Title

Use of at-home sperm concentration testing in a male hormonal contraceptive efficacy clinical trial

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RESEARCH LETTER

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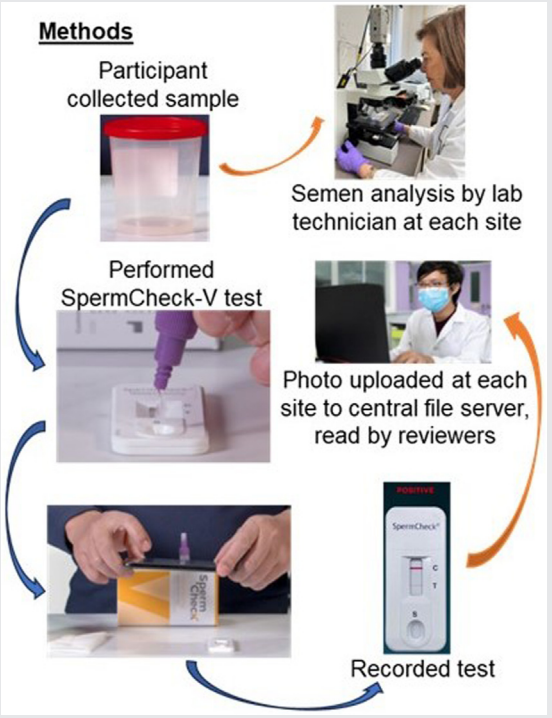
OBJECTIVE

In hormonal male contraception (HMC) trials, the likelihood of conception is related to sufficient suppression of sperm concentration, with ≤1 million/mL associated with effective contraception (1), regardless of motility assessment (2). Participants in HMC trials typically provide semen samples for laboratory analysis, which is burdensome for them and costly for trial sites. We previously demonstrated that 38 participants at one site in a multicenter HMC trial performed and interpreted the result of an at-home sperm concentration test kit under supervision of a laboratory scientist at the study site with 100% accuracy for sperm concentrations of >0.2 million sperm/mL as positive and 99% accuracy for sperm concentrations of ≤0.2 million sperm/mL as negative (3). To examine the practicality of this test in a broader population, we recruited participants from the same HMC trial to perform at-home testing and compared their reported results with the interpretations by two masked reviewers and sperm concentrations determined by laboratory-based semen analysis.

STUDY DESIGN

Fifty-nine participants enrolled in a contraceptive efficacy trial "Study of Daily Application of Nestorone® (NES, segesterone acetate) and Testosterone (T) Combination Gel for Male Contraception" (NCT 03452111) from four US sites (Los Angeles, Seattle, Sacramento, and Salt Lake City) and one UK site (Edinburgh) participated in this substudy. Eligible male

FIGURE 1



Study flow of at-home and laboratory sperm concentration analyses. Participants provided semen samples, performed and interpreted at-home testing, photographed the cartridge using a mobile phone, and brought samples to clinics. Clinic staff uploaded the collection date and time, time of test reading, participants' interpretation, and cartridge photographs to a central file manager. Each site's laboratory determined sperm concentration following the World Health Organization Laboratory Manual for the Examination and Processing of Human Semen, Fifth Edition (4). At the end of the substudy, independent reviewers interpreted the tests from the uploaded photographs.

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Attestation statements: Subjects in this trial have not concomitantly been involved in other randomized trials. Data regarding any subjects in the study has not been previously published unless specified. Data will be made available to the editors of the journal for review or query on request.
Data sharing statement: The data will be made available to others only after the product has been approved by the Food and Drug Administration.

TABLE 1

SpermCheck Vasectomy interpretations by participants and reviewers compared with laboratory-determined concentrations.

	SpermCheck Vasectomy interpretation					
	Participants n = 254 semen samples			Laboratory reviewers[a] n = 254 semen samples		
Laboratory sperm concentration	Negative[b]	Positive[c]	Total	Negative[b]	Positive[c]	Total
≤0.2 million/mL	85 (88.5%)	11 (11.5%)	96 (37.8%)	89 (92.7%)	7 (7.3%)	96 (37.8%)
>0.2 million/mL	17 (10.8%)	141 (89.2%)	158 (62.2%)	23 (14.6%)	135 (85.4%)	158 (62.2%)
Total	102 (40.2%)	152 (59.8%)	254 (100%)	112 (44.1%)	142 (55.9%)	254 (100%)
Sensitivity	141/158 (89.2%; 95% CI, 84.9%–93.6%)			135/158 (85.4%; 95% CI, 80.6%–90.2%)		
Specificity	85/96 (88.5%; 95% CI, 82.0%–95.0%)			89/96 (92.7%; 95% CI, 87.5%–97.9%)		

Note: The dark gray–shaded cell indicated that the false-negative rates for participants' and laboratory reviewers' readings were 10.8% (95% CI, 6.4%–16.7%) and 14.6% (95% CI, 9.1%–20.1%), respectively. The light gray–shaded cell indicated that the false-positive rates for participants' and laboratory reviewers' readings were 11.5% (95% CI, 5.1%–17.8%) and 7.3% (95% CI, 2.1%–12.5%), respectively. The concordance rate of the participants' and reviewers' readings was 92% (κ, 0.83; 95% CI, 0.77–0.91). CI = confidence interval.

[a] Two laboratory-based scientists masked to the participant's and laboratory's results reviewed photographs of the test kits at the end of the study. The concordance rate of the two masked laboratory reviewers' readings was 95% ($\kappa = 0.89$; 95% CI, 0.83–0.95).

[b] The test should be negative with a sperm concentration of ≤0.2 million/mL.

[c] The test should be positive with a sperm concentration of >0.2 million/mL.

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participants entered the suppression phase and applied Nestorone/Testosterone gel on both shoulders and upper arms daily. Laboratory-evaluated sperm concentrations were assessed every 2 to 4 weeks, and the couple entered the efficacy phase when two consecutive sperm concentration were ≤1 million/mL. The substudy flow and procedures are shown in Figure 1 (4). Participants completed a questionnaire assessing at-home sperm test acceptability (3) after completing the substudy (the details on study participants and study design are shown in the Supplemental Materials, available online).

The at-home test kits (SpermCheck Vasectomy) were provided by the manufacturer to US sites and purchased by the UK study site. The test kit is a sensitive lateral flow immune-chromatographic device that detects sperm-specific acrosome protein SP-10 (5). All semen samples were analyzed in each site's laboratory following World Health Organization Laboratory Manual for the Examination and Processing of Human Semen, Fifth Edition (4). Decisions for the main study were based only on laboratory-assessed sperm concentration (the methods and statistical analysis are shown in the Supplemental Materials).

RESULTS

Fifty-nine participants produced 278 samples; 254 samples (91.4%) had readings from both the participant and laboratory reviewers. Table 1 shows the participants' at-home reading, laboratory reviewers' interpretation of cartridge photographs, laboratory sperm concentration, and sensitivity and specificity of the assessments. The false-negative rates for participants' and laboratory reviewers' readings were 10.8% (95% confidence interval [CI], 6.4%–6.7%) and 14.6% (95% CI, 9.1%–20.1%), respectively. The percentage of samples in which both the participants' and laboratory reviewers' readings were false-negative was 7.6% (95% CI, 4.0%–12.9%). The percentage of samples in which either or both participants' or reviewers' readings were false-positive was 11.5% (95% CI, 6.0%–19.6%).

Seven of 12 false-negative readings had sperm concentrations of ≤1 million/mL; using a threshold of 1 million/mL provided a false-negative rate of 3.2% (95% CI, 0.4-5.9%). Ten of 12 participants with false-negative tests repeated the test, and all interpreted the subsequent semen sample correctly. Nearly all reported the test kit to be easy to use (98.0%) and interpret as positive for sperm or negative for no/very few sperm (89.9%); 75.5% would prefer using at-home test kits (the results and discussion are shown in the Supplemental Materials).

CONCLUSION

Trial participants accurately performed and interpreted the at-home sperm test. It is possible that accuracy may be further improved with additional training. Although the false-negative rate for participants was 10.8%, no participants had two false-negative tests in a row. Because the HMC trials require two consecutive sperm concentrations of ≤1 million/mL to enter the efficacy phase, false-negative interpretations would be detected by this criterion. Our data suggest that at-home testing can be used with high acceptability by users to monitor sperm concentration and confirm adequate spermatogenesis suppression in HMC studies.

CRediT Authorship Contribution Statement

Christina Wang: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Yanhe Lue:** Writing – review & editing, Writing – original draft, Validation, Resources, Methodology, Investigation, Data curation, Conceptualization. **Ronald S. Swerdloff:** Writing – review & editing, Supervision, Resources, Methodology, Investigation. **Dayton Morris:** Writing – review & editing, Validation, Methodology, Investigation, Data curation. **Youngju Pak:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Brian T.**

Nguyen: Writing – review & editing. **Peter Y. Liu:** Writing – review & editing, Investigation. **Mitchell D. Creinin:** Writing – review & editing, Validation, Supervision, Methodology, Investigation. **Prasanth Surampudi:** Writing – review & editing, Methodology, Investigation. **David Turok:** Writing – review & editing, Supervision, Resources, Investigation. **Kenneth I. Aston:** Writing – review & editing, Resources, Methodology, Investigation. **Richard Anderson:** Writing – review & editing, Supervision, Resources, Investigation. **John Reynolds-Wright:** Writing – review & editing, Validation, Resources, Investigation. **Stephanie T. Page:** Writing – review & editing, Supervision, Resources, Investigation. **John K. Amory:** Writing – review & editing, Supervision, Resources, Investigation. **Clint Dart:** Writing – review & editing, Supervision, Resources, Project administration. **Jeffrey M. Kroopnick:** Writing – review & editing, Supervision, Resources, Funding acquisition. **Min S. Lee:** Writing – review & editing, Resources, Methodology, Funding acquisition. **Regine Sitruk Ware:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition. **Diana L. Blithe:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of Interests

C.W. has nothing to disclose. Y.L. has nothing to disclose. R.S.S. has nothing to disclose. D.M. has nothing to disclose. Y.P. has nothing to disclose. B.T.N. has nothing to disclose. P.Y.L. has nothing to disclose. M.D.C. has nothing to disclose. P.S. has nothing to disclose. D.T. has nothing to disclose. K.I.A. has nothing to disclose. R.A. has nothing to disclose. J.R.-W. has nothing to disclose. S.T.P. has nothing to disclose. J.K.A. has nothing to disclose. C.D. has nothing to disclose. J.M.K is an employee of National Institutes of Health and sponsor of the study. M.S.L. is an employee of National Institutes of Health and sponsor of the study. R.S.W. is an employee of the Population Council, a nonprofit research organization, and a sponsor of the study. D.L.B. is an employee of National Institutes of Health and sponsor of the study.

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