinical Miscarriage	14.0%	20.7%	0.0466
Ongoing Pregnancy	58.9%	29.6%	<0.0001
Total Pregnancy Loss	23.6%	33.7%	0.0066

Conclusions

- PGT-A for a single blastocyst increases clinical pregnancy and live birth rates and decreases total pregnancy losses per transfer regardless of age.

- After an euploid embryo is found, the live birth rate per embryo transfer almost doubles compared to the live birth rate following a single embryo transfer without PGT-A

- PGT-A decreases the number of futile transfers which could otherwise result in **implantation failure, miscarriage**, **fetal aneuploidy**.

- On the other hand, the patient should **be aware of the high rate of embryo transfer cancellation**. **(But these would be futile transfers)**

- It would be appropriate to decide whether to perform PGT-A only after providing detailed information to the low responder patients and assessing their wants.

All these issues need to be considered during pre-PGT-A counselling in low responder cases to assist clinicians and even more importantly, enable patients to make better informed choices.

PGT-A reduces futile transfers

Futile transfers can result in:

- Physical damage risk to uterus and endometrium
- Emotional burden of miscarriage and ongoing aneuploid pregnancies

Pregnancy Loss

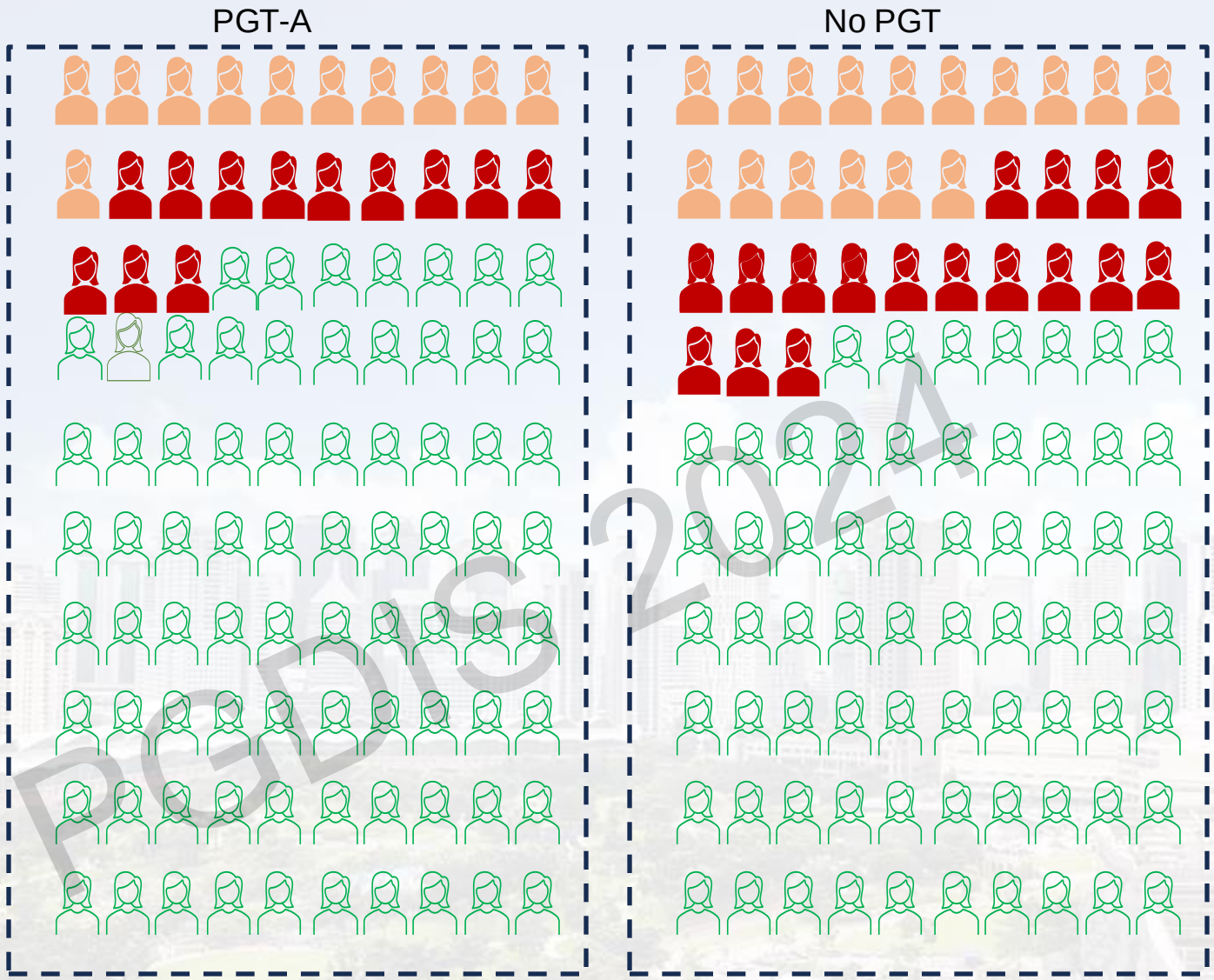
Pregnancy loss is associated with short- and long-term psychological effects, which are often underestimated by health professionals

It is important for clinicians to be familiar with factors in the development of adverse mental outcomes.

Miscarriage can lead to problems with mental health such as

Depression,
Anxiety and
Post-traumatic stress disorder (PTSD)

If PGT-A was performed for all cases



- For every100 pregnant women, 94 fewer transfers are required for PGT-A
- Total pregnancy losses would be decreased by 10
- 30% fewer women would have any pregnancy loss-related physical and/or emotional complications

What can be done?

Offer PGT-A to all patients,

The decision for PGT-A is not only for clinicians to make

Modern medicine should provide the best treatment options available for every patient

Ultimately, it is the couple that can choose what's right for them

Because,

Biopsy is safe

PGT-A prevents a significant % of pregnancy losses

Helps couples to have healthy, reduced-risk pregnancies (and a healthy baby)

Thus it can help patients of all ages

In the future,

We must improve the sensitivity of PGT-A to further increase implantation rates and decrease pregnancy losses

Introduce new proven techniques and methods to provide the best treatment options for all couples,

Minimum number of blastocysts to perform PGT-A?

1 (One)

If a blastocyst is considered
- to have potential for implantation
- to be of morphological quality for biopsy
- then it is a candidate for PGT-A

- *The true aim of PGT-A is to reduce futile transfers and improve transfer outcomes by reducing the accidental choosing of an aneuploid embryo instead of just doing an embryo transfer*

Performing ‘rescue embryo transfers’ (with poor quality blastocysts)
- **15.6% ongoing pregnancy rate**
- **43.5% total pregnancy loss rate**
- May be considered but might not fully benefit patients since almost half of the women subsequently experience pregnancy loss- miscarriage!

THANK YOU