Semen quality and pregnancy loss in a contemporary cohort of couples recruited before conception: data from the Longitudinal Investigation of Fertility and the Environment (LIFE) Study

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Objective: To study the relationship between semen quality and pregnancy loss in a cohort of couples attempting to conceive.

Design: Observational prospective cohort.

Setting: Not applicable.

Patient(s): Three hundred and forty-four couples with a singleton pregnancy observed daily through 7 postconception weeks of gestation.

Intervention(s): None.

Main Outcome Measure(s): Association between semen quality and pregnancy loss.

Result(s): Ninety-eight (28%) of the couples experienced a pregnancy loss after singleton pregnancy. No differences were observed in semen volume, sperm concentration, total sperm count, sperm viability, or sperm morphology (World Health Organization [WHO] and strict criteria) by couple’s pregnancy loss status irrespective of whether they were analyzed continuously or as dichotomous variables per the WHO 5th edition semen criteria. A dichotomous DNA fragmentation measure of ≥30% was statistically significantly associated with pregnancy loss. No association was identified with other sperm morphometric or movement measures. Of the 70 couples who re-enrolled after a pregnancy loss, 14 experienced a second loss. Similar findings were identified when examining semen quality from couples with recurrent pregnancy loss.

Conclusion(s): Although a few trends were identified (e.g., DNA fragmentation), general semen parameters seemed to have little relation with risk of pregnancy loss or recurrent pregnancy loss at the population level. However, given that 30% of pregnancies end in miscarriage and half the fetal genome is paternal in origin, the findings await corroboration.

Keywords: DNA fragmentation, fertility, male infertility, semen analysis, spontaneous abortion

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Received February 14, 2017; revised June 7, 2017; accepted July 10, 2017.

M.L.E. is an advisor for Sandstone Diagnostics and Glow. K.J.S. has nothing to disclose. S.D.K. has nothing to disclose. G.M.B.L. has nothing to disclose.

Supported by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (contracts N01-HD-3-3355, N01-HD-3-3356, N01-HD-3-3358, and HHSN275200001). Reprint requests: Michael L. Eisenberg, M.D., Department of Urology, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94305-5118 (E-mail: eisenberg@stanford.edu).

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Pregnancy loss affects 30% of pregnancies (1–3). Although most pregnancy losses are multifactorial in nature, most identified etiologies center around the woman. However, as a man contributes 50% of the genome to an embryo, it is reasonable to assume that male factors may also contribute to pregnancy loss. Indeed, up to 50% of all cases of infertility are due to a male factor (4, 5). To date, there are relatively limited data
on male factors contributing to pregnancy loss, especially research that captures loss during the peak weeks in early gestation. However, a recent study by our group using the same cohort for the present analysis did identify an association between paternal lifestyle factors (i.e., caffeine consumption) and pregnancy loss in a prospective cohort study (6).

Recurrent pregnancy loss (RPL), defined as two or more consecutive losses for a couple, affects 1% to 5% of women (1, 3). As with pregnancy loss, the evaluation for RPL centers around the woman. Yet even after uterine, oocyte, and chromosomal factors are excluded, an idiopathic etiology is left approximately 50% of the time (3). Investigators have also attempted to determine the male factors associated with RPL. Zidi-Draj et al. (7) reported higher levels of sperm immotility, abnormal morphology, and elevated sperm DNA fragmentation in the male partners in couples with RPL. Elevated levels of sperm aneuploidy have also been reported among men from couples with RPL (8). However, as these studies relied on case control designs with fertile couples serving as the control groups, prospective studies are required to confirm the reported associations.

Surprisingly, few studies have attempted to assess semen quality and the risk of incident pregnancy loss. This may reflect the very few couple-based preconception cohort studies conducted worldwide, with even fewer collecting semen samples (9). Preconception cohort studies are needed to address this question, given the marked concentration of losses early in pregnancy or before seeking prenatal care. Using data from the Longitudinal Investigation of Fertility and the Environment (LIFE) Study, we examined the association between semen quality and pregnancy loss in a prospective study. Given that RPL represents a unique group, we also performed a subanalysis on couples with two or more losses.

MATERIALS AND METHODS

Study Design and Population

The study cohort comprised 347 couples (69%) whose female partners had an observed pregnancy (denoted by a positive urine pregnancy test) while participating in the LIFE Study, which was designed to examine the association between environmental and lifestyle factors and fecundity end points, including pregnancy loss. Three couples with twin pregnancies were excluded, resulting in a cohort comprising 344 couples with singleton pregnancies.

The LIFE Study used population-based sampling frameworks to recruit couples discontinuing contraception for purposes of becoming pregnant from 16 counties in Michigan and Texas. By design, the eligibility criteria were minimal and included [1] couples in a committed relationship; [2] ability to communicate in English or Spanish; [3] women aged 18 to 40 and men aged ≥ 18 years; [4] women with menstrual cycles between 21 and 42 days, as required by the fertility monitors; [5] no history of injectable hormone contraception in the past year; [6] no clinically diagnosed infertility in either partner; and [7] off contraception < 2 months. Before enrollment, the women’s urines were tested to ensure they were not already pregnant.

Human subjects approval was obtained from the participating institutions, and all men and women gave written informed consent before data collection. Complete details about the study design of LIFE have been previously published elsewhere (10).

Data Collection and Follow-up

Couples were interviewed individually upon enrollment to ascertain their sociodemographic, lifestyle, and medical history information, followed by measurement of height and weight to calculate body mass index (BMI). The couple was then instructed in the completion of daily journals to record their lifestyle in a manner consistent with how people think about such exposures (e.g., number of cigarettes smoked per day, number of alcoholic and caffeinated beverages consumed per day, number of daily multivitamins). Pregnant women completed their journals daily through 7 postconception weeks’ gestation then continued as monthly journals until a loss or delivery. Couples experiencing a loss had the option of re-entering the study.

Biospecimen Collection and Analysis

Semen samples were collected via masturbation without the use of any lubricant after 2 days of abstinence using home collection kits, which included an insulated shipping container (Hamilton Research) for maintaining sperm integrity at the time of enrollment. Other studies have used similar approaches (11, 12). All semen samples were received at the study’s andrology laboratory.

The complete laboratory methodology has been previously reported (10). Briefly, an aliquot of semen was placed in a 20-μm-deep chamber slide (Leja), and sperm motility was assessed using the HTM-IVOS (Hamilton Thorne) computer-assisted semen analysis system (CASA). Sperm concentration was also measured using the IVOS system and the IDENT stain. Microscope slides were prepared for sperm morphometry and morphology assessments. An aliquot of whole semen was diluted in TNE (Tris, NaCl, and EDTA) buffer with glycerol and frozen for the sperm chromatin stability assay (SCSA) analysis (13). Sperm viability was determined by hypo-osmotic swelling (HOS) assay.

To ensure integrity of the 24-hour analysis, steps were taken to ensure the quality of the semen parameters. A thermometer was attached to all collection jars to ensure the temperature of the sample was within acceptable limits (all were). Upon receipt, the andrology laboratory assessed the integrity of the samples, and all were found to be acceptable.

Home Fertility and Pregnancy Testing

Women were trained in the use of the Clearblue digital fertility monitor (SPD Swiss Precision Diagnostics GmbH), which has been demonstrated to be accurate in detecting ovulation relative to the gold-standard, ultrasound visualization (14). The monitor records the ratios of estrone-3-glucuronide (E3G) and luteinizing hormone (LH) and stores data for up to 6 months. Study personnel downloaded the data every 45 days. Day of ovulation in the study was approximated by the day of peak LH as indicated by the fertility monitor.
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