PREIMPLANTATION GENETIC TESTING FOR MONOGENIC DISORDERS - WHAT SHOULD WE EXPECT?

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Background: Patients at risk for a monogenic disorder or a known carrier couple can utilize preimplantation genetic testing (PGT-M) to transfer an unaffected embryo to prevent disease inheritance. Prior studies have reported no difference in pregnancy outcomes or cumulative live birth (LB)per retrieval for PGT-M patients when compared to patients using preimplantation genetic testing for aneuploidy (PGT-A) (1,2). However, no studies have examined the time to pregnancy and cumulative IVF cycle number for PGT-M patients to achieve unaffected live birth.

Objective: To determine the time and number of oocyte retrievals to achieve live birth for patients undergoing PGT-M for autosomal dominant (AD), autosomal recessive (AR), and X-linked (XL) monogenic disorders.

Methods: We performed an IRB approved retrospective data query of Shady Grove Fertility patients utilizing PGT-A and concurrent PGT-M from 2013 to 2023. The primary outcomes were number of oocyte retrievals to live birth and time from ovarian stimulation start to frozen embryo transfer (FET), clinical pregnancy (CP), live birth (LB) following euploid, unaffected FET. Secondary outcomes included the number of FET cycles to LB and proportion of patients that did not achieve FET, CP, or LB. Kaplan-Meier curves were used to calculate median time to FET, CP and LB for each inheritance pattern group.

Results: There were 664 patients who underwent PGT-A and PGT-M. This included 187 patients with AD disorders, 345 carriers for AR disorders, and 117 with XL disorders. Age at treatment start, BMI, and ovarian reserve markers were comparable.

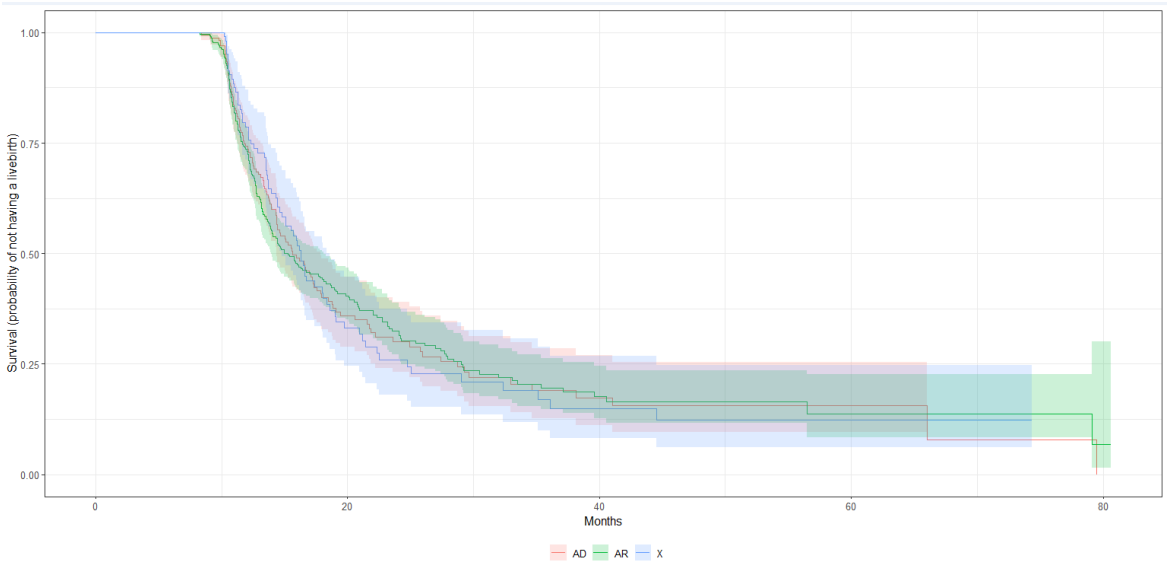
For AD, AR, and XL for cycles, the mean number of oocyte retrievals to LB were 1.7, 1.54, and 1.66, respectively. Of patients who underwent oocyte retrieval, 18.2% of AD, 12.2% of AR, and 15.4% of XL failed to produce a single euploid, unaffected embryo. For AD patients, the median time to FET, CP, and LB were 5.1, 7.1, and 15.6 months, respectively. For AR patients, the median time to FET, CP, and LB were 3.8, 6.4, and 15.3 months, respectively. For XL patients, the median time to FET, CP, and LB were 5.2, 7.9, and 16.3 months, respectively. At one year, 69.7% of AD, 70.7% of AR, and 69.5% of XL patients were pregnant following euploid, unaffected FET. At 2 years, 70% of AD, 67.5% of AR, and 74% of XL patients had a LB following euploid, unaffected FET. The mean number of FETs to LB per patient was 1.41 – 1.47.

Conclusions: In a group of patients with mean normal ovarian reserve markers pursuing PGT-A and concurrent PGT-M, there was a mean requirement of 1.54 - 1.77 oocyte retrievals and 1.42 – 1.47 embryo transfers to achieve live birth following unaffected, euploid FET. The median time to LB was 15.3 – 16.3 months. Of patients who underwent at least one oocyte retrieval, 12.2 – 18.2% ultimately did not have an unaffected, euploid embryo to transfer. Despite an a priori probability of more unaffected euploid embryos for transfer, PGT-M for AR disorders required a similar time to achieve a live birth. Characterizing the treatment history of PGT-M cycles can guide patient counseling and manage expectations.

Demographics, n (%) unless noted otherwise	Autosomal Dominant	Autosomal Recessive	X-linked
n	187	345	117
Age, mean (SD)	33.1 (4.0)	34.1 (3.9)	33.6 (4.2)
< 35 years	121 (64.7)	200 (58.0)	69 (59.0)
35 - <37 years	29 (15.5)	54 (15.7)	16 (13.7)
37 - <40 years	25 (13.4)	57 (16.5)	19 (16.2)
>= 40 years	12 (6.4)	34 (9.9)	13 (11.1)
Race/Ethnicity			
White	102 (65.4)	144 (45.9)	69 (64.5)
Black	4 (2.6)	66 (21.0)	11 (10.3)
Hispanic/Latinx	4 (2.6)	14 (4.5)	2 (1.9)
Asian	19 (12.2)	47 (15.0)	12 (11.2)
Jewish	14 (9.0)	21 (6.7)	6 (5.6)
Multiple/Other	3 (1.9)	4 (1.3)	3 (2.8)
Unknown	10 (6.4)	18 (5.7)	4 (3.7)
BMI, mean (SD)	25.3 (5.2)	26.1 (5.3)	25.5 (5.2)
AMH, median (IQR)	2.92 (1.48, 5.07)	2.94 (1.60, 4.79)	2.51 (1.26, 4.90)
AFC, median (IQR)	19 (12, 26)	17 (12, 26)	18 (12, 27)
Day 3 FSH, mean (IQR)	7.61 (6.38, 9.13)	7.46 (6.18, 8.93)	7.30 (6.12, 9.26)

PGT results			
	Autosomal Dominant	Autosomal Recessive	X-linked
mean embryos biopsied, cycle 1	6.7 (5.9)	5.8 (4.8)	5.2 (4.1)
mean euploid embryos biopsied, cycle 1	3.7 (4.3)	3.4 (3.3)	3.1 (2.8)
mean euploid, unaffected embryos, cycle 1	1.8 (2.2)	2.4 (2.4)	1.9 (1.9
mean embryos biopsied, total	11.2 (7.5)	8.9 (6.4)	8.9 (6.2)
mean euploid embryos biopsied, total	6.3 (5.2)	5.2 (4.0)	5.4 (4.6)
mean euploid, unaffected embryos, total	2.9 (2.5)	3.5 (2.7)	3.3 (3.0)
Euploid embryo (%; total)	54.8	58.5	59.8
Euploid, affected embryo (%; total)	52	28.8	38
Euploid, unaffected embryo (%; total)	48	71.2	62

Reproductive outcomes			
	Autosomal Dominant	Autosomal Recessive	X-linked
Oocytes retrieved, mean (SD)	18.8 (12.4)	18.3 (11.2)	16.9 (9.5)
MIIs, mean (SD)	13.6 (10.1)	12.7 (9.4)	11.7 (8.3)
2PN, mean (SD)	10.8 (8.5)	10.0 (7.9)	9.4 (7.1)
Blast conversion, mean (SD)	5.8 (6.1)	5.1 (4.8)	4.7 (4.2)
Biochemical pregnancy rate (among pregnancies)	8 (5.4)	17 (6.3)	4 (4.4)
SAB rate (among pregnancies)	10 (6.8)	24 (8.9)	12 (13.2)
1-year pregnancy rate, % (95% CI)	69.7 (61.7 - 75.9)	70.7 (65.2 - 75.4)	69.5 (59.4 - 77.1)
2-year LBR, % (95% CI)	70.0 (60.9 - 76.9)	67.5 (61.1 - 72.9)	74.0 (62.5 - 82.0)
Number of retrievals to LB, mean (SD)	1.70 (0.97)	1.54 (0.94)	1.66 (0.93)
Number transfers to LB, mean (SD)	1.47 (1.32)	1.46 (0.91)	1.42 (0.90)
No embryo transfer (%)	34 (18.2)	42 (12.2)	18 (15.4)
No clinical pregnancy (%)	39 (20.9)	74 (21.4)	26 (22.2)
No live birth (%)	69 (36.9)	131 (38.0)	41 (35.0)
Months to embryo transfer, median (95% CI)	5.1 (4.1 - 6.1)	3.8 (3.4 - 4.2)	5.2 (4.6 - 6.5)
Months to clinical pregnancy, median (95% CI)	7.1 (6.5 - 9.6)	6.4 (5.6 - 7.6)	7.9 (6.0 - 9.4)
Months to live birth, median (95% CI)	15.6 (14.4 - 17.9)	15.3 (13.9 - 18.1)	16.3 (14.8 - 18.4)



Financial disclosures:

No financial disclosures

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