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Relationship between paternal somatic health and assisted reproductive technology outcomes

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Objective: To study the association between paternal medical comorbidities and the outcomes of assisted reproductive technology (ART).
Design: Retrospective cohort study.
Setting: Academic reproductive medicine center.
Patient(s): We analyzed fresh ART cycles uszing freshly ejaculated sperm from the male partner of couples undergoing ART cycles from 2004 until 2014. We recorded patient and partner demographic characteristics. The cohort was linked to hospital billing data to obtain information on selected male partners' comorbidities identified using ICD-9-CM codes.
Intervention(s): None.
Main Outcome Measure(s): Fertilization, clinical pregnancy, miscarriage, implantation, and live-birth rates as well as birth weights and gestational ages.
Result(s): In all, we identified 2,690 men who underwent 5,037 fresh ART cycles. Twenty-seven percent of men had at least one medical diagnosis. Men with nervous system diseases had on average lower pregnancy rates (23% vs. 30%) and live-birth rates (15% vs. 23%) than men without nervous system diseases. Lower fertilization rates were also observed among men with respiratory diseases (61% vs. 64%) and musculoskeletal diseases (61% vs. 64%) relative to those without these diseases. In addition, men with diseases of the endocrine system had smaller children (2,970 vs. 3,210 g) than men without such diseases. Finally, men with mental disorders had children born at an earlier gestational age (36.5 vs. 38.0 weeks).
Conclusion(s): The current report identified a possible relationship between a man's health history and IVF outcomes. As these are potentially modifiable factors, further research should determine whether treatment for men's health conditions may improve or impair IVF outcomes. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Male infertility, fertilization in vitro, comorbidity, health

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Aberrations in reproductive fitness may be a harbinger of medical diseases in men. For example, most studies demonstrate that obesity and tobacco use impair semen quality (1, 2). Indeed, infertile men have higher rates of medical comorbidities compared with fertile controls (3). Moreover, a recent study found an association of medical comorbidity and medication use with reduced semen quality (4). Little is known about how a man's somatic health influences fertility outcomes.

Evidence suggests that a woman's health can impact her fertility. Obesity, diabetes, and thyroid disease are some of the factors that have been shown to impair reproductive outcomes (5–7). However, limited data suggest that male factors may affect the outcomes of assisted reproductive technology (ART). Some but not all studies of paternal age suggest adverse effects on IVF success (8, 9). Male obesity also has uncertain effects on male fertility and IVF outcomes (10–14). One report of eight couples with a diabetic male partner reported lower pregnancy rates but similar

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fertilization rates compared with cycles performed among couples with nondiabetic men (15). To date, no study has examined the association between a man's overall health and IVF outcomes. Given that somatic health has been shown to influence semen quality, we sought to determine the relationship between a man's medical comorbidities and IVF outcomes.

METHODS

Study Population

After Institutional Review Board approval, we identified couples undergoing IVF cycles at the Stanford Fertility and Reproductive Health Center from January 2004 until 2014. We examined only IVF cycles using fresh ejaculated sperm from the male partner for whom complete outcome data were available. We recorded patient and partner demographic characteristics from standard cycle data collection. The cohort was linked to hospital billing data to obtain information on the male partners' comorbidities identified using ICD-9-CM codes and limited to men evaluated within the health care system. Neoplasms were defined as codes 140-239.9; endocrine, nutritional, metabolic, and immunity disorders as codes 240-279.9; diseases of the blood and blood-forming organs as 280-289.9; mental health disorders as 290-319; diseases of the nervous system and sense organs as 320-389.9; diseases of the circulatory system as 390-459.9 (excluding 456.4; varicocele was excluded given its strong association with male factor infertility); diseases of the respiratory system as 460-519.9; diseases of the digestive system as 520-579.9; diseases of the genitourinary system as 580-629.9; diseases of the skin and SC tissue as 680-709.9; and diseases of the musculoskeletal system and connective tissue as 710-739.9. The score on the Charlson Comorbidity Index (CCI) was calculated using the modifications of Quan et al. (16).

Outcome Ascertainment

Cycle outcomes were queried from the Stanford IVF clinical database. We calculated fertilization rate (number of embryos derived per oocyte injected or inseminated), clinical pregnancy rate (fetal heartbeat on ultrasound per IVF cycle started), miscarriage rate (spontaneous abortion per IVF cycle started), implantation rate (gestational sacs per embryo transferred), live-birth rate (births per IVF cycle started), singleton birth weight, and gestational age at singleton delivery.

Data Analysis

Associations between selected medical history variables and binary outcome variables (i.e., pregnancy, miscarriage, implantation, and live-birth rates) were modeled using generalized estimating equation models; continuous outcome variables (i.e., fertilization rate, birth weight, and gestational age) were analyzed using mixed effects linear regression models. All models allowed a man to contribute more than one IVF cycle to the analysis. Models (fertilization, pregnancy, implantation, miscarriage, and live-birth rate) were adjusted for male age, female age, year of IVF cycle, and female smoking based on review of the literature of relevant factors associated with male health history and IVF outcomes. Birth weight models were adjusted for male age, female age, year, female smoking, race, number of eggs retrieved, number of embryos transferred, prior pregnancy, and gestational age at delivery. Gestational age models were adjusted for male age, female age, year, female smoking, race, number of eggs retrieved, number of embryos transferred, and prior pregnancy. Birth outcome data are limited to singletons. All P values were two sided, with $P<.05$ considered statistically significant. Analyses were performed using SAS (ver. 9.4, SAS).

RESULTS

In all, we identified 2,690 men who had outpatient data available. The partners of those men underwent 5,037 fresh ART cycles—2,278 were IVF only, and 2,459 used intracytoplasmic sperm injection (ICSI). Of the cycles, 7.2% were classified as having a male factor. Overall, the mean age of the man was 38.5 years (interquartile range [IQR], 34.5–41.7), and the mean age of the female partner was 38.2 years (IQR, 35–42; Table 1). Of the 59% of men with available data on race, 46% were Caucasian. Twenty-seven percent of men had at least one medical diagnosis, and 15% had two or more diagnoses. Ninety-six percent of men had a CCI of 0. There was no significant association between the diagnosis of male factor infertility and medical comorbidity.

After stratifying by organ system and controlling for the covariates described above, differences were noted for ART outcomes based on any medical condition in the male partner (Table 2). Men with nervous system diseases had partners with lower pregnancy rates (23% vs. 30%; $P=.04$) and live-birth

TABLE 1

Characteristics of cohort.

Characteristic	Value
N	2,690
Fresh cycles, n	5,037
Male age at SA, n (%)	38.5 (5.7)
20–29	61 (1.2)
30–39	2,443 (48.6)
40–50	2,276 (45.2)
50+	252 (5.0)
Race, n (%)	
Caucasian	1,360 (27.29)
Asian	500 (10.03)
Other	1,103 (22.13)
Unlisted	2,021 (40.55)
Partner age, n (%)	38.2 (4.5)
20–29	173 (3.4)
30–39	2,789 (55.4)
40+	2,075 (41.2)
Year of evaluation	
2004–7	2,911 (57.8)
2008–14	2,126 (42.2)
Female smoking, n (%)	61 (1.2)
CCI, n (%)	
0	4,959 (98.5)
1	57 (1.1)
≥2	21 (0.4)

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