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Influence of increasing body mass index on semen and reproductive hormonal parameters in a multi-institutional cohort of subfertile men

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Objective: To determine whether obesity affects serum and seminal measures of male reproductive potential among a multi-institutional cohort.
Design: Retrospective multi-institutional cohort study.
Setting: Infertility clinics.
Patient(s): All men referred for male infertility evaluation from 2002 to 2014 (n = 4,440).
Intervention(s): None.
Main Outcome Measure(s): Collected reproductive parameters included hormonal (gonadotropins, T, E_2, PRL) and semen analysis (ejaculate volume, sperm concentration, motility, normal morphology) data. Body mass index (BMI) was calculated for all patients with comparisons to reproductive parameters using univariate and multiparametric models.
Result(s): Based on World Health Organization definitions, 30.9% of the cohort was normal weight (BMI 18.5–24.9), 45.1% overweight (25–29.9), and 23.3% obese (>30). Neither FSH nor LH demonstrated significant correlations with BMI on multivariate analysis. Total T ($r = -0.27$) and the T:E_2 ratio ($r = -0.29$) inversely varied with BMI, whereas E_2 ($r = 0.13$) had a direct correlation. On univariate analyses, BMI had weak but significant negative correlations with ejaculate volume ($r = -0.04$), sperm concentration ($r = -0.08$), motility ($r = -0.07$), and morphology ($r = -0.04$). All parameters remained significant on multivariate modeling with the exception of sperm motility. Rates of azoospermia and oligospermia were also more prevalent among obese (12.7% and 31.7%, respectively) compared with normal weight men (9.8% and 24.5%).
Conclusion(s): In one of the largest cohorts of male fertility and obesity, serum hormone and semen parameters demonstrated mild but significant relationships with BMI, possibly contributing to subfertility in this population. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Body mass index, obesity, semen analysis, endocrinology, male infertility

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For the past several decades, the Centers for Disease Control have raised awareness on the obesity epidemic that is now spreading to global proportions (1–3). Overweight and obese individuals currently make up more than two-thirds of the American adult population (4). With increasing waistlines comes an increased rate of comorbid conditions secondary to associated metabolic and anatomic pathophysiologic changes. Disease processes known to correlate with obesity include diabetes, hypertension, hyperlipidemia, and sleep

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apnea and collectively contribute to the diagnosis of the metabolic syndrome. These obesity-associated comorbidities have ultimately been linked to increased mortality and a reduction in life expectancy (5–7).

The metabolic changes of obesity can also affect reproductive function, thus altering the fecundity of much of our population as evidenced by the recent Centers for Disease Control statistics. In women, obesity is clearly linked to subfertility, as manifested by ovulatory disorders and idiopathic infertility (8). For men, there has been a concerning trend of declining sperm quality noted that mirrors the increasing rates of obesity (9). Spermatogenesis normally requires a controlled testicular environment and intact endocrine signaling through the hypothalamic-pituitary-gonadal axis. Increasing adiposity may alter the testicular milieu in such a way to alter normal sperm production and health.

Cohort studies of specific relationships between semen parameters and obesity in the literature, however, have been inconsistent. Although some data have shown correlations with abnormal sperm number, motility, or morphology, others have suggested that no adverse effects were noted with increasing measures of obesity. Gathering data from individual studies, two meta-analyses completed on the topic came to contradictory conclusions with Sermondade et al. (10) reporting that detrimental changes may occur with increasing body mass index (BMI) and a smaller review by MacDonald et al. (11) countering that no significant relationships were found in their review of the data. In the latter meta-analysis, MacDonald et al. (11) also reported on reproductive hormone changes with obesity with a majority of trials finding negative correlations with T and a few observing positive relationships with estrogen (E) levels.

Although changes in male reproductive hormones with increasing adiposity have been more evident, the effects on sperm number and health remain unclear. An understanding of the relationship between obesity and male fertility will allow physicians to better counsel men planning a family about their body habitus. This study correlates measures of obesity with hormonal and semen parameters among men presenting for fertility evaluation at multiple centers, together representing one of the largest cohorts ever published.

MATERIALS AND METHODS

Patient demographics were captured in institutional review board-approved databases at three North American male infertility clinics. All men referred for clinical infertility evaluation and agreeing to inclusion were entered into respective databases. Two study centers (Study Centers 1 and 2) collected self-reported height and weight at the time of initial patient intake, whereas the remaining center (Study Center 3) measured height and weight at the initial visit. The BMI was calculated for each patient as a ratio of the weight (in kilograms) to height squared (in meters squared). The BMI was then categorized as underweight (<18.5), normal (18.5–24.9), overweight (25–29.9), or obese (>30) based on World Health Organization classifications (12). In addition, obesity was subcategorized as class I (30–34.9), class II (35–39.9), or class III (>40).

Laboratory data including reproductive hormones and semen analyses were collected for all men with available height and weight data from 2002 to July 2014. Only hormonal blood work and semen analyses performed at the time of initial patient evaluation were selected for inclusion to reduce any confounding from fertility-related treatments. Patients without available laboratory data were excluded including those referred for vasectomy reversal, as we do not routinely check preoperative hormones or semen analyses in these men. The reproductive hormone parameters collected included total T, E_2, FSH, LH, and PRL. Units were standardized across the centers for T (in nanomoles per liter) and E_2 (in picomoles per liter). Standard units were used for FSH (in IU per milliliter), LH (in IU per milliliter), and PRL (in nanograms per milliliter). The T:E_2 ratio was calculated as a simple ratio for each patient with available data.

Semen samples were obtained from patients by masturbation with 2–5 days of abstinence before collection. Samples were then prepared in respective CLIA (Clinical Laboratory Improvement Amendments) certified andrology laboratories by one or two technicians specializing in semen analyses. Study Center 1 performed computer-assisted semen analysis quantification, whereas technicians at Centers 2 and 3 performed manual semen evaluation. Ejaculate volume and sperm concentration, motility, and morphology parameters were graded based on World Health Organization 5th edition criteria (13). Morphology data from Center 3 were excluded as they graded based on Kruger strict criteria alone and could not be compared with the other centers. The total motile count was calculated for each patient as the product of ejaculate volume, sperm concentration, and motility. Azoospermia was defined as zero sperm found on initial semen analysis and oligospermia included men with sperm present at concentrations <15 million/mL.

Descriptive statistics were calculated for the overall cohort and individual study centers. Analysis of variance and χ^2 tests were used to compare continuous and categorical variables between study groups with $P<.05$ reported as significant. Nonparametric univariate analyses with Spearman's rank correlation were used to describe relationships between patient BMI and reproductive variables. Due to the high frequency of genetic or congenital abnormalities, azoospermic men were also excluded from subgroup analyses to ascertain whether any variable effects existed. As multiple tests were being performed on the same data set, false discovery correction was performed using the Benjamini-Hochberg procedure. Multiparametric linear models were additionally created to control for any variability due to patient age or study center. Statistical analyses were performed using the R software platform, version 2.15.2.

RESULTS

During the study time period, complete height and weight results with evaluable laboratory data were available for 4,440 men with a mean age (±SD) of 36.1 years (±7.6 years) (Table 1). Study Center 1 included data from 835 patients, Center 2 included 3,309, and Center 3 included 296 patients. The average age of men evaluated at each institution was significantly different between the various centers