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Title:

The Degree to Which PGS Increases IVF Efficiency is Correlated With Increased Maternal Age

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Objective:
While preimplantation genetic screening (PGS) has been demonstrated to improve the embryo implantation rate and reduce the early pregnancy loss rate, the age-weighted contribution to these benefits has yet to be precisely established. In calculating the burden of treatment, it is also important to consider both these advantages as well as the disadvantage of the lengthened treatment cycle associated with biopsy, vitrification, and subsequent rewarming and transfer. This study sought to compare the cumulative number of egg retrievals and embryo transfer cycles and length of time required for patients to achieve pregnancy after undergoing IVF with and without PGS.

Design:
Retrospective cohort study

Materials and Methods:
Patients who underwent an IVF cycle(s), with and without PGS from 2010 to 2015 were included. All PGS cycles involved trophectoderm biopsy. Cycles with male factor and single-gene disorder were excluded. Cox proportional hazards models with the restricted mean time to event estimate were used to analyze, with respect to age, the mean number of fresh IVF cycles required to obtain a euploid embryo (in PGS group only) and the mean number of embryo transfers (ETs) to achieve first clinical pregnancy. The mean time to clinical pregnancy was modelled from time estimates and outcomes of fresh IVF and subsequent fresh and frozen ET cycles in non-PGS patients (following ASRM ET guidelines) and PGS patients (frozen-thawed SET (FET) performed exclusively). The following time estimates were used: 21 days for fresh IVF, 45 days for freeze-all w/FET,

21 days for a subsequent FET cycle, 31 days added for a biochemical loss, 91 days for a clinical loss, 16 days for no pregnancy, and 42 days for ongoing pregnancy.

Results:
A total of 10,642 IVF cycles (2,758 with PGS, 7,884 unscreened) were analyzed. When controlling for age, ovarian reserve markers, number of embryos transferred; PGS improved clinical pregnancy rate (HR 1.4 [1.01-2.0] p = 0.045) with a progressive increase in older cohorts (age 38-20: HR 2.0 [1.4-2.9], 41-42: HR 3.4 [2.0-5.8], >42: HR 7.5 [4.4-12.8], p < 0.001). Cycle characteristics and outcomes for the non-PGS and PGS cohort are shown in Tables 1 & 2, respectively. In the PGS cohort, there was an age-related increase in mean number of fresh IVF cycles prior to obtaining a euploid embryo (1.8 in the oldest vs. 1.0 in the youngest patients). A reduction in mean number of ETs required to achieve a clinical pregnancy was seen in PGS patients aged >39. A reduction in time to clinical pregnancy was observed in PGS patients aged >41. There was a decrease in multiple pregnancy rate of 13.3% across all PGS cohorts, with the greatest decline (29.3%) shown in patients aged 36-38. There was an overall 3.5% reduction in early pregnancy loss rate with the greatest benefit (10% decrease) in PGS patients aged >41.

Conclusion:
The use of PGS for embryo selection increases the efficacy of IVF treatment in patients of all ages. In women over 40, PGS was demonstrated to markedly improve the efficiency of treatment, hastening time to pregnancy by up to 4 months with a 45.5% relative reduction in pregnancy loss. The reduction in treatment burden for younger PGS patients is less dramatic, most likely a result of the lower aneuploidy rate found in younger oocytes, and is correlated with the significant decrease in pregnancy loss and multiple pregnancy associated with transfer of a single screened embryo. This data can aid clinicians in precisely counseling patients regarding the incremental effect to be anticipated by adding PGS to their treatment plan

Table 1: Non-PGS cohort with fresh IVF followed by fresh and frozen unscreened ETs according to ASRM guidelines

Age	Unscreened embryos transferred	Average transfers to clinical pregnancy	Average time to clinical pregnancy (months)	Multiple pregnancy rate (observed)	Clinical loss rate (observed)
28	1	2.27	4.42	4.1%	9.0%
32	1	2.91	5.32	2.3%	10.0%
36	2	2.14	4.14	30.1%	10.0%
39	2	3.39	6.25	19.6%	12.1%
41	3	4.29	8.15	29.6%	16.5%
43	3	6.88	11.35	8.0%	11.0%

Table 2: PGS cohort with freeze-all IVF and frozen SETs

Age	Euploid embryos transferred	Average retrievals to euploid embryo	Average transfers to clinical pregnancy	Average time to clinical pregnancy (months)	Multiple pregnancy rate (observed)	Clinical loss rate (observed)
28	1	1.03	1.76	4.49	2.9%	5.6%
32	1	1.11	2.12	5.46	4.3%	9.9%
36	1	1.23	2.18	5.87	0.8%	8.2%
39	1	1.44	2.2	6.76	2.8%	11.3%
41	1	1.63	1.96	6.79	3.2%	6.5%
43	1	1.82	2.01	7.42	0.0%	6.2%