American Society for Reproductive Medicine 2018 Scientific Congress & Expo
October 6 to 10, 2018 ● Denver, Colorado, USA

Title:

OLIGOSPERMIA, ASTHENOZOOSPERMIA, AND TERATOZOOSPERMIA ARE NOT ASSOCIATED WITH MORPHOLOGICAL TROPHECTODERM SCORE

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Objective:

The paternal and maternal genomes differentially express developmental genesduring embryogenesis. In mouse-model studies, the trophectoderm (TE) was unable to to proliferate in the absence of the paternal genome despite normal inner cell mass (ICM) formation.[1] This finding suggests a significant male contribution to embryonic TE development, which may be impacted by genomic and clinical consequences of defective spermatogenesis. The current study aimed to evaluate whether the morphologic grade of the TE is affected by impaired spermatogenesis and quantitative and qualitative deficiencies in semen function.

Design:

Retrospective cohort study

Materials and Methods:

The study included patients who underwent IVF stimulation from 2006-2018. Oocyte donation cycles were excluded from analysis. Trophectoderm biopsy and pre-implantation genetic testing for aneuploidy (PGT-A) were performed on select blastocysts. The following data were collected: female partner age and body mass index (BMI), male partner age, days of abstinence preceding semen analysis (SA), type of ejaculate (fresh or frozen ejaculate vs. testicular sperm),

SA parameters (volume, concentration, motility, total motile count (TMC), and morphology), type of oocyte insemination (intracytoplasmic sperm injection (ICSI) vs. conventional insemination), number of blastocysts biopsied, and number of euploid embryos. Embryos were grouped by TE quality, where "high" quality embryos were assigned grades of A or B while "low" quality embryos were assigned grades of C or D. Data were analyzed using a Student's T-test, Chi-square, Fisher's Exact test, and multivariate logistic regression.

Results:

A total of 64,937 embryos from autologous IVF cycles were included for analysis. Embryos with a high TE grade of A or B were from younger patients (female: 34.7 ± 4.4 y, $p<0.0001$, male: 39.1 ± 5.2 y, $p=0.04$). High TE grade embryos were more likely to have an expansion grade of 5 (28.7%, $p<0.0001$), an ICM grade of A (51.6%, $p<0.0001$), undergo biopsy for PGT-A (42.2%, $p<0.0001$), and have a euploid result (55.8%, $p<0.0001$). Low TE grade embryos were more likely to result from ICSI (76.5%, $p<0.0001$). SA parameters, including morphology, concentration, motility and TMC, days of abstinence, type of ejaculate and rate of re-biospy were similar between groups. When adjusting for confounders and conducting a sub-analysis of severe male factor cases utilizing testicular sperm, TE grade was not associated with SA parameters.

Conclusions:

Trophectoderm development is not impaired in embryos created using sperm from males found to be oligospermic, asthenozoospermic or teratozoospermic. While the presence of the paternal genome is essential for oocyte fertilization and initiation of embryo development, poor sperm quality and quantity do not impede this process. Genome-wide association studies are needed to further uncover genes associated with male factor infertility that may impact oocyte activation, fertilization and early embryo development. Future study of the sperm genome and epigenome may also offer insight into methods optimizing reproductive outcomes from ART.

Support:

None.

References:

1. Barton SC, et al., "Development of gynogenetic and parthenogenetic inner cell mass and trophectoderm tissues in reconstituted blastocysts in the mouse." *Development* (90) 1985: 267-285.
2. Hardy K and Handyside A, "Metabolism and cell allocation during parthenogenetic pre-implantation mouse development." *Molec Rep and Dev* (43) 1996: 313-322.

Table 1:

Baseline Demographics and Cycle Characteristics for Embryos with High Quality (A/B) vs. Low Quality (C/D) Trophectoderm Grades

	High TE Grade (n=40,945)	Low TE Grade (n=23,992)	P Value
Female Partner Age (y)	34.7 ± 4.4	35.5 ± 4.6	<0.0001
Male Partner Age (y)	39.1 ± 5.2	39.7 ± 5.3	0.04
Female Partner BMI (kg/m^2)	24.0 ± 4.6	24.0 ± 4.5	0.51
SA Volume (mL)	2.8 ± 2.1	2.8 ± 2.3	0.52
SA Concentration (million sperm)	64.6 ± 49.9	64.0 ± 49.5	0.14
% Motility	53.0 ± 17.6	52.8 ± 17.4	0.29
SA Total Motile Count (million sperm/mL)	104 ± 128	103 ± 133	0.21
% Morphology	5.2 ± 4.2	5.1 ± 4.0	0.18
% Morphology - Normal - Abnormal	 25,632 (69.9%) 11,054 (30.1%)	 14,857 (69.2%) 6623 (30.8%)	0.08
Oligospermia	3809 (9.3%)	2097 (8.7%)	0.15
Days of Abstinence preceding SA	4.0 ± 3.5	4.0 ± 3.7	0.84
Embryo Expansion Grade - 3 - 4 - 5 - 6	 4361 (10.7%) 21,311 (52.1%) 11,764 (28.7%) 3503 (8.6%)	 7400 (30.9%) 12,803 (53.4%) 2877 (12.0%) 909 (3.8%)	<0.0001
Embryo Inner Cell Mass Grade - A - B - C - D	 21,049 (51.6%) 12,515 (30.7%) 5594 (13.7%) 1650 (4.0%)	 6100 (25.6%) 7673 (32.3%) 7029 (29.5%) 3030 (12.7%)	<0.0001
Insemination Type - Conventional - ICSI - Split	 10,203 (20.8%) 29, 406 (71.8%) 1336 (3.3%)	 4983 (20.8%) 18,343 (76.5%) 666 (2.8%)	<0.0001
Ejaculate - Fresh - Frozen	 36,315 (88.7%) 4630 (11.3%)	 21,200 (88.4%) 2792 (11.6%)	0.20

Sperm Source - Fresh Ejaculate - Frozen Ejaculate - Testicular	 20,794 (86.7%) 2570 (10.7%) 628 (2.6%)	 35,608 (87.0%) 4250 (10.4%) 1087 (2.7%)	 0.40
% Biopsied for PGT	17,386 (42.2%)	7829 (32.6%)	<0.0001
% Re-biopsied	476 (2.7%)	184 (2.35%)	0.07
Euploid Embryo	9692 (55.8%)	2984 (38.1%)	<0.0001