Semen quality and time to pregnancy: the Longitudinal Investigation of Fertility and the Environment Study

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Objective: To assess semen parameters and couple fecundity as measured by time to pregnancy (TTP).
Design: Observational prospective cohort with longitudinal measurement of TTP.
Setting: Sixteen Michigan/Texas counties.
Patient(s): A total of 501 couples discontinuing contraception were followed for 1 year while trying to conceive; 473 men (94%) provided one semen sample, and 80% provided two samples.
Intervention(s): None.
Main Outcome Measure(s): Using prospectively measured TTP, fecundability odds ratios (FORs) and 95% confidence intervals (CIs) were estimated for 36 individual semen quality parameters accounting for repeated semen samples, time off contraception, abstinence, enrollment site, and couples' ages, body mass indices, and serum cotinine concentrations.
Result(s): In adjusted models, semen quality parameters were associated with significantly shorter TTP as measured by FORs >1: percent motility, strict and traditional morphology, sperm head width, elongation factor, and acrosome area. Significantly longer TTPs or FORs <1 were observed for morphologic categories amorphous and round sperm heads and neck/midpiece abnormalities. No semen quality parameters achieved significance when simultaneously modeling all other significant semen parameters and covariates, except for percent coiled tail when adjusting for sperm concentration (FOR 0.99; 95% CI 0.99–1.00). Male age was consistently associated with reduced couple fecundity (FOR 0.96; 95% CI 0.93–0.99), reflecting a longer TTP across all combined models. Female but not male body mass index also conferred a longer TTP (FOR 0.98; 95% CI 0.96–0.99).
Conclusion(s): Several semen measures were significantly associated with TTP when modeled individually but not jointly and in the context of relevant couple-based covariates. (Fertil Steril® 2014;101:453–62. ©2014 by American Society for Reproductive Medicine.)
Key Words: Epidemiology, fecundity, semen, sperm, time to pregnancy

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Semen quality is believed to be informative about male fecundity, which is defined as men's biologic capacity for reproduction irrespective of pregnancy intentions (1). Semen analysis remains the clinical standard for assessing male fecundity and related impairments, including hormone production (2), and key components, such as sperm concentration, motility, and morphology, are reported to be capable of classifying men by fertility potential (3). The World Health Organization (WHO) publishes reference values for semen parameters as derived from a compilation of largely retrospective research that represents men from various countries (4, 5). However, the predictive value of these reference value parameters has long been debated, with no single or set of

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semen parameters being highly predictive of male fertility (6–8). To this end, authors have noted the need for inclusion of the female partner for etiologic and prediction models (9), along with the development of new biomolecular or methodologic (e.g., sperm energy index, omics) approaches beyond functional tests for assessing and predicting male fecundity (10, 11).

A valuable literature suggests that semen quality is important for pregnancy, although most research relies on samples of couples seeking infertility treatment or pregnant women (12–14). Noticeably absent are prospective cohorts with the preconception recruitment of couples of unknown fertility status (15). Only two previous studies used prospective cohort designs with preconception enrollment of couples in which semen quality was assessed in relation to time to pregnancy (TTP) (16, 17). Unique strengths of this design are the inclusion of all couples trying for pregnancy and not just those achieving a recognized pregnancy, and the ability to assess semen quality in the context of couples' demographics and lifestyle, consistent with the couple-dependent nature of reproduction. Bonde et al. (16) first assessed the association between semen quality and the probability of pregnancy within 6 months of observation for 430 Danish couples planning their first pregnancies who were recruited from trade unions. Although no significant associations were observed between semen volume and motility, sperm concentration up to 40 $\times$ 10^6/mL and percent normal morphology (10%–60%) were independently associated with the probability of pregnancy. The findings were corroborated using computer-assisted semen analysis (CASA) techniques (18). Zinaman et al. (17) recruited a convenience sample of 210 US couples who were either discontinuing or off contraception for $<$3 months for purposes of becoming pregnant. Using prospectively measured TTP for up to 12 months, both sperm count and percentage of normal sperm were associated with couple fecundity (17). Statistical analyses for both studies included attention to couples' ages, body mass indices (BMIs), and cigarette smoking histories. At least one study reported no association between semen quality parameters and TTP in either fresh samples or after density gradient separation among fertile men (19). We designed the Longitudinal Investigation of Fertility and the Environment (LIFE) Study to fully explore a spectrum of environmental and lifestyle factors and couple fecundity.

MATERIALS AND METHODS

Design and Study Population

The LIFE Study used a prospective cohort design to enroll 501 couples discontinuing contraception for purposes of becoming pregnant from 16 targeted counties in Michigan and Texas. State-specific sampling frameworks were needed for recruiting purposes, given the absence of uniform registries for identifying couples planning pregnancy. Specifically, we utilized the Texas fishing/hunting license registry and a commercial marketing database for Michigan. Introductory letters were sent to the target population, followed by telephone screening with each partner within 2 weeks. Few differences were observed with regard to socio-demographic or reproductive characteristics by site (20). Given the limited empirical evidence regarding the determinants of couple fecundity from a population perspective, the cohort was designed to be inclusive and only excluded couples with clinically diagnosed infertility. Inclusion criteria were [1] women aged 18–40 and men aged $\geq$ 18 years; [2] in a committed relationship; [3] women's menstrual cycles between 21 and 42 days; [4] no injectable contraceptives within the past year; [5] planning a pregnancy and off contraception for $<$2 months; and [6] an ability to communicate in English or Spanish.

Data Collection and Operational Definitions

Research assistants traveled to couples' homes and completed baseline in-person interviews that were conducted separately with each partner of the couple, followed by anthropometric assessments to measure height (in centimeters), weight (in kilograms), and hip and waist circumferences (in centimeters) (21). Baseline urine samples were tested to ensure that women were not pregnant. Women recorded menstruation and sexual intercourse in daily journals and used the Clearblue Easy home urinary-based fertility monitor (Swiss Precision Diagnostics, formerly Unipath). This monitor tracks the rise in estrone-3-glucuronide, a metabolite of estrogen, and LH, and displays a low, high, or peak fertility prompt for timing intercourse relative to ovulation. The monitor is reported to be 99% accurate in detecting the LH surge compared with vaginal ultrasonography (22). We used the monitor date for menses along with daily journal information to establish menstrual cycles and TTP. Women also were trained in the accurate use of the Clearblue Easy home pregnancy test, which is sensitive for detecting 25 mIU/L of hCG. Each partner of the couple was remunerated $75 for complete participation. Human subjects' approval was received from all collaborating institutions, and all study participants gave informed consent before data collection.

Semen Collection

Male partners were asked to collect a baseline sample and another the following month, irrespective of pregnancy status. Men collected samples via masturbation without the use of any lubricant after 2 days of abstinence using home collection kits that comprised an insulated shipping container (Hamilton Research) for maintaining sperm integrity (23), a glass specimen jar with an attached temperature data logger (I-Button, Maxim Integrated), a sperm migration straw filled with hyaluronic acid and plugged at one end, and packing materials (Vitrotubes #3520, VitroCom) (24). Couples were instructed to freeze insulation packs, refrigerate migration straws, and to keep the remainder of the kit at room temperature. After collection, the male placed the open end of the migration straw into the semen as a global marker of motility at specimen collection and recorded the date of last ejaculation and any spillage on labels. Semen was shipped via prepaid overnight service, and analyses were conducted the next day, consistent with the survival of some sperm past 24 hours and the integrity of chromatin structure (25, 26).