Operating characteristics of follicle-stimulating hormone in azoospermic men

Matthew S. Christman, M.D.,[a] Suzanne R. Gudeman, M.D.,[a] Justin J. Nork, D.O.,[a] R. Chanc Walters, M.D.,[b] James O. L'Esperance, M.D.,[a] and Donald S. Crain, M.D.[a]

[a] Department of Urology, Naval Medical Center San Diego, San Diego, California; and [b] Department of Urology, Naval Medical Center Portsmouth, Portsmouth, Virginia

Objective: To validate factors predictive of nonobstructive azoospermia (NOA) and to determine the operating characteristics of FSH for predicting NOA.
Design: Retrospective cohort study.
Setting: Tertiary care military treatment facility.
Patient(s): One hundred forty azoospermic males undergoing infertility evaluation.
Intervention(s): Standard evaluation included history and physical, hormonal workup, and genetic evaluation. Diagnostic testicular biopsy was offered to characterize patients as obstructive azoospermia (OA) or NOA.
Main Outcome Measure(s): Semen volume, semen fructose, FSH, T, E_2, PRL, testicular atrophy.
Result(s): Seventy-eight of 140 azoospermic patients underwent a biopsy. The ability to predict NOA based on logistic regression was statistically significant for FSH and testicular atrophy. On multivariate analysis, only FSH remained predictive of NOA. The area under the FSH receiver operating characteristic curve was 0.847, which is significant. The cut point of FSH with the highest likelihood ratio of predicting NOA on biopsy was $\geq$12.3 mIU/mL.
Conclusion(s): FSH remains the best predictor of NOA. With full knowledge of the operating characteristics of FSH in this population, a patient can be properly educated and treatment can be individualized, based on the specific risk associated with that subject's measured FSH. (Fertil Steril® 2014;101:1261–5. ©2014 by American Society for Reproductive Medicine.)
Key Words: Follicle stimulating hormone, infertility, azoospermia, operating characteristics

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Azoospermia is defined as the complete absence of sperm in the ejaculate of two separate specimens. It is responsible for 10%–15% of male factor infertility (1). The incidence of azoospermia in the general male population is estimated to be 2% overall (2). The initial azoospermia evaluation consists of a complete history, physical, and FSH and T measurement (3). Once azoospermia has been identified, the goal is to determine prognosis and direct treatment options. Azoospermia is generally categorized as either obstructive azoospermia (OA) or nonobstructive azoospermia (NOA).

FSH is released by the anterior pituitary and stimulates spermatogenesis in the testis. Its role in the hypothalamic-pituitary-testicular axis allows FSH to be used as a serum marker of spermatogenesis (4). Values in the upper normal range often indicate impaired spermatogenesis, while marked elevation of FSH is diagnostic of abnormal spermatogenesis and therefore suggestive of NOA. In these latter cases, no testicular biopsy is necessary (3). However, no specific FSH cut points were suggested in this American Urological Association best practice statement to aid with management of these patients.

We aimed to validate factors predictive of NOA and determine the operating characteristics of FSH for predicting NOA. We hypothesized that an optimal cut point of FSH, based on sensitivity and specificity, could be determined to identify NOA and prevent unnecessary testicular biopsies.

Received October 4, 2013; revised December 20, 2013; accepted January 20, 2014; published online March 3, 2014.
M.S.C. has nothing to disclose. S.R.G. has nothing to disclose. J.J.N. has nothing to disclose. R.C.W. has nothing to disclose. J.O.L. has nothing to disclose. D.S.C. has nothing to disclose.
The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.
Reprint requests: Matthew S. Christman, M.D., Naval Medical Center San Diego, 34800 Bob Wilson Drive, San Diego, California, 92134 (E-mail: matthew.christman@med.navy.mil).

Fertility and Sterility® Vol. 101, No. 5, May 2014 0015-0282/$36.00
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http://dx.doi.org/10.1016/j.fertnstert.2014.01.034

MATERIALS AND METHODS

A retrospective cohort study was conducted from 2004 to 2012 after approval by the local Institutional Review Board. Records were reviewed for subjects who presented to an infertility clinic at a tertiary care military treatment facility. Subjects were identified based on an ICD-9 code consistent with azoospermia (606.0).

Azoospermia was confirmed by pellet exam of at least two semen analyses. Standard evaluation of azoospermic men included a history and physical, hormonal workup, and genetic evaluation. The physical was performed with attention to the presence or absence of the vas deferens and testicular size. Testicular atrophy in this series was defined as a testicular long axis (TLA) <4.0 cm. Hormone evaluation consisted of FSH, LH, T, E_2, and PRL. Genetic evaluation included a karyotype, Y-chromosome microdeletion testing, and, when indicated, testing for cystic fibrosis transmembrane conductance regulator. In addition to the semen analysis, some men had evaluation of semen fructose based on low semen volume.

Diagnostic testicular biopsy was offered to all patients with azoospermia. Subjects desiring sperm cryopreservation or sperm extraction for assisted reproduction underwent microdissection testicular sperm extraction. At the time of the procedure, the testicular biopsy was simultaneously obtained for histopathological diagnosis. Some patients had no desire for assisted reproduction and underwent testicular biopsy for diagnostic purposes only. Those suspected clinically to have NOA were counseled that the diagnostic biopsy might not provide any additional value and could induce scarring. Men undergoing sperm extraction underwent T optimization with a goal of 300 ng/dL or greater before the procedure; however, data for the independent variables (predictors) were taken from the initial evaluation, before any prescribed treatments. Those subjects who underwent testicular biopsy were included in the analysis. Specimens with normal spermatogenesis were classified as representing OA; those with absent spermatogenesis or hypospermatogenesis, as representing NOA.

Logistic regression was used to analyze potential predictors of biopsy-proven NOA: semen volume, semen fructose, FSH, T, E_2, PRL, and testicular atrophy. Receiver operating characteristic (ROC) curves were then generated for the factors that predicted NOA on multivariate analysis. Sensitivity, specificity, positive and negative predictive values (PPV, NPV), and positive and negative likelihood ratios (LR+, LR−) were calculated. LR+ is defined as [sensitivity/(1 − specificity)]. LR− is calculated as [specificity/(1 − sensitivity)] (5). Statistical analysis was performed using STATA 12 (StataCorpLP).

RESULTS

A total of 140 azoospermic subjects were identified, of whom 78 had undergone a testicular biopsy. None of the remaining 62 subjects who declined biopsy underwent a sperm extraction procedure. Two subjects were excluded owing to incomplete biopsy reports that prevented classification as either OA or NOA. The median [interquartile range (IQR)] age of the cohort was 30 [27, 33.5] years. Sixty-seven percent (51/76) were classified as NOA, with the remainder having OA. Seventeen of the 51 subjects classified with NOA had hypospermatogenesis, while 34 had no sperm identified at the time of biopsy.

Testicular atrophy was present in 9% (2/22, three missing values [MVs]) and 48% (23/48, three MVs) of OA and NOA subjects, respectively. Those with OA had median [IQR] values of FSH, 4.1 [2.2, 5.5] mIU/mL; LH, 4.4 [3.0, 6.0] IU/L; T, 391 [295, 486] ng/dL; E_2, 21.3 [14.4, 33.1] pg/mL; and PRL, 7.7 [5.6, 12.3] ng/mL. Those with NOA had median [IQR] results of FSH, 15.4 [6.8, 25.5] mIU/mL; LH, 6.7 [5.3, 10.4] IU/L; T, 383 [279, 453] ng/dL; E_2, 21.9 [15.7, 29.9] pg/mL; and PRL, 8.1 [5.5, 12.1] ng/mL. For OA subjects, chromosome analysis revealed 46,XY in 100% (19/19, six MVs) and no Y-chromosome microdeletions (18/18, seven MVs). Similarly, there were no microdeletions in the NOA subcohort (42/42, nine MVs); however, karyotype results demonstrated 46,XY in 91% (39/43), 46,XY with Y-translocation to chromosome 19 in 2% (1/43), 47,XXY in 5% (2/43), and 46,XX in 2% (1/43), with eight MVs. The subject with 46,XX had received a bone marrow transplant from his sister; testicular biopsy in this individual revealed Sertoli cell–only syndrome. Semen volume was 2.0 [1.0, 4.5] mL and 3.0 [2.0, 3.5] mL for OA and NOA, respectively. Semen fructose was negative in 31% (4/13, 12 MVs) of the OA subcohort and in 21% (7/34, 17 MVs) of those with NOA.

The ability to predict NOA based on logistic regression was significant for FSH ($P<.001$) and testicular atrophy ($P=.005$). Odds ratios (ORs) and 95% confidence intervals (CI) were 1.24 [1.10, 1.40] and 9.57 [2.00, 45.82], respectively (Table 1). T ($P=.972$), E_2 ($P=.546$), PRL ($P=.664$), semen volume ($P=.331$), and semen fructose ($P=.464$) were not significant predictors of NOA. On multivariate analysis, FSH remained predictive of NOA (OR, 1.21 [1.06, 1.38]); however, atrophy was not (OR, 4.13 [0.71, 23.86]).

The operating characteristics of FSH were analyzed (Table 2). The area under the ROC curve was 0.847 [0.755, 0.939], which is significant (Fig. 1). The cut point of FSH with the highest LR+ of predicting NOA on biopsy was ≥12.3 mIU/mL. At this value, findings were sensitivity, 63% [48%, 76%]; specificity, 96% [79%, 99.9%]; PPV, 97% [84%, 99.9%]; NPV, 55% [39%, 70%]; LR+, 15.1 [2.2, 104]; and LR−, 0.39 [0.27, 0.56]. The lowest LR− was at a cut point of FSH ≥2.8 mIU/mL. The results were as follows: sensitivity, 94% [84%, 99%]; specificity, 38% [19%, 59%]; PPV, 76% [64%, 86%]; NPV, 75% [43%, 95%]; LR+, 1.5 [1.1, 2.1]; and LR−, 0.16 [0.05, 0.53]. At these respective cut points (≥12.3, ≥2.8), 73% and 76% of the cohort were classified correctly. With a cut point of ≥5.9 mIU/mL, the largest proportion of the cohort was correctly categorized (83%). The results were as follows: sensitivity, 84% [71%, 93%]; specificity, 79% [58%, 93%]; PPV, 90% [77%, 97%]; NPV, 70% [50%, 86%]; LR+, 4.1 [1.8, 8.9]; and LR−, 0.20 [0.10, 0.39].

DISCUSSION

While a diagnostic testicular biopsy can differentiate OA from NOA and establish whether or not spermatogenesis is

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