Male waist circumference in relation to semen quality and partner infertility treatment outcomes among couples undergoing infertility treatment with assisted reproductive technologies

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Sources of Support: National Institute of Environmental Health Sciences (NIEHS) grants (R01ES022955, R01ES009718 and P30ES000002) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grant (P30DK046200). H.B. was supported by the China Scholarship Council.

Running title: Male waist circumference and ART outcome

Abbreviations:

ART, assisted reproductive technologies; BMI, body mass index; GEE, generalized estimating equation; GnRH, gonadotropin-releasing hormone; ICSI, intracytoplasmic sperm injection; IVF, conventional in-vitro fertilization; WC, waist circumference; WHO, World Health Organization

Data Sharing:

Data described in the manuscript and analytic code will be made available upon request pending IRB approval and establishment of institutional data sharing agreements.

ABSTRACT

Background: Male obesity has been related to poor semen quality and may also have a negative effect on assisted reproductive technologies (ART) outcomes. Whether male waist circumference (WC), as a measure of central obesity, impacts a couple's fertility independently of body mass index is unclear.

Objective: To examine the associations of male WC with semen quality and couples' outcomes of infertility treatment with ART.

Design: Couples presenting to the Massachusetts General Hospital Fertility Center were invited to participate in the study. Between 2009 and 2019, 269 males provided 671 semen samples and 176 couples underwent 317 ART cycles. Height, weight and WC were measured on-site. We analyzed the association of male WC with semen quality and pregnancy outcomes using cluster-weighted regression models to account for repeated observations while adjusting for potential confounders. Models were also stratified by male BMI (<25 vs. ≥25 kg/m^2).

Results: Median male age, WC and BMI were 36.1 years, 96.0 cm and 26.8 kg/m^2, respectively. A 5 cm increase in WC was associated with a 6.3% (95% confidence interval: 2.1, 10.5%) lower sperm concentration after adjustment for potential confounders including BMI. Male WC was also inversely related to the probability of achieving a live birth. For each 5 cm increase in male WC, the odds (95% confidence interval) of live birth per initiated cycle decreased by 9.0% (1.1, 16.4%) after accounting for several anthropometric and demographic characteristics of both partners.

These associations were stronger among males in the normal BMI category (<25 kg/m^2) than among overweight or obese males.

Conclusions: Higher male WC may be an additional risk factor for poor outcomes of infertility treatment, even after accounting for male and female partner BMI, and particularly in couples where the male partner has a normal BMI.

Keywords: central obesity; fat distribution; in vitro fertilization; male infertility; paternal factor; semen quality

Introduction

The age-adjusted prevalence of obesity among adults in the U.S. is 42.4% (1), and the prevalence of central obesity – defined by waist circumference (WC) cutoffs (2) – is 58.9% (3). High WC is a risk factor for non-communicable diseases independently of body mass index (BMI) (4-6). Emerging evidence suggests that the excess accumulation of visceral fat plays an important role in the deleterious effects of central obesity (7, 8). The utility of WC as a marker of adiposity appears to be most salient in subgroups of the population in which BMI is less useful in discriminating between fat mass and overall mass, such as in elderly individuals and among younger adults within the normal BMI range (9, 10). WC in combination with BMI could differentiates obesity phenotype related to visceral fat accumulation (11).

The role of overall adiposity on reproduction and fertility has been extensively evaluated. Female obesity has been related to higher risk of ovulation disorders and anovulation, delayed time to pregnancy, higher risk of infertility, and lower success rates of infertility treatment with assisted reproductive technologies (ART) (12). Likewise, male obesity has been related to lower circulating testosterone and other changes in reproductive hormones (13, 14), erectile dysfunction (15, 16), poor semen quality(17), male factor infertility (18, 19), and may also have a negative effect on ART outcomes(20). Central obesity, however, has not received much attention on its potential role in reproduction. Female central obesity has been inversely related to reduced fecundity (21, 22) and lower success in infertility treatment with ART (23). Among males, some studies have reported inverse associations between WC and semen quality, but none have accounted for overall obesity (24-29). Moreover, whether male WC impacts a couple's fertility independently of their and their

partner's BMI is not clear. Given that semen quality parameters are poor predictors of fertility, there is a need to directly evaluate the impact of male WC on treatment outcomes of ART. Therefore, we investigated the relationship of male WC with semen quality and couples' outcomes of infertility treatment with ART in a cohort of subfertile couples presenting to an academic fertility center in Boston, Massachusetts (USA). We hypothesized that men's WC would be inversely related to live birth rates after accounting for male and female partner BMI.

Materials and methods

Study population

Participants were subfertile couples participating in the Environment and Reproductive Health (EARTH) Study (30), which started in 2004 to assess the impact of environment, nutritional and lifestyle factors on human fertility. Couples seeking infertility evaluation and treatment at Massachusetts General Hospital (MGH) Fertility Center, Boston, MA, were invited to participate either independently or as a couple. Males were eligible if they were 18 to 55 years old, no history of vasectomy and were not taking anabolic steroids at enrollment. Approximately 60% of males approached were eligible and agreed to participate. The anthropometry protocol was modified in October 2009 to add the measurement of WC. Males were eligible to be included in this analysis if they had a measurement of WC along with at least one complete semen analysis (n=276), or if their partner had completed at least one infertility treatment cycle with ART by January 2019 (n=180). For semen quality analyses, azoospermic males (n=6) and a man with implausible anthropometric information were excluded. For analyses of ART outcomes, cycles using

donor sperm (n=3) or donor oocyte (n=6) were excluded. After exclusions, 269 males (671 semen samples) were included in the semen quality analyses and 176 couples (317 cycles) were included in the ART outcomes analyses (Figure 1). Participants included in the analysis had similar characteristics compared to those excluded (Supplemental Table 1). Written informed consent was obtained from all participants. The study was approved by the Institutional Review Boards of MGH and the Harvard T.H. Chan School of Public Health.

Anthropometry and other key measurements

At enrollment, weight, height, and WC were measured on-site by trained personnel. For measurement of WC, participants were instructed to stand and hold their shirts above the abdomen with their crossed arms. A Gullick II Plus Measuring Tape was horizontally placed at the level of the umbilicus and tied snugly around the bare midriff by reference to the tape's pressure indicator. The measurement results were recorded to the nearest 0.1 cm. During the same visit, participants completed a staff-administered questionnaire regarding demographics, medical history and lifestyle factors. Participants were also asked to complete a questionnaire to provide more detailed information on medical, occupational and reproductive history, diet, and lifestyle. Time spent in time physical activities (including walking) and diet were assessed using validated questionnaires (31, 32). All relevant clinical information, including infertility diagnosis, was extracted from the electronic medical records and described elsewhere(30).

Semen analysis, Clinical Management and Assessment of Outcomes

The primary outcome in this study was live birth and the secondary outcomes were semen quality as well as other ART outcomes (fertilization, implantation, and clinical pregnancy). Males were asked to abstain from ejaculation for at least 48 hours prior to producing a semen sample. Males produced semen samples on-site by masturbation. Of these 269 males, 34.2% provided 1 semen sample, 29.4% provided 2 samples, and 36.4% provided 3 or more samples (a maximum of 9). Samples were analyzed and reported according to the 2010 World Health Organization (WHO) manual procedures (33). Briefly, samples were placed at 37 ℃ for 20 minutes to liquefy before analysis. Ejaculate volume was measured using a graduated serological pipet. Sperm concentration and motility were evaluated with a computer-aided semen analysis system (CASA; Hamilton-Thorne Biosciences Ceros, version 14) as previously described (34). Sperm motility was classified as total (progressive + non-progressive) and progressive motility. Sperm morphology was determined using the strict criteria proposed by Kruger (35). Results of motility and morphology were expressed as the percentage of motile sperm and normal spermatozoa, respectively.

Female partners underwent one of three ovarian stimulation protocols as clinically indicated: 1) long phase gonadotropin-releasing hormone (GnRH) agonist protocol; 2) follicular phase GnRH-agonist flare protocol; 3) GnRH-antagonist protocol. During gonadotropin stimulation, clinical staff monitored serum estradiol, follicle size and counts, and endometrial thickness before oocyte retrieval. For triggering final oocyte maturation, human chorionic gonadotropin (β-hCG) was administered approximately 36 hours before oocyte retrieval. Embryologists categorized oocytes into germinal vesicle, metaphase I, metaphase II (M2), or degenerated. Fertilization rate was calculated as the number of oocytes with two pronuclei divided by the number of M2 oocytes at 17 to 20 hours after

insemination. Either programmed estrogen and progesterone replacement or natural cycle monitoring was performed for cryo-thaw cycles. Clinical outcomes were assessed in all cycles following embryo transfer. Successful implantation was defined as an elevation in β-hCG levels > 6 mIU/mL, typically measured 2 weeks after embryo transfer. Clinical pregnancy was defined as the presence of intrauterine pregnancy confirmed by ultrasound at 6 weeks. Live birth was defined as the birth of a neonate ≥ 24 weeks of gestation.

Statistical Analysis

Males/couples were classified into tertiles according to the male WC. Baseline demographic and reproductive characteristics across tertiles of male WC were compared using Fisher exact tests for categorical variables and Kruskal-Wallis tests for continuous variables. Sperm concentration and count were log-transformed to more closely approximate a normal distribution.

To account for within-person correlations in repeated observations within individuals/couples and the possibility that the number of observations per subject/couple was informative, we used cluster-weighted generalized estimating equation (GEE) models (36) with a first-order autoregressive correlation structure to examine the association of male WC, as a continuous variable and also divided in tertiles, with semen quality parameters and ART treatment outcomes. Specifically, each semen sample or initiated cycle was weighted by the inverse of the total number of the observations per individual (semen analyses) or couple (ART cycles). For semen quality outcomes, we used linear GEE models. To facilitate clinical interpretation, we present the results of models for semen parameters as multivariable-adjusted marginal means (37). For fertilization rate and

clinical outcomes, we used logistic GEE models. Linear trend tests were performed by including the continuous male WC in the models, and the effects of each 5 cm WC increase on outcomes of interest were estimated by ORs.

Confounding was evaluated by directed acyclic graphs based on prior knowledge and descriptive statistics in the study population (Supplementary Figure 1). Multiple sets of regression models were fit. For semen analysis: the first set of models adjusted for male age, race, education, smoking status, history of varicocele and abstinence time; the second included an additional term for BMI; and the third was further adjusted for height. For analysis of ART outcomes, the first set of models included male age and BMI; the second set of models included additional terms for male height, race, education, smoking status and history of varicocele; the third set of models included all covariates in the second set of models plus female age, BMI, WC, height, education and primary infertility diagnosis. We also evaluated whether the association of WC and study outcomes differed across strata of BMI. Tests for interaction using cross-product terms in to the multivariable-adjusted models. Stratum-specific estimates were derived from separate models fit in each stratum. We also assessed the effect of male WC on clinical outcomes using WHO suggested cutoff points (94 and 102 cm) (2). To test the robustness of the findings, we conducted sensitivity analyses stratifying by mode of insemination (conventional in-vitro fertilization [IVF] vs. intracytoplasmic sperm injection [ICSI]) for fertilization rate. We also conducted analyses restricted to fresh embryo cycles, to the first treatment cycle of each couple, and to males with available information on both semen quality parameters and ART outcomes. Last, to examine the impact of our choice of covariance structure, we fit models for our main

findings using an unstructured and a compound symmetry covariance structure instead. Analyses were performed using SAS (version 9.4; SAS Institute).

Results

Male median (interquartile range, IQR) age, WC and BMI were 36.1 years (32.9, 39.6), 96 cm (89, 105) and 26.8 kg/m^2 (24.3, 30.0), respectively. Most males were white (86%), had a graduate degree (63%), and had never smoked (67%). None of the males were underweight (BMI <18.5 kg/m^2). Females had a median (IQR) age of 34.5 years (32.0, 38.0), BMI of 22.8 kg/m^2 (20.8, 25.5) and WC of 80 cm (75, 88.5). Male WC was positively correlated with their BMI (r=0.57) and height (r=0.26), and with their partner's WC (r=0.40). BMI was also positively correlated within couples (r = 0.29). No statistically significant difference was found in other baseline demographic or reproductive characteristics between the tertiles of male WC (Table1).

Higher male WC was related to lower sperm concentration (Table 2). In models adjusting for BMI, demographic and reproductive characteristics, a 5 cm increase in WC was associated with a 6.3% (95% confidence interval [CI]: 2.1, 10.5%) lower sperm concentration. Results were similar after further adjustment for height (Table 2). Males with a WC larger than 100.5 cm had 33.5% (3.9, 54.0%) lower total sperm count than male with a WC of 90 cm or less after accounting for BMI, demographic and reproductive characteristics. WC was unrelated to sperm motility or morphology.

Since WC may be more useful in differentiating lean mass from fat mass within the normal range of BMI than in the extremes of the BMI distribution, we then evaluated the association of WC with semen parameters within categories of BMI (Table 3). In these

analyses, WC was inversely related to all semen quality parameters among males in the normal BMI category but not among overweight/obese males (Table 3).

We then investigated the relation between WC with ART outcomes. Male WC was unrelated to fertilization rates overall. However, for couples undergoing ART with conventional IVF, the odds of fertilization decreased by 21.8% (4.0, 36.4%) per 5 cm increase in male WC when accounting for male and female demographic, reproductive and anthropometric characteristics (Supplemental Table 1, Model 3). Nevertheless, WC was inversely related to the probabilities of implantation, clinical pregnancy and live birth during the course of infertility treatment with ART (Figure 2 and Supplementary Table 2). In models adjusted for male and female demographic, reproductive and anthropometric characteristics, a 5 cm increase in male WC was associated with a 14.2% (2.8, 24.2%) lower odds of implantation, 12.1% (3.0, 20.3%) lower odds of clinical pregnancy and 9.0% (1.1, 16.4%) lower odds of live birth (Supplemental Table 2). When we assessed the associations of male WC with these outcomes within strata of BMI, the inverse relations of WC with ART outcomes were stronger among couples with leaner males (Table 4).

Adjustment for dietary patterns and physical activity did not have any impact on the relation between WC and ART outcomes (Supplementary Table 2, Model 4-6). The inverse relation between WC and ART outcomes was similar when using WHO suggested cutoff points for male WC (Supplemental Table 3). Results were also comparable when restricting analyses to fresh embryo cycles (Supplemental Table 4), to the first treatment cycle of each couple (Supplemental Table 5), and to males with available information on both semen quality and ART outcomes (Supplemental Table 6). Of note, in this last subgroup of men, the association between WC and ART outcomes persisted after adjustment for semen

quality parameters (Supplemental Table 6). Last, results did not change when using different correlation structures to model the within-person correlation in outcomes (Supplemental Tables 7 and 8).

Discussion

We examined the association of male WC with semen quality and clinical outcomes of ART among couples seeking for infertility treatment. WC was inversely related to sperm concentration independently of key potential confounders including BMI, dietary patterns, and physical activity. Although male WC was not associated with fertilization rate, it was negatively associated with clinical outcomes including implantation, clinical pregnancy and live birth, even after accounting for both partners' BMI. Notably, results were stronger among males within the normal BMI range than among overweight/obese males. Moreover, the association of male WC with clinical ART outcomes was independent of the effect on semen quality. These findings suggest that male WC may provide independent and additional information to BMI for the prediction of achieving fatherhood with ART, particularly in couples with normal weight males.

Our findings of inverse associations of WC with semen quality and worse ART outcomes are in agreement with the scant literature in this area. In line with our findings of an inverse relation between WC and sperm concentration, previous studies carried in males from subfertile couples (24, 25) and males without known infertility (26-29) also report this relation. However, previous studies did not adjust for BMI raising concerns that this relation may partially reflect well described associations with BMI. In our analysis, we observed stronger associations between WC and semen quality parameters after adjusting

for BMI, and in analyses restricted to males with a normal BMI (18.5-25 kg/m^2), suggesting that the relation of abdominal adiposity and semen quality may not only be independent of overall adiposity but may also be of concern among males not considered obese based on BMI criteria. We also found that male WC was associated to worse outcomes of infertility treatment with ART. This finding is consistent with the growing literature showing that higher male BMI is related to ART failure (20). Data regarding male central obesity and fertility specifically are sparse. In fact, to our knowledge, this is the first study to assess the association between male WC and outcomes on infertility treatment with ART. The Longitudinal Investigation of Fertility and the Environment (LIFE) Study did not find an association between male central obesity and fecundability among pregnancy planners without a known history of infertility (22). Reasons for discordant findings may include the fact that couples presenting to fertility centers may be more sensitive to the effects of male central obesity than pregnancy planners in the general population. It should be noted, however, that differences in BMI and WC distribution could also account for the differences. In the LIFE Study 83% of male participants were overweight or obese, while the corresponding figure in our study was 67%. Given that the associations between WC and ART outcomes were more pronounced among males with normal BMI, if this were also true in the general population, the high prevalence of obesity in the LIFE study may have masked this true relation. Clearly, additional research on the relation between male WC and reproductive fitness is warranted, particularly among males within the normal BMI range since findings from this study, as well as our previous findings among females in this cohort (23), suggest that WC may be an important factor influencing fertility above and beyond overall adiposity.

The relation of WC with worse semen quality and ART outcomes is biologically plausible. As a marker of visceral adipose tissue depots (38), central obesity has been linked with chronic inflammation and metabolic disorders, including insulin resistance and dyslipidemia, independently of overall obesity (39-41). The high load of systemic oxidative stress may drive changes in testicular and epididymal environments, affect the sperm membrane integrity, and induce genetic or epigenetic alterations of gametes (42, 43). Previous work has shown restoration of the reproductive hormonal profile and improved semen quality following abdominal fat loss (44). The inverse association with semen quality parameters are likely due to factors previously attributed to the relation between obesity and semen quality, including altered reproductive hormonal profile, as well as physical factors such as elevated scrotal temperature (45, 46). These factors, however, may not necessarily explain the inverse relation with chances of successful treatment outcomes with ART. In fact, our finding that further adjustment for semen parameters has little to no impact on the association of WC with ART outcomes, as well previous findings showing that pre-processing semen parameters do not predict ART outcomes (47), support this interpretation. Since in the setting of ART sperm is concentrated and selected to achieve better treatment outcomes, damage to the sperm in other ways, including damage to sperm DNA integrity or epigenetic changes, as we and others have documented in relation to obesity, could be the mechanism underlying these relations (14, 48, 49). As the sperm genome is not expressed until day 2-3 of embryo development, exposures affecting the integrity of sperm DNA could result in no effects on fertilization rate but rather be manifested as failure of implantation or pregnancy loss (50, 51). This mechanism is consistent with our results.

Limitations of our study include its relatively small sample size. While the study was sufficiently large to document relations with clinically relevant outcomes, larger studies could evaluate these relations with more granularity, as well as possible interactions with female anthropometric factors. Second, WC was measured at the level of umbilicus which may result in loss of accuracy compared with the measurement at the level of the iliac crest or the mid-point between the iliac crest and last rib. However, as most of the participants' BMI were less than 35 kg/m^2, there might be little difference between measurement results with umbilicus or anatomical landmarks. Moreover, previous work has shown that the measurement site for WC has little impact on its relation to direct measurements of abdominal fat mass or markers of cardiometabolic risk (52-56). Third, it is unknown whether these findings are generalizable to the couples attempting conception without medical assistance. Nevertheless, this cohort is comparable to couples presenting to infertility practices nationwide. Strengths of the study include the collection of anthropometric information by trained personnel using standardized protocols, the availability of repeated semen samples as well as complete follow-up for ART outcomes across multiple treatment cycles. Last, having enrolled men into a study of ART outcomes *per se* is a major strength of the study not only as it allowed us to address the specific hypothesis of central obesity in the male partner, but also as it allows more generally for a comprehensive evaluation of prognostic factors of ART outcomes.

Conclusions

In summary, we found that higher male WC was associated with lower sperm concentration, and lower probability of achieving a live birth among couples undergoing infertility

treatment. These associations were present even in men within the normal BMI range. These results suggest that central obesity may be an independent risk factor for male factor infertility, and highlight the need for infertility care providers to assess male partner factors in their clinical management of infertile couples.

Acknowledgments

The authors thank all members of the EARTH Study team, especially research nurses Jennifer B. Ford and Myra Keller, physicians, fellows and clinical staff at the Massachusetts General Hospital Fertility Center, as well as all the study participants.

JEC was involved in study concept and design. HB and JEC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; HB, LMA, PLW and JEC. interpreted the data; LMA, ASH and DB contributed to statistical analyses; JEC, PLW, IS and JA. were involved in acquisition of the data. All authors were involved in the critical revision of the manuscript and approved the final manuscript. None of the authors declared a conflict of interest.

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Table 1. Study sample characteristics by tertile of male waist circumference

Characteristics	All participants	Male waist circumference, cm			*P* value[1]
		≤90	90.1-100.5	>100.5	
Males					
n	269	85	91	93	
Waist circumference, cm	96.0 (89.0, 105.0)	85.5 (81.0, 89.0)	95.0 (92.5, 98.5)	109.0 (104.0, 116.0)	<0.001
Age, y	36.1 (32.9, 39.6)	35.8 (32.6, 38.4)	35.7 (32.9, 39.6)	37.4 (33.5, 40.6)	0.27
BMI, kg/m^2	26.8 (24.3, 30.0)	24.0 (22.6, 24.9)	26.2 (24.9, 27.8)	31.0 (29.1, 34.1)	<0.001
Height, cm	180.0 (175.0, 184.0)	178.0 (173.0, 182.0)	181.0 (175.0, 185.0)	180.0 (176.0, 185.0)	0.01
White/Caucasian, n (%)	231 (86)	68 (80)	81 (89)	82 (88)	0.20
Educational level, n (%)					0.10
High school or some college	29 (11)	8 (9)	5 (6)	16 (17)	
College degree	72 (27)	20 (24)	26 (29)	26 (28)	
Graduate degree	168 (63)	57 (67)	60 (66)	51 (55)	
Abstinence time, days	2.4 (2.0, 3.0)	2.2 (2.0, 3.0)	2.4 (2.1, 3.1)	2.2 (2.0, 3.3)	0.36
Ever smoker, n (%)	88 (33)	31 (37)	25 (28)	32 (34)	0.41
Total energy intake, kcal/d	1843.1 (1456.8, 2254.4)	1877.9 (1633.9, 2227.8)	1879.3 (1483.4, 2381.8)	1779.8 (1428.2, 2214.9)	0.74
Prudent pattern score	-0.3 (-0.7, 0.3)	-0.3 (-0.8, 0.1)	-0.3 (-0.8, 0.3)	-0.1 (-0.6, 0.5)	0.16
Western pattern score	-0.2 (-0.7, 0.6)	-0.2 (-0.6, 0.3)	0 (-0.6, 0.8)	-0.4 (-0.9, 0.4)	0.20
Total exercise, including walking, h/wk	4.5 (0.3, 10.0)	5.0 (0.8, 10.0)	5.2 (0.3, 11.5)	3.0 (0, 7.3)	0.13
Moderate-to-vigorous physical activity, h/wk	2.0 (0, 5.7)	2.5 (0, 5.9)	2.0 (0, 6.5)	2.0 (0, 5.0)	0.40
History of varicocele, n (%)	20 (7)	9 (11)	5 (6)	6 (7)	0.43
History of cryptorchidism, n (%)	10 (4)	2 (2)	6 (7)	2 (2)	0.28
Females					
n	176	58	59	59	
Age, y	34.5 (32.0, 38.0)	34.5 (31.0, 37.0)	34.0 (31.0, 38.0)	35.0 (33.0, 38.0)	0.40
BMI, kg/m^2	22.8 (20.8, 25.5)	22.0 (20.0, 24.2)	23.0 (20.7, 25.4)	23.9 (21.5, 28.4)	0.002
Waist circumference, cm	80.5 (75.0, 88.5)	77.5 (71.0, 82.0)	80.0 (75.5, 87.0)	87.0 (79.0, 98.0)	<0.001
Height, cm	165.0 (160.0, 170.0)	163.5 (158.0, 169.0)	165.0 (161.0, 169.0)	167.5 (163.0, 172.0)	0.01
White/Caucasian, n (%)	145 (82)	45 (78)	47 (80)	53 (90)	0.18

Educational level, n (%)					0.06
High school or some college	9 (5)	2 (4)	2 (3)	5 (9)	
College degree	54 (31)	15 (26)	14 (24)	25 (42)	
Graduate degree	113 (64)	41 (71)	43 (73)	29 (49)	
Day 3 FSH, IU/L	6.7 (5.9, 8.0)	6.7 (5.9, 7.9)	6.5 (5.7, 8.3)	6.7 (6.0, 8.1)	0.81
Ever smoker, n (%)	43 (24)	14 (24)	13 (22)	16 (27)	0.82
Ever pregnant, n (%)	73 (42)	28 (48)	20 (34)	25 (42)	0.29
Total energy intake, kcal/d	1682.7 (1317.8, 1999.0)	1660.4 (1334.2, 1765.8)	1682.7 (1318.9, 2007.5)	1682.7 (1190.1, 2158.1)	0.75
Prudent pattern score	-0.2 (-0.6, 0.4)	-0.4 (-0.8, -0.2)	-0.2 (-0.5, 0.4)	-0.2 (-0.6, 0.8)	0.04
Western pattern score	-0.2 (-0.6, 0.4)	-0.2 (-0.5, 0.5)	-0.2 (-0.5, 0.3)	-0.2 (-0.6, 0.5)	0.93
Initial treatment protocol, n (%)					0.06
Antagonist	33 (19)	6 (10)	12 (20)	15 (25)	
Flare	15 (9)	5 (9)	4 (9)	6 (10)	
Luteal phase agonist	117 (67)	40 (69)	39 (66)	38 (64)	
Endometrial preparation	11 (6)	7 (12)	4 (7)	0 (0)	
Couples					
Primary infertility diagnosis, n (%)					0.93
Male factor	67 (25)	19 (22)	22 (24)	26 (28)	
Female factor	83 (31)	28 (33)	28 (31)	27 (29)	
Unexplained	119 (44)	38 (45)	41 (45)	40 (43)	

FSH, follicle-stimulating hormone.

Data are median (interquartile range) or n (%).

[1] From Kruskal-Wallis tests for continuous variables and Fisher exact tests for categorical variables.

Table 2. Semen quality parameters in relation to male waist circumference[1]

Semen quality parameters	Male waist circumference, cm			Difference (95% CI)
	⩽90	90.1-100.5	> 100.5	per 5 cm increase in male waist circumference[2]
Number of semen samples	205	231	235	
Number of males	85	91	93	
Sperm concentration (% difference)				
Model 1	39.9 (28.6, 55.8)	31.9 (22.4, 45.5)	28.8 (20.7, 40.1)[3]	-4.07 (-7.54, -0.60)
Model 2	41.5 (29.6, 58.2)	31.8 (22.4, 45.0)	26.7 (19.0, 37.6)[3]	-6.33 (-10.54, -2.12)
Model 3	40.8 (29.1, 57.2)	31.9 (22.5, 45.2)	27.5 (19.4, 38.8)[3]	-5.58 (-10.21, -0.96)
Total sperm count (% difference)				
Model 1	91.4 (63.9, 130.7)	78.8 (54.5, 114.1)	65.7 (46.8, 92.3)[3]	-3.37 (-7.19, 0.44)
Model 2	93.9 (65.9, 134.0)	78.6 (54.4, 113.6)	62.4 (43.2, 90.2)[3]	-4.37 (-8.90, 0.15)
Model 3	91.5 (64.8, 129.4)	78.9 (54.7, 113.8)	64.9 (44.7, 94.1)	-2.86 (-7.47, 1.76)
Sperm motility (% motile)				
Model 1	42.1 (34.8, 49.3)	37.1 (29.8, 44.5)	37.0 (29.3, 44.7)	-0.69 (-1.56, 0.18)
Model 2	42.7 (35.0, 50.4)	37.1 (29.8, 44.3)	35.9 (28.1, 43.7)	-1.08 (-2.35, 0.20)
Model 3	42.6 (34.8, 50.4)	37.1 (29.9, 44.3)	36.0 (28.0, 44.0)	-1.10 (-2.57, 0.38)
Progressive motility (% progressively motile)[4]				
Model 1	23.9 (19.3, 28.4)	20.7 (16.0, 25.3)	21.2 (16.0, 26.3)	-0.43 (-1.08, 0.21)
Model 2	24.2 (19.3, 29.1)	20.7 (16.1, 25.3)	20.6 (15.4, 25.7)	-0.69 (-1.55, 0.18)
Model 3	24.3 (19.2, 29.3)	20.7 (16.1, 25.2)	20.5 (15.3, 25.7)	-0.78 (-1.77, 0.20)
Sperm morphology (% normal)[5]				
Model 1	5.9 (4.8, 7.0)	5.2 (3.9, 6.6)	5.4 (4.3, 6.6)	-0.07 (-0.22, 0.07)
Model 2	5.9 (4.7, 7.0)	5.2 (3.9, 6.6)	5.4 (4.3, 6.6)	-0.09 (-0.27, 0.09)
Model 3	5.9 (4.7, 7.0)	5.2 (3.9, 6.6)	5.5 (4.3, 6.7)	-0.08 (-0.30, 0.14)

[1] All analyses were conducted by using cluster-weighted generalized estimating equations. Estimates under the columns for tertiles of WC are multivariable-adjusted marginal means for each semen parameter for the specified model. Estimates under the last column are multivariable-adjusted differences in each semen parameter for the specified model.

Model 1 was adjusted for age (continuous), race (white, non-white), education (high school or some college, college, graduate), smoking status (ever, never), history of varicocele (yes, no) and abstinence time (<2 days, 2-3 days, 3-4days, and ⩾4 days).

Model 2 included model 1 variables plus BMI (continuous).

Model 3 included model 2 variables plus Height (continuous).

[2] Sperm concentration and total count were log-transformed to more closely approximate normal distribution. Thus estimates represent percent differences for concentration and total count and absolute differences for all other semen parameters.

[3] $P < 0.05$ compared with tertile 1.

[4] Contains data from 658 samples because evaluation on progressive motility was not performed for all samples.

[5] Contains data from 639 samples because morphologic evaluation was not performed for all samples.

Table 3. Adjusted difference[1] of semen quality parameters per 5 cm increase in male waist circumference within categories of BMI[2]

Semen quality parameters	BMI, kg/m^2		*P* value for interaction
	18.5 ⩽ BMI < 25	⩾ 25	
Number of semen samples	229	442	
Number of males	89	180	
Sperm concentration (%)			0.24
Model 1	-13.06 (-27.12, 1.01)	-2.30 (-5.79, 1.19)	
Model 2	-24.76 (-41.20, -8.33)	-4.16 (-8.06, -0.26)	
Model 3	-22.01 (-40.18, -3.85)	-3.54 (-7.93, 0.85)	
Total sperm count (%)			0.16
Model 1	-11.29 (-23.84, 1.27)	-1.65 (-5.96, 2.66)	
Model 2	-23.12 (-38.77, -7.47)	-2.45 (-7.33, 2.43)	
Model 3	-22.05 (-37.04, -7.06)	-0.65 (-5.69, 4.38)	
Sperm motility (% motile)			0.47
Model 1	-2.41 (-5.48, 0.67)	-0.43 (-1.43, 0.57)	
Model 2	-4.39 (-8.12, -0.66)	-0.72 (-1.96, 0.51)	
Model 3	-5.15 (-8.96, -1.34)	-0.58 (-2.02, 0.86)	
Progressive motility (%)[3]			0.61
Model 1	-1.42 (-3.48, 0.64)	-0.27 (-1.05, 0.51)	
Model 2	-2.21 (-4.77, 0.35)	-0.48 (-1.36, 0.40)	
Model 3	-3.09 (-5.68, -0.5)	-0.43 (-1.43, 0.57)	
Sperm morphology (% normal)[4]			0.85
Model 1	-0.30 (-0.73, 0.14)	-0.03 (-0.21, 0.15)	
Model 2	-0.62 (-1.15, -0.09)	-0.05 (-0.24, 0.15)	
Model 3	-0.74 (-1.32, -0.16)	-0.02 (-0.25, 0.22)	

[1] Sperm concentration and total count log-transformed to achieve normality. Thus estimates represent percent differences for total count and concentration and absolute differences for all other semen parameters.

[2] All analyses were conducted by using cluster-weighted generalized estimating equations. Model 1 was adjusted for age (continuous), race (white, non-white), education (high school or some college, college, graduate), smoking status (ever, never), history of varicocele (yes, no) and abstinence time (<2 days, 2-3 days, 3-4days, and ⩾4 days). Model 2 included model 1 variables plus BMI (continuous). Model 3 included model 2 variables plus Height (continuous).

[3] Contains data from 658 samples because evaluation on progressive motility was not performed for all samples.

[4] Contains data from 639 samples because morphologic evaluation was not performed for all samples.

Table 4. Odds ratios (95% CI) per 5 cm increase in male waist circumference for clinical outcomes per initiated treatment cycle within categories of BMI[1]

Clinical outcomes	BMI, kg/m^2		P value for interaction
	18.5 ⩽ BMI < 25	⩾ 25	
Number of cycles	113	204	
Number of couples	58	118	
Implantation			0.05
Model 1	0.58 (0.35, 0.95)	0.95 (0.87, 1.04)	
Model 2	0.54 (0.32, 0.89)	0.91 (0.84, 1.00)	
Model 3	0.31 (0.17, 0.56)	0.90 (0.82, 0.99)	
Clinical Pregnancy			0.04
Model 1	0.58 (0.34, 1.00)	0.96 (0.87, 1.05)	
Model 2	0.60 (0.35, 1.03)	0.90 (0.81, 0.99)	
Model 3	0.31 (0.18, 0.51)	0.90 (0.82, 0.98)	
Live Birth			0.10
Model 1	0.60 (0.33, 1.09)	0.99 (0.90, 1.08)	
Model 2	0.63 (0.33, 1.19)	0.89 (0.81, 0.98)	
Model 3	0.29 (0.14, 0.59)	0.89 (0.82, 0.97)	

[1] All analyses were conducted by using cluster-weighted generalized estimating equations. Model 1 was adjusted for male age (continuous) and BMI (continuous). Model 2 included model 1 variables plus male height (continuous), race (white, non-white), education (high school or some college, college, graduate), smoking status (ever, never), and history of varicocele (yes, no). Model 3 included model 2 variables plus partner's age (continuous) and BMI (continuous), height (continuous), education (high school or some college, college, graduate) and primary infertility diagnosis (male factor, female factor, unexplained).

Figure legends

Figure 1. Flowchart of the study participants. SA, semen quality analysis; ART, assisted reproductive technology; WC, waist circumference; ESA, epididymal sperm aspiration.

Figure 2 Associations between male waist circumference and infertility treatment outcomes in 176 couples (317 initiated cycles) from the Environment and Reproductive Health Study (2009–2019). The analyses were conducted by using cluster-weighted generalized estimating equations with a binomial distribution and log link function with adjustment for male age (continuous) and BMI (continuous), height (continuous), race (white, non-white), education (high school or some college, college, graduate), smoking status (ever, never), and history of varicocele (yes, no), and their partner's age (continuous) and BMI (continuous), height (continuous), education (high school or some college, college, graduate) and primary infertility diagnosis (male factor, female factor, unexplained).

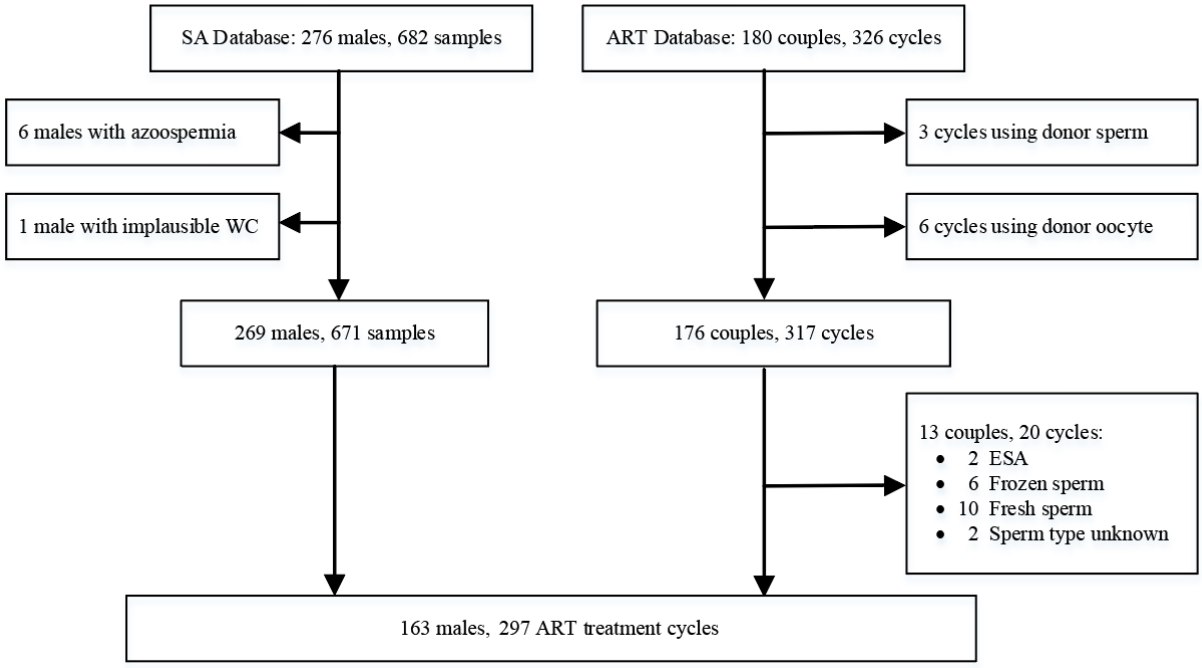

Figure 1. Flowchart of the study participants.

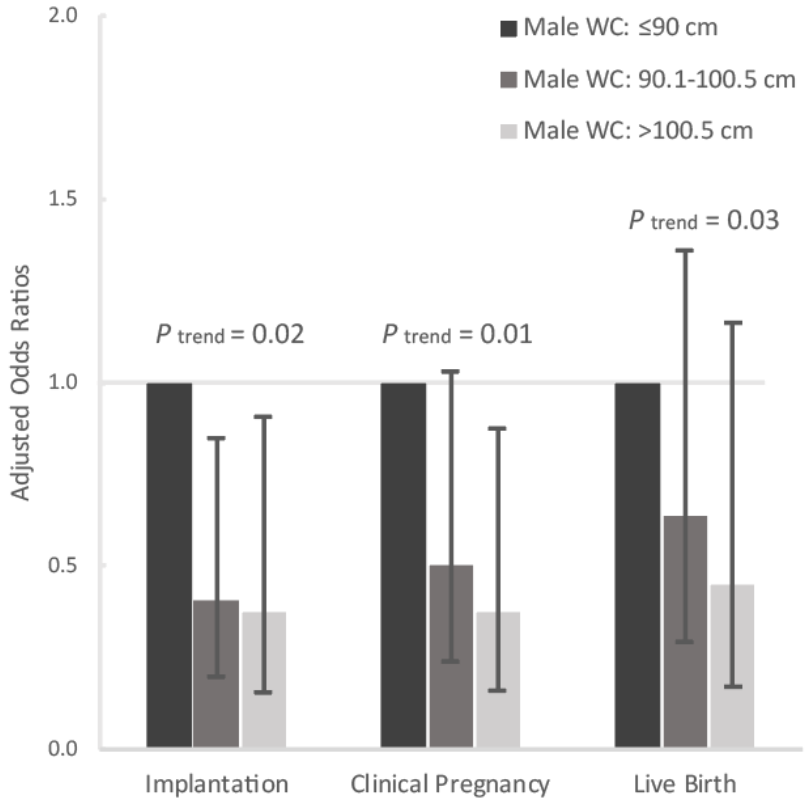

Figure 2 Associations between male waist circumference and infertility treatment outcomes