SUBMISSION OF REVISION TO AUSTRALIAN AND NEW ZEALAND JOURNAL OF OBSTETRICS AND GYNAECOLOGY (ANZJOG-2017-0123)

Title Page

Concise Title: Assisted reproductive technology (ART) cumulative live-birth rates using preimplantation genetic diagnosis to screen for embryo aneuploidy: a cohort analysis

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Acknowledgements
The authors acknowledge the contribution of Melbourne IVF in the provision of data. We are grateful for the assistance of Ms Sophie Falle from Melbourne IVF in the interpretation of the clinic data.

No specific funding was used to undertake this study.
Associate Professor Georgina Chambers previously received grant support to her institution from the Australian Government, Australian Research Council (ARC) Linkage Grant No. LP1002165; ARC Linkage Grant Partner Organisations were IVF Australia, Melbourne IVF and Queensland Fertility Group.
Title: Assisted reproductive technology (ART) cumulative live birth rates following preimplantation genetic diagnosis for aneuploidy (PGD-A) or morphological assessment of embryos: a cohort analysis

Short Title: Cumulative live-birth rate following PGD-A

Word Count: Abstract (250 words)
Main text (2,839 words)

Manuscript statistics:
Two Tables
Two Figures
Two Supplementary Tables
One Supplementary Figure

Key words: assisted reproductive technologies; preimplantation genetic diagnosis; aneuploidy; embryo selection based on morphological assessment; cumulative live-birth rates
Abstract

Background: Preimplantation genetic diagnosis for aneuploidy (PGD-A) for all 24 chromosomes improves implantation and clinical pregnancy rates per single assisted reproductive technology (ART) cycle. However, there is limited data on the live-birth rate of PGD-A over repeated cycles.

Aim: To assess the cumulative live-birth rates (CLBR) of PGD-A compared with morphological assessment of embryos of up to three ‘complete ART cycles’ (fresh plus frozen/thaw cycles) in women aged 37 years or older.

Materials and Methods: A retrospective cohort study of ART treatments undertaken by ART-naïve women at a large Australian fertility clinic between 2011 and 2014. Cohorts were assigned based on the embryo selection method used in their first fresh cycle [(PGD-A, n=110 women (PGD-A group); morphological assessment of embryos, n=1983 women (control group)]. CLBR, time to clinical pregnancy and cycles needed to achieve a live-birth were measured over multiple cycles.

Results: Compared to the control group, the PGD-A group achieved a higher per cycle live-birth rate (14.47% vs 9.12%, p<0.01), took a shorter mean time to reach a clinical pregnancy leading to a live-birth (104.8 days vs 140.6 days, p<0.05) and required fewer cycles to achieve a live-birth (6.91 cycles vs 10.96 cycles, p<0.01). However, after three ‘complete ART cycles’, the CLBR was comparable for the two groups (30.90% vs 26.77%, p=0.34).

Conclusion: This is the first study to assess the effectiveness of PGD-A over multiple ART cycles. These real-world findings suggest that PGD-A leads to better outcomes than using morphological assessment alone in women of advanced maternal age.

Introduction

Assisted reproductive technologies (ART), such as in vitro fertilisation (IVF), have revolutionized the treatment of infertility during the past generation, with more than 6 million children conceived worldwide following ART. In Australia and New Zealand, more than 70,000 ART cycles are undertaken each year, resulting in the birth of 1 in 25 children, rising to 1 in 12 for women aged over 35 years.

Advanced maternal age remains a significant challenge to achieving pregnancy and a live birth using ART. Increasing aneuploidy is an important contributing factor, with almost three
quarters of oocytes in women aged over 40 are affected by aneuploidy compared with one quarter in women in their early thirties.  

Advanced preimplantation genetic diagnosis (PGD-A) techniques, such as array comparative genomic hybridization (array CGH) which allows 24-chromosome screening for aneuploidy have been shown to improve implantation and clinical pregnancy rates during ART.  

However, although promising, there remains a paucity of high quality evidence to support the clinical effectiveness of PGD-A, particularly in women of advanced maternal age (generally considered to be 37 years or older seeking fertility treatment). To date, only four randomised controlled trials (RCTs) comparing PGD-A to morphological assessment of embryos have been published. Three of these were limited to young, good prognosis women, and only reported outcomes of the first embryo transfer cycle. The fourth RCT, published in 2017, was conducted in older women (38-41 years) with a relatively good prognosis and reported outcomes from the first ‘complete ART cycle’, that is including frozen/thawed embryos originating from the oocyte pick-up (OPU).  

While RCTs are considered the gold standard for maximizing the likelihood of observing an effect from a single intervention if one exists (efficacy), they often lack external validity (generalisability), over-estimate treatment effects, are difficult to recruit for, and may require years to complete if treatment or outcomes require extended follow-up (as is the case with ART treatment).  

Because women usually undergo multiple ART cycles, cumulative live-birth rates (CLBR) which account for outcomes over repeated cycles are important in assessing the effectiveness of ART techniques, particularly with embryo screening techniques such as PGD-A, which often results in fewer embryos available for transfer.  

The aim of this study is to assess the clinical effectiveness of PGD-A compared to morphological assessment of embryos in women of advanced maternal age (≥37 years) over repeated ART treatment cycles.  

**Methods**  

**Study population**  

The retrospective cohort study comprised infertile women aged 37 years or older (N=2,093) commencing their first fresh ART cycle at a large private fertility clinic in Melbourne, Australia between January 2011 and June 2013. Treatment outcomes from their first and
subsequent fresh and frozen/thaw cycles were collected through to March 2014, or to the birth a live-born baby.

The study cohort was stratified into women whose first OPU used either PGD-A (PGD-A group, n=110 women) or morphological assessment for selection of embryos (control group, n=1,983 women). The decision of whether to use PGD-A or morphological assessment was made by the clinician in consultation with the patient. Exclusion criteria included women who had PGD testing for monogenic disease, chromosomal translocation or rearrangements, or sex selection and those who used donor oocytes or initiated a cycle with the intent of freezing all embryos for later use.

**Embryo development and evaluation**

**Ovarian stimulation**

Cycles were programmed using the oral contraceptive pill. Ovarian hyperstimulation protocols used down regulation with GnRH agonist (Synarel®, Pfizer Australia Pty Ltd) and recombinant follicle-stimulating hormone (FSH) or antagonist protocol with Orgalutran® (Merck Sharp & Dohme Australia Pty Ltd). Choice of cycle protocol and FSH dosage was clinician directed. FSH dosage was chosen with regards to the anti-Müllerian hormone assay and antral follicle count with a maximum dosage of 300iu.

**Embryo culture and biopsy**

All oocytes in PGD-A cycles were fertilised with a single sperm using intra-cytoplasmic sperm injection (ICSI). In the control group, fertilisation was achieved by co-incubation of up to three oocytes with approximately 100,000 motile sperm, except where ICSI was indicated. Embryos were cultured in Quinn’s Advantage Medium (Sage ®).

In the PGD-A group, a single nucleated blastomere was biopsied from embryos that had at least six cells and less than 30% fragmentation on the morning of day 3 of embryo development.

**Embryo Selection**

Array CGH was performed using 24Sure™ (Illumina, Inc., San Diego, CA) and following the manufacturer’s instructions to enumerate chromosomes in single blastomeres. Morphological assessment of cleavage-stage embryos included the cell number and, the degree of cellular fragmentation, with grade 1, 2, 3, 4, and 5 embryos having <10%, 11-20%, 21-30%, 31-50% and >50% fragmentation respectively.
Embryo transfer and cryopreservation

In the control group, embryo transfer was performed predominantly on day 2, but occasionally at later stages. In the PGD-A group, embryo transfer was performed predominantly on day 5, but occasionally on day 6.

Supernumerary embryos of good quality were stored in liquid nitrogen for possible use in subsequent cycles.

Clinical outcomes

In this study, a ‘single cycle’ refers to the outcomes of a discrete fresh or frozen/thaw cycle and a ‘complete ART cycle’ refers to the outcomes from all embryos created from an OPU, including fresh and any subsequent frozen/thaw embryo transfer (FET) cycles. The CLBR is defined as the number of live births divided by the total number of women who started treatment in either the PGD-A group or the control group.

Clinical outcomes include pregnancy rate [i.e. presence of a heart beat per initiated cycle or embryo transfer (ET) procedure] and live-birth rate (i.e. birth of at least one live born baby per initiated cycle or ET procedure). Time taken to reach a clinical pregnancy leading to a live-born baby for each woman was calculated from the date of their first OPU.

Statistical analysis

All data were analysed according to intention-to-treat and per-protocol principles. The intention-to-treat analysis assigned all outcomes from the first and any subsequent (fresh or frozen/thaw) treatment cycles to the strategy that the women received in the first fresh cycle (PGD-A or morphological assessment alone), reflecting the actual experience and clinical pathway of women undergoing treatment.

The per-protocol analysis censored women from the analysis if they crossed over to the alternate treatment strategy in their subsequent fresh cycle during the study period to avoid contamination of the results by the alternate embryo selection strategy.

Chi-square or Fisher’s exact test was used for categorical variables and the t-test for continuous variables. A p value of less than 0.05 is considered statistical significant.

The log rank test was performed to test difference in the time taken to achieve a clinical pregnancy leading to the first live-born baby for each woman in the two study groups. All analyses were conducted using Stata software version 11.2 (Stata Corp, College Station, TX).
Ethical approval

The study was approved by the University of New South Wales, Human Research Ethics Advisory (HREA) Panel 1 and the Melbourne IVF Research Ethics Committee.

Results

A total of 2,093 women were included in this study. Of these, 110 had their embryos assessed using PGD-A in their first fresh cycle (PGD-A group) and another 1,983 women had their embryos selected based on morphological assessment alone in their first fresh cycle (control group). The pathway profile of women who met the inclusion criteria is presented in Supplementary Figure 1.

Overall ‘single cycle’ success rates

The study cohort undertook 288 PGD-A cycles and 5,771 morphological assessment cycles regardless of the group they were assigned to in their first fresh cycle. The overall live-birth rate per initiated ‘single cycle’ (fresh or frozen/thaw) was higher following PGD-A compared to cycles that used morphological assessment alone (15.28% vs 9.03%, p<0.001). The live-birth rate per ET procedure was almost three times higher following PGD-A compared to morphological assessment alone (32.12% vs 11.27%, p<0.001).

Intention-to-treat analysis: first three ‘single cycles’

Table 1 presents the demographic data for the 2,093 women and the characteristics of their first three ‘single cycles’. Not all women undertook three cycles because some had a live-birth or discontinued treatment before their third cycle. Women in the two study groups were similar in their mean age at the initial OPU (40.06 years vs 40.05 years) and had similar embryos quality.

On average, women in the PGD-A group undertook fewer fresh or frozen/thaw ‘single cycles’ than the control group (2.00 vs 2.31, p<0.001). PGD-A patients had more oocytes collected per OPU (10.83 vs 6.89, p<0.001), achieved better fertilisation rate (61.77% vs 56.61%, p<0.001), and a higher average number of embryos was created per OPU than the control group (6.69 vs 3.90, p<0.001). However, the PGD-A group had fewer embryos available for transfer or cryopreservation per OPU (0.84 vs 2.57, p<0.001) and fewer embryos transferred per ET procedure (1.11 vs 1.36, p<0.001) than the control group.

Table 1 also presents the clinical outcomes of the first three ‘single cycles’. Compared to the control group, the PGD-A group achieved a higher implantation rate (36.75% vs 13.75%, p<0.001).
p<0.001), and pregnancy rate per ET procedure – (per fresh ET procedure: 36.76% vs 17.87%, p<0.001; per FET procedure: 53.33% vs 17.52%, p<0.01). The PGD-A group achieved a higher per initiated cycle live-birth rate (14.47% vs 9.12%, p<0.01), and had a significantly lower pregnancy loss rate than the control group (19.51% vs 34.78%, p<0.05).

Importantly, women in the PGD-A group underwent fewer ‘single cycles’ than the control group to achieve a live-birth [6.91 cycles (221 ‘single cycles’ initiated/32 live-births) in the PGD-A group vs 10.96 cycles (4593 ‘single cycles’ initiated/419 live-births) in the control group; p<0.01].

To account for the fact that most cycles from the PGD-A group transferred blastocysts (94.6%) compared to the control group (6.7%), a subanalysis was performed to compare single embryo blastocyst transfer between the two groups (PGD A: n= 88 vs control group: n=155). The live-birth rate per ET procedure remained higher in the PGD-A group compared to the control group (34.09% vs 12.26%, p<0.001), indicating that the type of embryo transferred in the control group (day 2/3 or day 5/6), did not alter the interpretation of the live-birth rate.

**Intention-to-treat analysis: Cumulative live-birth rates (CLBR)**

**Table 2 and Figure 1** present the CLBR of up to three ‘complete ART cycles’ for the PGD-A group and the control group. The results indicate that based on the intention-to-treat analysis, comparable CLBR are achieved between the PGD-A group and the control group (30.90% vs 26.77%, p=0.34, after three ‘complete ART cycles’).

To account for the high proportion of women who did not reach an ET procedure in the PGD-A group compared to the control group in the first fresh cycle (58.18% vs 20.32%), we also undertook a restricted analysis of the CLBR including only women who reached an ET procedure in their first fresh cycle. In this analysis, the CLBR of up to three ‘complete ART cycles’ was significantly higher in the PGD-A group than in the control group (50.0%; vs 30.89%, p<0.01) (Figure 1).

The cycle characteristics and clinical outcomes, including the CLBR based on per-protocol analysis, were similar to those obtained from the intention-to-treat analysis (Supplementary Tables 1 and 2)

**Time to pregnancy leading to a live-birth**
Figure 2 presents the Kaplan-Meier curves for the time taken to reach a clinical pregnancy leading to a live birth. The intention-to-treat analysis revealed that on average it took women in the PGD-A group 25% less time (35.8 fewer days) than the control group to achieve a clinical pregnancy leading to a live birth (104.8 days vs 140.6 days, log rank test p<0.05).

Discussion

This is the first study to comprehensively analyse the cumulative effectiveness of PGD-A over repeated cycles in women attending a fertility clinic for routine care.

Our study found that in women aged 37 years or older, a strategy of PGD-A led to a better live-birth rate per initiated ‘single cycle’ (fresh or frozen/thaw cycle), fewer ART cycles to achieve a live-birth, a shorter average time to a clinical pregnancy leading to a live-birth and a lower rate of pregnancy loss. However, the CLBR over one or multiple ‘complete ART cycles’ (all ETs from one OPU) was comparable for the two study groups.

The higher live-birth rate per ‘single cycle’ and lower rate of pregnancy loss after PGD-A in our study is consistent with the findings from previous studies. In particular, our study findings are similar to the recently published RCT of PGD-A by Rubio and colleagues conducted in women of advanced maternal age, and which used a similar platform of cleavage-stage biopsy and aCGH. Rubio and colleagues’ study is the only RCT of PGD-A in women of advanced maternal age, and was undertaken in women with a relatively good prognosis. While our study is a retrospective observation study that cannot confirm causality, the findings complement this RCT, by providing a longitudinal perspective over multiple ‘complete ART cycles’ performed in an unrestricted population of ART-naïve women attending a fertility clinic. Such ‘real-world’ data are necessary for generalising RCT findings to clinical practice.

In our study, the women in the PGD-A and the control groups were of a similar age and exhibited similar embryo quality. However, there was a higher number of oocytes collected in the PGD-A group than the control group (10.83 oocytes vs. 6.89 oocytes), suggesting a better prognosis for the women in the PGD-A group. However, the higher number of oocytes in the PGD-A was intentionally protocol-driven by treating clinician to achieve a sufficient number of embryos for testing, and therefore does not confound the findings.

Due to the embryo screening process, the mean number of embryos available for transfer or cryopreservation per OPU was significantly lower in the PGD-A group than in the control group (0.84 embryos vs. 2.57 embryos). Therefore, it is perhaps not surprising that the
CLBRs for the two groups converged over time because women in the control group had more cryopreserved embryos available for subsequent FET cycles. Given the apparent similarity in CLBRs, some have argued that sequential transfer of untested embryos over repeated cycles is preferable to PGD-A, particularly for older women with limited and marginal quality embryos available for transfer. However, undergoing multiple transfer cycles wastes reproductive time, particularly in older women whose fertility potential decreases rapidly with age, and increases the stress experienced with repeated ART failure associated with transferring aneuploid embryos. This is exemplified in our study where women in the control group undertook an average of 11 cycles compared to 7 cycles in PGD-A group to achieve a live-birth.

In this study, we have reported on outcomes of cleavage-stage biopsy and analysis of a single cell as this was the clinic’s preferred approach during the study period. In recent years, many PGD-A laboratories have favoured the use of day 5 or day 6 blastocyst biopsy where 5-10 cells are removed from each embryo. However, cleavage-stage biopsy continues to be practiced in laboratories throughout the world including in Spain, India, United Arab Emirates (C. Rubio, Valencia, personal communication) and the United Kingdom (D. Wells and E. Fragouli, Oxford, personal communication), thus these results remain relevant to women of advanced maternal age.

Some practitioners believe that chromosomal mosaicism in cleavage-stage embryos confounds PGD-A diagnoses. However, mosaicism affects both cleavage-stage embryos and blastocysts with estimated frequencies ranging from 4% to 90% depending on the diagnostic method used and the source of the embryonic material. More recent evidence suggests that the frequency of chromosomal mosaicism in preimplantation embryos has been significantly over-estimated because of sub-optimal testing methods.

However, a limitation of this study is that the results may be confounded by the type of embryo transferred. Blastocysts were mainly transferred in the PGD-A group (91.42%), whereas most embryos in the control group were transferred at cleavage-stage (94.15%). While this may have introduced bias, a recent Cochrane review of 27 RCTs found that the live-birth rate after fresh transfer was higher following blastocyst transfer, but there was no evidence of a difference in the cumulative pregnancy rate over a ‘complete cycle’.

Furthermore, when we restricted our analysis comparing only single blastocyst transfer in both the PGD-A and the control groups, the live-birth rate after three ‘single cycles’ remained higher in the PGD-A group (34.09% vs 12.26%, p<0.001).
Our study has several strengths which distinguish it from earlier studies. This is the first study to undertake a longitudinal reporting approach to assess the effectiveness of PGD-A over repeated cycles. We have also chosen to report a number of clinically important endpoints (ie. CLBR, number of cycles needed to treat, and time taken to reach a clinical pregnancy leading to a live birth).

In conclusion, this study complements efficacy research obtained from RCTs, providing important information of the effectiveness of PGD-A over repeated cycles in a ‘real-world’ clinic setting. Our study showed that, despite similar CLBR in women of advanced maternal age who have either PGD-A or morphological assessment of embryos in the first cycle, the PGD-A group achieved a higher live-birth rate per ‘single cycle’, undertook almost half the number of initiated and ET cycles, and took significantly less time to achieve a live-birth.

References:


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17 Rothwell PM. External validity of randomised controlled trials: “to whom do the results of this trial apply?” *The Lancet.* 2005; 365: 82-93.


Table 1: Demographic characteristic and outcomes of first three ‘single cycles’ (fresh or frozen/thaw cycles) based on intention-to-treat analysis

<table>
<thead>
<tr>
<th>Total number of women at start of first fresh cycle</th>
<th>PGD-A n= 110</th>
<th>Control n= 1983</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first oocyte pick-up (OPU), mean ± SD, range</td>
<td>40.06 ± 1.97, 37-45</td>
<td>40.05 ± 2.34, 37-49</td>
<td>p=0.96</td>
</tr>
<tr>
<td>‘Single cycles’§ initiated n, mean per woman ± SD,</td>
<td>221, 2.00 ± 0.81</td>
<td>4593, 2.31 ± 0.83</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Fresh cycle initiated, n</td>
<td>203 (91.86)</td>
<td>3312 (72.13)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Frozen/thaw cycle initiated ¶ n</td>
<td>18 (8.14)</td>
<td>1281 (27.87)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>OPU cycles, n, mean per woman ± SD</td>
<td>196,1.78 ± 0.79</td>
<td>3194,1.61 ± 0.72</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Oocytes collected, mean per OPU ± SD</td>
<td>10.83 ± 6.60</td>
<td>6.89 ± 5.67</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Fertilisation rate (2-pronuclei/oocytes collected), %</td>
<td>61.77</td>
<td>56.61</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Embryos created per OPU, mean ± SD</td>
<td>6.69 ± 4.58</td>
<td>3.90 ± 3.75</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Embryos numbers and quality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2-4 embryos, mean grade ± SD, (1=good, 5=bad)</td>
<td>2.28 ± 0.75</td>
<td>2.03 ± 0.81</td>
<td>p=0.12</td>
</tr>
<tr>
<td>Day 5 &amp; 6 embryos, mean grade ± SD, (1=good, 8=bad)</td>
<td>3.47 ± 1.53</td>
<td>3.46 ± 1.27</td>
<td>p=0.55</td>
</tr>
<tr>
<td>Embryos available for transfer or cryopreservation, mean per cycle with OPU ± SD</td>
<td>0.84 ± 1.19</td>
<td>2.57 ± 2.64</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Embryo transfer procedures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Embryo transfer (ET) procedures, n (% per cycle started)</td>
<td>105 (47.51)</td>
<td>3625 (78.94)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Embryos transferred, mean per ET procedure ± SD, range</td>
<td>1.11 ± 0.32, 1-2</td>
<td>1.36 ± 0.48, 1-3</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>
### Implantation rate,
(gestational sacs/total embryos transferred), %

<p>| | | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>36.75</td>
<td>13.75</td>
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</table>

<table>
<thead>
<tr>
<th>Total number of women at start of first fresh cycle ‡, (continue)</th>
<th>PGD-A n= 110</th>
<th>Control n= 1983</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy rate ††</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per cycle initiated, %</td>
<td>18.55</td>
<td>14.02</td>
<td>p=0.06</td>
</tr>
<tr>
<td>Per fresh ET procedure, %</td>
<td>36.76</td>
<td>17.87</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Per frozen/thaw ET procedure, %</td>
<td>53.33</td>
<td>17.52</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Percentage of pregnancies that failed to reach birth, ‡‡ %</td>
<td>19.51</td>
<td>34.78</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Live-birth ‡§ rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per cycle initiated, %</td>
<td>14.47</td>
<td>9.12</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Per ET procedure, %</td>
<td>30.47</td>
<td>11.56</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Multiple live-birth rate, (% of live-birth delivery)</td>
<td>6.25</td>
<td>7.16</td>
<td>p=0.81</td>
</tr>
<tr>
<td>Discontinue rate ¶¶, (% of women without a live born)</td>
<td>71.80</td>
<td>50.00</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

† The intention-to-treat analysis assigned all outcomes from the first and any subsequent fresh or frozen/thaw ‘single cycles’ to the embryo selection strategy that the woman received in her first fresh cycle (PGD-A or morphological assessment alone).

‡ The study cohort is stratified into women whose first OPU used either PGD-A or morphological assessment for selection of embryos.

§ A ‘single cycle’ refers to the outcomes of a discrete fresh or frozen/thaw cycle.

¶ An initiated fresh cycle is defined as commencing with the administration of follicle stimulating hormone (FSH). An initiated frozen/thaw cycle is defined as the thawing of one or more embryos.

†† Pregnancy rate is defined as the presence of a heart beat per initiated cycle or embryo transfer (ET) procedure.

‡‡ Pregnancy that failed to reach birth include miscarriages, missed abortions, blighted pregnancies, ectopic pregnancies and terminations.

‡§ A live-birth is defined as the birth of at least one live born baby, with twins and triplets counted as one live-birth.

¶¶ Discontinue rate refers to women who discontinue with treatment without a live birth during the study period.

A p-value of less than 0.05 is considered statistically significant.
Table 2: Clinical outcomes for up to three ‘complete cycles’† based on intention-to-treat analysis‡

<table>
<thead>
<tr>
<th>Total number of women at the start of first fresh cycle§, n</th>
<th>PGD-A (n=110)</th>
<th>Control (n=1983)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative live-birth rate (CLBR), ‣ %</td>
<td>30.90</td>
<td>26.77</td>
<td>p=0.34</td>
</tr>
<tr>
<td>Proportion of women who did not have an embryo transfer (ET) procedure in their first fresh cycle, (% of first fresh cycle initiated)</td>
<td>58.18</td>
<td>20.32</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>CLBR of women with an ET procedure in first fresh cycle, %</td>
<td>50.00</td>
<td>30.89</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Discontinue rate†† (% of women without a live-born)</td>
<td>61.72</td>
<td>55.97</td>
<td>p=0.31</td>
</tr>
<tr>
<td>Follow-up time‡‡ mean ± SD (days)</td>
<td>503.62 ± 335.53</td>
<td>560.05 ± 338.73</td>
<td>p=0.08</td>
</tr>
</tbody>
</table>

† A ‘complete cycle’ refers to the outcomes from all embryos created from an oocyte pick-up (OPU), including fresh and any subsequent frozen/thaw embryo transfer (FET) cycles.
‡ The intention-to-treat analysis assigned all outcomes from the first and subsequent ‘complete cycle’ (fresh and any FET cycles) to the embryo selection strategy that the woman received in her first fresh cycle (PGD-A or morphological assessment alone).
§ The cohort is stratified into women whose first OPU used either PGD-A or morphological assessment for selection of embryos.
¶ Cumulative live-birth rate (CLBR) is defined as the number of live births divided by the total number of women who started treatment in either the PGD-A group or the control group.
†† Discontinue rate refers to women who did not undertake up to 3 ‘complete cycles’ during the study period.
‡‡ Mean follow-up time is based on the date of first OPU through to 31 Mar 2014 or to the first clinical pregnancy leading to a live born baby.
A p-value of less than 0.05 is considered statistically significant.
Figure 1: Cumulative live-birth rates (CLBR) † of first and subsequent ‘complete cycles’ ‡ for all women and among women who had an embryo transfer (ET) procedure in their first fresh cycle.§

Cumulative live-birth rate (CLBR) is defined as the number of live-births divided by the total number of women who started treatment in either the PGD-A group or the control group (i.e. 110 women in PGD-A group and 1983 women in the control group).

A ‘complete cycle’ refers to the outcomes from all embryos created from an oocyte pick-up (OPU), including fresh and any subsequent frozen/thaw embryo transfer (FET) cycles.

CLBR of woman with an embryo transfer (ET) procedure in the first fresh cycle refers to the number of live births achieved by the number of women who commenced treatment and have an ET procedure in the first fresh cycle (i.e. 46 women in the PGD-A group and 1580 women in the control group have an ET procedure in their first fresh cycle).

** P<0.01 *** P<0.001 PGD-A group versus control group

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Title:
Assisted reproductive technology (ART) cumulative live birth rates following preimplantation genetic diagnosis for aneuploidy (PGD-A) or morphological assessment of embryos: A cohort analysis.

Date:
2018-10

Citation:

Persistent Link:
http://hdl.handle.net/11343/294074