Asian Journal of Andrology (2017) 19, 368–373
www.asiaandro.com; www.ajandrology.com

Open Access

ORIGINAL ARTICLE

Male Fertility

Metabolic syndrome in White-European men presenting for secondary couple's infertility: an investigation of the clinical and reproductive burden

Eugenio Ventimiglia[1,2], Paolo Capogrosso[1,2], Alessandro Serino[1], Luca Boeri[1], Michele Colicchia[1], Giovanni La Croce[1,2], Roberta Scano[1], Enrico Papaleo[3], Rocco Damiano[4], Francesco Montorsi[1,2], Andrea Salonia[1,4]

We aimed to determine the impact of metabolic syndrome (MetS) on reproductive function in men with secondary infertility, a condition that has received relatively little attention from researchers. Complete demographic, clinical, and laboratory data from 167 consecutive secondary infertile men were analyzed. Health-significant comorbidities were scored with the Charlson Comorbidity Index (CCI; categorised 0 *vs* 1 *vs* 2 or higher). NCEP-ATP III criteria were used to define MetS. Semen analysis values were assessed based on the 2010 World Health Organization (WHO) reference criteria. Descriptive statistics and logistic regression models tested the association between semen parameters and clinical characteristics and MetS. MetS was found in 20 (12%) of 167 men. Patients with MetS were older ($P < 0.001$) and had a greater BMI ($P < 0.001$) compared with those without MetS. MetS patients had lower levels of total testosterone ($P = 0.001$), sex hormone-binding globulin, inhibin B, and anti-Müllerian hormone (all $P \leq 0.03$), and they were hypogonadal at a higher prevalence ($P = 0.01$) than patients without MetS. Moreover, MetS patients presented lower values of semen volume, sperm concentration, and sperm normal morphology (all $P \leq 0.03$). At multivariate logistic regression analysis, no parameters predicted sperm concentration, normal sperm morphology, and total progressive motility. Our data show that almost 1 of 8 White-European men presenting for secondary couple's infertility is diagnosed with MetS. MetS was found to be associated with a higher prevalence of hypogonadism, decreased semen volume, decreased sperm concentration, and normal morphology in a specific cohort of White-European men.

Asian Journal of Andrology (2017) **19**, 368–373; doi: 10.4103/1008-682X.175783; published online: 18 March 2016

Keywords: infertility; metabolic syndrome; sperm count

INTRODUCTION

According to the World Health Organization (WHO), secondary infertility is defined as a couple's inability to bear a child, either due to the failure to conceive or the inability to carry a pregnancy to live birth following either a previous pregnancy or a previous ability to carry a pregnancy to live birth.[1] Despite being poorly studied, secondary infertility rates have been increasing over time and are not negligible compared to primary infertility rates; overall, a male factor is involved in up to 50% of cases.[2]

Several factors are recognized as potential causes of secondary couple's infertility.[3] Among them, the potential detrimental contribution of advanced age in terms of male reproductive function remains ambiguous.[4] Although not unequivocal,[5] epidemiological data have suggested that increasing paternal age (more than 35–40 years) is associated with delayed conception,[6] an increased risk of spontaneous pregnancy loss,[7] and a decreased success rate at both intra-uterine insemination[8] and *in vitro* fertilization.[9,10] Likewise, it has been previously shown that semen volume, sperm motility, and sperm morphology decrease with age. In contrast, the relationship between increasing age and sperm concentration remains unclear.[4,11] More specifically, sperm concentration and the percentage of sperm with normal morphology, sperm motility, and ejaculate volume were found to decrease after 40, 43, and 45 years, respectively, whereas total sperm count declines even earlier.[11] A significant role of paternal age has been postulated for a number of genetic factors including numerous severe age-dependent structural chromosomal aberrations, with several X-linked recessive and autosomal dominant disorders have already been clearly confirmed.[4,12]

Besides advanced age, several comorbidities are regarded as possible contributing factors. To this regard, infertile men appear to share a lower general health status regardless of the reasons for infertility.[13,14] More specifically, a deranged metabolism was shown to be actively involved in affecting male reproductive function. In this context, substantial evidence indicates that complex interactions underlie the pathologic relationship between obesity, metabolic syndrome (MetS), and the reproductive axis.[15] Obesity is known to affect fertility in

[1]Division of Experimental Oncology, Unit of Urology, URI, IRCCS Ospedale San Raffaele, 20132 Milan, Italy; [2]Università Vita-Salute San Raffaele, 20132 Milan, Italy; [3]Infertility Unit, Unit of Obstetrics/Gynecology, IRCCS Ospedale San Raffaele, 20132 Milan, Italy; [4]Research Doctorate Program in Urology, Magna Graecia University, 88020 Catanzaro, Italy.
Correspondence: Dr. A Salonia (salonia.andrea@hsr.it)
Received: 12 April 2015; Revised: 26 July 2015; Accepted: 08 January 2016

women and is alleged also for men.[2] An excess of adipose tissue is responsible for hormonal imbalance, especially when considering the hypothalamic-pituitary-gonadal (HPG) axis.[16] Nevertheless, the evidence linking obesity to impaired semen parameters is still not univocal despite extensive recent attempts to provide clarity on this controversial topic and its related issues.[17–20] Similarly, diabetes mellitus (DM) also perturbs both sexual and reproductive hormonal homeostasis and seems to affect spermatogenesis at various levels.[21]

Although MetS was shown to have a detrimental effect on male reproductive health[22,23] in primary infertile men, the impact of MetS on male reproductive function has never been analyzed before in White-European men seeking medical help for secondary infertility. Likewise, the lack of previous clinical evidence and the increasing prevalence of MetS,[24] with its potential impact on both the hormonal milieu and the overall health status of men, prompted us to investigate the role of MetS in male secondary infertility, assessing (i) the prevalence of MetS, (ii) correlations between MetS and clinical characteristics, and (iii) the impact of MetS on semen and hormonal parameters in a cohort of White-European men presenting for secondary couple's infertility.

MATERIALS AND METHODS

Patients

The analyses of this cross-sectional study were based on a sample of 167 consecutive White-European men assessed at a single academic center for secondary couple's infertility (noninterracial infertile couples only) between September 2005 and April 2013. Patients were enrolled if they were older than 18 years of age and had either male factor infertility (MFI) or mixed factor infertility (MxFI). MFI was defined after a comprehensive diagnostic evaluation of the female partners. According to the WHO clinical criteria, infertility is defined as not conceiving a pregnancy after at least 12 months of unprotected intercourse regardless of whether or not a pregnancy ultimately occurred.[1] Secondary infertility is defined as the inability to conceive following a previous pregnancy.[1]

Patients were assessed with a thorough self-reported medical history including age and comorbidities. Comorbidities were scored with the Charlson Comorbidity Index (CCI).[25] We used the International Classification of Diseases, 9th Revision. For the specific purpose of the analysis, CCI was categorized as 0, 1, ≥2.

Weight and height were measured for each participant; body mass index (BMI), defined as weight in kg/height in m^2, was assessed for each patient. Testes volume was assessed through a Prader orchidometer. Patients underwent at least two consecutive semen analyses both depicting a condition below the standard values for normal semen parameters according to the WHO criteria.[26]

A venous blood sample was drawn from each patient between 7 a.m. and 11 a.m. after an overnight fast. In all cases, fasting glucose levels were measured via a glucose oxidase method (Aeroset Abbott, Rome, Italy). Total cholesterol, HDL-C, and triglyceride levels were measured with the automated enzymatic colorimetric method (Aeroset Abbott, Rome, Italy). Follicle-stimulating hormone (FSH); luteinizing hormone (LH), prolactin (PRL), thyroid-stimulating hormone (TSH), and 17β-estradiol (E_2) were measured using a heterogeneous competitive magnetic separation assay (Bayer Immuno 1 System, Bayer Corporation, Tarrytown, NY, USA). Inhibin B (InhB) and anti-Müllerian hormone (AMH) were measured by an enzyme-linked immunosorbent assay (Beckman Coulter AMH Gen II ELISA). Total testosterone (tT) levels were measured via a direct chemiluminescence immunoassay (ADVIA Centaur; Siemens Medical Solutions Diagnostics, Deerfield, IL, USA), and sex hormone-binding globulin (SHBG) levels were measured via a solid-phase chemiluminescent immunometric assay on Immulite 2000 (Medical Systems SpA, Genoa, Italy). Calculated free testosterone (cfT) was derived from the Vermeulen formula. Hypogonadism was defined as tT <3 ng ml^{-1}.[27] Calculated free testosterone (cfT) was derived from the Vermeulen formula.[28] The same laboratory was used for all patients.

MetS was defined according to the 2004 updated National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (ATP III) criteria (at least 3 of the following criteria: waist circumference >102 cm; triglycerides equal to or >150 mg dl^{-1} (1.7 mmol l^{-1}); HDL <40 mg dl^{-1} (1.03 mmol l^{-1}); blood pressure equal to or >130/85 mmHg or use of medication for hypertension; and fasting glucose equal to or >100 mg dl^{-1} (5.6 mmol l^{-1}) or use of medication for hyperglycemia).[29]

Data collection followed the principles outlined in the Declaration of Helsinki; all patients signed an informed consent agreeing to supply their own anonymous information for future studies. The study was approved by our Local Ethical Committee.

Statistical analyses

Data abstraction was performed by six different abstractors on 100% of the medical records at the time of office admission. The data quality analysis showed an error rate of 0.3%.

Data are presented as means (medians; ranges). The statistical significance of differences in means and proportions was tested with the one-way analysis of variance and Pearson Chi-square test, respectively; 95% confidence intervals (95% CIs) were estimated for the association of categorical parameters. Exploratory analyses were initially applied to all variables; variables were retained when clinically significant to the results. Univariable (UVA) and multivariable (MVA) logistic regression models tested associations between the clinical predictors and pathologic semen parameters. Odds ratios and their 95% CIs were estimated.

Statistical tests were performed using SPSS version 19 (IBM Corp., Armonk, NY, USA). All tests were two-sided, with a significance level set at 0.05.

RESULTS

Table 1 lists the characteristics and the descriptive statistics of our secondary infertile patients. Overall, MFI and MxFI were found in 138 patients (82.6%) and 29 patients (17.4%), respectively. MetS was found in 20 (12%) secondary infertile patients. The analysis of our data allowed us to highlight several features capable of segregating patients diagnosed with MetS (+MetS) from their non-MetS counterpart (−MetS). From the descriptive standpoint, +MetS patients were older and with a higher BMI (all $P < 0.001$). Further differences were observed in terms of hormonal profile (lower InhB, AMH, tT, and SHBG circulating levels in men with MetS; all $P \leq 0.03$); consistent with these findings, hypogonadism was more common in the +MetS group ($P = 0.01$). When considering seminal parameters, lower semen volume, sperm concentration, and rates of normal morphology (all $P \leq 0.03$) were observed in patients with MetS.

Table 2 details logistic regression models testing the associations between clinical predictors and pathologic sperm parameters. At univariable analysis, higher FSH, lower InhB levels, and lower mean right testis volume were associated with pathologic sperm concentrations (all $P \leq 0.04$). Conversely, age, CCI, and +MetS were

Table 1: Characteristics and descriptive statistics of the entire cohort of patients according to positivity NCEP/ATP III criteria for MetS

	+MetS	*–MetS*	*P* (χ^2)*	*Mean difference (95% CI)*	*Overall*
Number of patients (%)	20 (12)	147 (88)			167
Age (years)					
Mean (median)	46.67 (45.00)	40.24 (39.00)	<0.001	–6.43 (–9.21––3.04)	40.97 (39)
Range	34–68	22–65			22–68
BMI (kg m^{-2})					
Mean (median)	32.47 (30.92)	25.49 (25.37)	<0.001	–6.98 (–8.62––5.34)	26.35 (25.70)
Range	22.49–41.66	18.86–35.10			18.86–41.66
CCI, *n* (%)					
CCI 0	15 (75.0)	127 (86.4)	0.31 (2.31)		142 (84.9)
CCI 1	3 (15.0)	12 (8.2)			15 (9.1)
CCI ≥2	2 (10.0)	8 (5.4)			10 (6.0)
Testis volume (Prader estimation)					
Right testis					
Mean (median)	17.85 (20)	18.98 (20)	0.56	1.13 (–2.67–4.94)	18.93 (20)
Range	2–25	2–25			2–25
Left testis					
Mean (median)	19.00 (20)	18.94 (20)	0.97	–0.06 (–3.50–3.37)	18.96 (20)
Range	10–25	2–25			2–25
Varicocele, *n* (%)	8 (40)	55 (37.4)	0.82 (0.05)		63 (37.7)
Smokers, *n* (%)	9 (45.0)	61 (41.5)	0.77 (0.09)		70 (41.9)
FSH (mIU ml^{-1})					
Mean (median)	9.49 (8.03)	6.74 (4.40)	0.46	–2.75 (–10.18–4.67)	7.00 (4.45)
Range	0.30–20.40	0.10–93.97			0.10–93.97
LH (mIU ml^{-1})					
Mean (median)	4.88 (4.70)	4.47 (3.40)	0.86	–0.41 (–3.29–2.48)	4.51 (3.45)
Range	0.10–10.00	0.60–32.80			0.1–32.80
InhB (pg ml^{-1})					
Mean (median)	75.3 (83.0)	114.6 (108.0)	0.01	39.3 (7.43–56.91)	109.20 (99.60)
Range	6.0–129.2	0.5–245.7			0.50–245.70
AMH (ng ml^{-1})					
Mean (median)	2.52 (2.3)	7.04 (6.7)	0.002	4.52 (0.12–8.91)	5.96 (4.40)
Range	1.3–4.4	0.6–19.3			0.60–19.30
tT (ng ml^{-1})					
Mean (median)	3.44 (3.07)	4.92 (4.69)	0.03	1.48 (0.15–2.81)	4.79 (4.60)
Range	2.00–6.26	1.75–9.73			1.75–9.73
tT <3 ng ml^{-1}, *n* (%)	10 (50.0)	21 (14.3)	0.01 (6.36)		31 (17.6)
E_2 (pg ml^{-1})					
Mean (median)	35.89 (31.87)	34.91 (32.00)	0.88	–0.98 (–14.07–12.12)	35.00 (32.00)
Range	12.00–69.00	11.00–104.00			11.00–104.00
SHBG (nmol l^{-1})					
Mean (median)	26.54 (23.21)	29.99 (29.00)	0.03	3.45 (0.65–7.10)	31.50 (28.00)
Range	9.6–110.00	7.00–84.60			7.00–110.00
PRL (ng ml^{-1})					
Mean (median)	15.58 (7.70)	14.29 (32.0)	0.79	–1.28 (–10.73–8.16)	14.42 (8.20)
Range	1.22–319.0	1.08–751.0			1.08–751
TSH (μUI ml^{-1})					
Mean (median)	1.98 (1.05)	1.83 (1.24)	0.32	–0.15 (–0.46–0.15)	1.69 (1.47)
Range	0.65–5.06	0.01–15.58			0.02–8.94
Semen volume (ml)					
Mean (median)	1.31 (0.75)	2.58 (2.50)	0.01	1.27 (0.32–2.21)	2.42 (2.40)
Range	0.10–5.00	0.10–10.0			0.10–10.00
Semen volume <1.5 ml, *n* (%)	9 (45.0)	19 (12.9)	<0.01 (8.50)		28 (16.8)
Sperm concentration					
Mean (median)	20.08 (15.70)	34.53 (20.80)	0.03	14.45 (1.45–27.45)	33.17 (20.80)
Range	0.0–52.20	0.00–167.00			0.00–167.00
Sperm concentration <15×10^6 ml^{-1}, *n* (%)	10 (50.0)	59 (40.1)	0.53 (0.40)		69 (41.4)

Contd...

Table 1: Contd...

	+MetS	*–MetS*	*P* (χ^2)*	*Mean difference (95% CI)*	*Overall*
Progressive motility					
Mean (median)	18.78 (13.00)	25.28 (24.00)	0.32	6.5 (–6.32–19.32)	24.75 (24.00)
Range	0.00–50.0	0.0–78.0			0.00–78.00
Progressive motility <32%, *n* (%)	15 (75.0)	93 (63.3)	0.39 (0.75)		108 (64.7)
Normal morphology					
Mean (median)	1.44 (1.00)	8.01 (2.00)	<0.001	6.75 (3.48–9.65)	7.45 (2.00)
Range	0.00–6.00	0.00–70.00			0.00–70.00
Normal morphology <4%, *n* (%)	18 (90)	92 (62.6)	0.12 (2.45)		110 (65.9)
Non obstructive azoospermia, *n* (%)	3 (15)	8 (5.4)	0.40 (0.70)		11 (6.7)
Obstructive azoospermia, *n* (%)	0 (0)	5 (1.3)	0.11 (2.61)		5 (3.0)
OAT, *n* (%)	10 (50.0)	60 (40.8)	0.91 (0.01)		70 (41.9)

**P* value according to two-tailed Student's *t*-test or Chi-square test, as indicated. Data are +MetS: positive criteria for metabolic syndrome; –MeTs: negative criteria for metabolic syndrome; BMI: body mass index; CCI: Charlson Comorbidity Index; FSH: follicle-stimulating hormone; LH: luteinizing hormone; InhB: inhibin B; AMH: anti-Müllerian hormone; tT: total testosterone; cfT: calculated free testosterone; E_2: 17β estradiol; tT–E_2 ratio: total testosterone/17β estradiol ratio; SHBG: sex hormone binding globulin; PRL: prolactin; TSH: thyroid-stimulating hormone; OAT: oligoasthenoteratozoospermia; NCEP/ATP III: National Cholesterol Education Program Adult Treatment Panel III; CI: confidence interval

Table 2: Logistic regression models predicting pathologic sperm parameters according to WHO 2010 criteria OR (95% CI) in the whole cohort of patients

	Sperm concentration <15×10⁶ ml⁻¹		*Progressive motility <32%*		*Normal morphology <4%*	
	UVA model	*MVA model*	*UVA model*	*MVA model*	*UVA model*	*MVA model*
Age	1.00 (0.94–1.06)	1.09 (0.83–1.42)	1.05 (0.98–1.04)	0.93 (0.68–1.26)	1.01 (0.95–1.09)	1.07 (0.83–1.39)
CCI 0	-	-	-	-	-	-
CCI 1	1.89 (0.48–7.46)	(0.00)	1.56 (0.29–8.50)	(0.00)	3.94 (0.40–30.31)	0.26 (0.00)
CCI ≥2	6.05 (0.65–56.06)	-	-	-	1.16 (0.10–13.35)	-
+MetS	1.47 (0.45–4.83)	1.32 (0.46–3.84)	2.02 (0.40–10.25)	1.51 (0.51–4.48)	4.72 (0.57–39.31)	1.43 (0.51–4.48)
Right testis volume	0.90 (0.84–0.97)	1.25 (0.88–1.78)	0.94 (0.87–1.02)	1.00 (0.77–1.30)	0.99 (0.92–1.07)	0.97 (0.78–1.21)
FSH	1.14 (1.01–1.30)	0.94 (0.69–1.29)	1.55 (1.17–2.05)	2.39 (0.68–8.41)	1.07 (0.88–1.31)	0.97 (0.51–1.86)
InhB	0.98 (0.97–0.99)	0.96 (0.93–1.00)	0.99 (0.98–1.01)	1.01 (0.98–1.04)	1.00 (0.99–1.02)	1.00 (0.97–1.03)

Data are UVA: univariable analysis; MVA: multivariable analysis; CCI: Charlson Comorbidity Index; +MetS: positive criteria for metabolic syndrome; FSH: follicle-stimulating hormone; InhB: inhibin B; WHO: World Health Organization; OR: odds ratio; CI: confidence interval

not. Similarly, higher FSH levels were univariably associated with pathologic progressive motility ($P = 0.002$). No variable was associated with pathologic sperm morphology. At MVA, no variable reached statistical significance for any pathological sperm condition.

DISCUSSION

We cross-sectionally tested the rate of MetS in a relatively large sample of White-European men seeking first medical attention for secondary couple's infertility at a single academic outpatient center. Likewise, we assessed the impact of MetS on clinical and semen characteristics in the same sample. Our interest was fuelled by (i) epidemiologic data suggesting an increasing prevalence of secondary infertility;[1,30] (ii) previous data showing the increasing prevalence of MetS among European men;[24] (iii) the potential impact of MetS on the overall hormonal milieu,[15,31] and male's overall health status;[32] and (iv) the lack of published observations of an association between MetS and male secondary infertility.

To the best of our knowledge, these findings offer the first demonstration that more than one out of eight men presenting for secondary couple's infertility meets NCEP-ATP III criteria for MetS. This prevalence is higher than that observed in the general population of the same age range.[33]

We chose NCEP-ATP III criteria to define MetS because they are the most widely used and readily available to physicians, thus facilitating their clinical and epidemiological use. Moreover, this definition does not harbor any preconceived notion of the underlying cause of MetS, whether it be insulin resistance or obesity. By adopting stringent enrolment criteria we were able to select a homogeneous White-European male sample (including only noninterracial infertile couples), thus minimizing the impact of potential unpredictable genetic biases.

The current findings demonstrate that +MetS patients were older and had a higher prevalence of hypogonadism compared to their –MetS counterpart. When assessing patients' comorbidity burden by means of the CCI scoring system, we found no significant general health status decline in men with MetS. Conversely, we have previously reported that primary infertile men with MetS are generally less healthy than their –MetS counterparts;[34] to this regard, we may speculatively argue that this difference is not observed in secondary infertile men due to their higher age and their consequent higher age-related comorbidity load. Moreover, the CCI was originally designed to assess comorbidities typically associated with 1-year mortality; therefore, it includes medical conditions that are more frequently found in an older or even elderly population and usually not in a younger population (such as infertile men). Thus, by definition and by its inherent limits, CCI completely excludes any item related to blood hypertension or sexually transmitted diseases which, in contrast, may be relevant medical conditions in young infertile men in the real-life setting.[14,35]

The second aspect of major clinical importance for these findings is related to patient age. We report the novel finding of a significant age increase among secondary infertile men with MetS compared with other infertile patients, thus confirming our own previous findings in primary infertile men.[34] Stone *et al.*[11] recently observed that the 34–40 years age range appears to be indicative for the first manifestations of age-related effects on seminal parameters. In this context, the likelihood of pregnancy following intercourse declines

continuously in men older than 34 years of age, regardless of the female partner's age.[11] Sperm concentration and the percentage of sperm with normal morphology, sperm motility, and ejaculate volume were found to decrease after 40, 43, and 45 years, respectively, whereas total sperm count declines even earlier.[11] Increasing paternal age (above the age of 35–40 years) was found to be associated with delayed conception in a large cohort of British fertile couples,[6] with an increased risk of spontaneous pregnancy loss,[7] and a decreased success rate for couples undergoing assisted reproductive techniques,[8–10] although these findings were not always unanimously confirmed.[5] Considering the mean age of our secondary infertile patients, along with previous evidence indicating a drift over delayed fatherhood[12] and the possible detrimental consequences of this, +MetS infertile patients are at an even higher risk, as the current findings outlined that they are older than infertile not meeting the criteria for MetS.

Our analyses confirmed the association between MetS and male hypogonadism in the general population[36] and in infertile patients.[19,20] We found that tT was reduced in +MetS patients compared to the –MetS group whereas cfT did not seem to be affected by this condition. In contrast, Lotti *et al*.[22] reported decreased values of both tT and fT, while Leisegang *et al*.[23] only reported an fT reduction in this specific setting. Along with tT, SHBG was also found to be reduced in our subset of +MetS patients. Although obesity and MetS are known to lower SHBG levels,[37] the actual impact on fT is still under debate. In this context, the results of the Massachusetts Male Aging Study showed no difference in terms of fT in overweight men.[38] Conversely, MacDonald *et al*.[39] reported the results of a meta-analysis showing a negative relationship for tT, SHBG, and fT with increased BMI values. Contextual decreases in both SHBG and tT may partially account for unmodified fT levels in our patients. This is important to note, as the patients in the current study were considerably younger than those reported in the studies just cited, thus potentially disguising any age-related effect on T levels.[40] As a whole, obesity-related and MetS-related hypogonadism is known to be accompanied by a plethora of factors simultaneously acting centrally and peripherally.[15] However, the impact of MetS on endocrine testicular function does not appear to be restricted only to T homeostasis. We observed that InhB and AMH levels were both reduced in +MetS patients as reported in previous studies.[34,41]

Our findings show the potential role of MetS in affecting semen parameters in secondary infertile men. More specifically, semen volume, sperm concentration and normal morphology were reduced in the +MetS subcohort, with a lower, yet not significant, prevalence of oligospermic, asthenospermic, and teratospermic patients. To this regard, the relationship between MetS and seminal parameters remains controversial. Indeed, two observational studies[22,23] have shown an association between MetS and poor sperm parameters in men broadly presenting for couple infertility. Conversely, our previous findings regarding primary infertile men reported no noticeable detrimental effect induced by MetS.[34] We may speculate that several factors might account for these differences. Emphasis on obesity when defining MetS (such as the case of Lotti *et al*.[22] using the International Diabetes Federation worldwide definition) and older age (as observed in our secondary infertile patients) might unveil the impact of MetS on seminal parameters whereas younger age and NCEP-ATP III definition, as observed in our sample of primary infertile men, would not.[34]

A recent study reported that 45 oligo-terato-asthenospermic MetS patients treated with metformin for six consecutive months experienced improvements in hormonal, metabolic and, above all, semen characteristics.[42] Such evidence suggests that in selected patients, improvement of the metabolic component might positively impact male reproductive health.

Our study is not devoid of limitations. First, this was a hospital-based study, raising the possibility of a number of selection biases. The sample was recruited from a single academic outpatient clinic, and despite the fact that it was made up of probably the largest, to date, homogeneous group of White-European secondary infertile men (restricted to noninterracial infertile couples), several larger studies across different centers and populations will be needed to substantiate our findings. Second, the analyses were implemented in a cross-sectional setting that lacked a comparison with a same-race, age-matched sample of fertile individuals. Third, although one of the strengths of these analyses was the availability of a rather comprehensive and consistent hormonal milieu for each patient, we lacked data regarding potential molecular alterations in spermatogenesis, which might be of importance in investigating the eventual impact of MetS on semen health. Fourth, the observational nature of the study prevents any kind of causal interpretation between MetS and male infertility.

Overall, MetS emerged as a powerful modifier not only of the endocrine milieu but also of semen quality in the current sample of patients. Molecular alterations in spermatogenesis, assessed for instance through DNA sperm fragmentation analysis, will perhaps provide more detailed information.

AUTHOR CONTRIBUTIONS

EV collected the data and drafted the manuscript; LB, PC, and RS collected and manage the data; EV, EP, and AS analyzed and interpreted the data and performed the statistical analysis; EP, RD, and FM were responsible for the critical revision of the manuscript for important intellectual contents; AS was responsible for the study concept and design and drafted the manuscript.

COMPETING INTEREST

The authors declared no competing financial interests.

ACKNOWLEDGMENTS

The authors would like to thank Dana Kuefner PhD for reviewing the language in this manuscript.

REFERENCES

1 World Health Organization Web Chapter on Couple's Infertility. Available from: http://www.who.int/reproductivehealth/topics/infertility/definitions/en/. [Last accessed on 2014 Dec 31].
2 Winters BR, Walsh TJ. The epidemiology of male infertility. *Urol Clin North Am* 2014; 41: 195–204.
3 Katib AA, Al-Hawsawi K, Motair W, Bawa AM. Secondary infertility and the aging male, overview. *Cent European J Urol* 2014; 67: 184–8.
4 Sartorius GA, Nieschlag E. Paternal age and reproduction. *Hum Reprod Update* 2010; 16: 65–79.
5 Humm KC, Sakkas D. Role of increased male age in IVF and egg donation: is sperm DNA fragmentation responsible? *Fertil Steril* 2013; 99: 30–6.
6 Ford WC, North K, Taylor H, Farrow A, Hull MG, *et al*. Increasing paternal age is associated with delayed conception in a large population of fertile couples: evidence for declining fecundity in older men. The ALSPAC Study Team (Avon Longitudinal Study of Pregnancy and Childhood). *Hum Reprod* 2000; 15: 1703–8.
7 Slama R, Bouyer J, Windham G, Fenster L, Werwatz A, *et al*. Influence of paternal age on the risk of spontaneous abortion. *Am J Epidemiol* 2005; 161: 816–23.
8 Mathieu C, Ecochard R, Bied V, Lornage J, Czyba JC. Cumulative conception rate following intrauterine artificial insemination with husband's spermatozoa: influence of husband's age. *Hum Reprod* 1995; 10: 1090–7.
9 Klonoff-Cohen HS, Natarajan L. The effect of advancing paternal age on pregnancy and live birth rates in couples undergoing *in vitro* fertilization or gamete intrafallopian transfer. *Am J Obstet Gynecol* 2004; 191: 507–14.
10 de La Rochebrochard E, de Mouzon J, Thépot F, Thonneau P; French National IVF Registry (FIVNAT) Association. Fathers over 40 and increased failure to conceive: the lessons of *in vitro* fertilization in France. *Fertil Steril* 2006; 85: 1420–4.

11 Stone BA, Alex A, Werlin LB, Marrs RP. Age thresholds for changes in semen parameters in men. *Fertil Steril* 2013; 100: 952–8.
12 Salonia A, Matloob R, Sacca A, Ferrari M, Gallina A, *et al*. Are Caucasian-European men delaying fatherhood? Results of a 7 year observational study of infertile couples with male factor infertility. *Int J Androl* 2012; 35: 125–32.
13 Salonia A, Matloob R, Gallina A, Abdollah F, Saccà A, *et al*. Are infertile men less healthy than fertile men? Results of a prospective case-control survey. *Eur Urol* 2009; 56: 1025–31.
14 Eisenberg ML, Li S, Behr B, Pera RR, Cullen MR. Relationship between semen production and medical comorbidity. *Fertil Steril* 2015; 103: 66–71.
15 Michalakis K, Mintziori G, Kaprara A, Tarlatzis BC, Goulis DG. The complex interaction between obesity, metabolic syndrome and reproductive axis: a narrative review. *Metabolism* 2013; 62: 457–78.
16 Donato J Jr., Cravo RM, Frazao R, Elias CF. Hypothalamic sites of leptin action linking metabolism and reproduction. *Neuroendocrinology* 2011; 93: 9–18.
17 Eisenberg ML, Kim S, Chen Z, Sundaram R, Schisterman EF, *et al*. The relationship between male BMI and waist circumference on semen quality: data from the LIFE study. *Hum Reprod* 2014; 29: 193–200.
18 Sermondade N, Faure C, Fezeu L, Shayeb AG, Bonde JP, *et al*. BMI in relation to sperm count: an updated systematic review and collaborative meta-analysis. *Hum Reprod Update* 2013; 19: 221–31.
19 Tsao CW, Liu CY, Chou YC, Cha TL, Chen SC, *et al*. Exploration of the association between obesity and semen quality in a 7630 male population. *PLoS One* 2015; 10: e0119458.
20 Chavarro JE, Toth TL, Wright DL, Meeker JD, Hauser R. Body mass index in relation to semen quality, sperm DNA integrity, and serum reproductive hormone levels among men attending an infertility clinic. *Fertil Steril* 2010; 93: 2222–31.
21 Bhattacharya SM, Ghosh M, Nandi N. Diabetes mellitus and abnormalities in semen analysis. *J Obstet Gynaecol Res* 2014; 40: 167–71.
22 Lotti F, Corona G, Degli Innocenti S, Filimberti E, Scognamiglio V, *et al*. Seminal, ultrasound and psychobiological parameters correlate with metabolic syndrome in male members of infertile couples. *Andrology* 2013; 1: 229–39.
23 Leisegang K, Udodong A, Bouic PJ, Henkel RR. Effect of the metabolic syndrome on male reproductive function: a case-controlled pilot study. *Andrologia* 2014; 46: 167–76.
24 Scuteri A, Laurent S, Cucca F, Cockcroft J, Cunha PG, *et al*. Metabolic syndrome across Europe: different clusters of risk factors. *Eur J Prev Cardiol* 2015; 22: 486–91.
25 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373–83.
26 WHO. Laboratory Manual for the Examination and Processing of Human Semen. 5th ed. Geneva, Switzerland: WHO; 2010.
27 Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, *et al*. Testosterone therapy in men with androgen deficiency syndrome: an American Society clinical practice guidelines. *J Clin Endocrinol Metab* 2010; 95: 2536–59.
28 Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. *J Clin Endocrinol Metab* 1999; 84: 3666–72.
29 Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr., Clark LT, *et al*. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation* 2004; 110: 227–39.
30 Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. *PLoS Med* 2012; 9: e1001356.
31 Corona G, Rastrelli G, Morelli A, Vignozzi L, Mannucci E, *et al*. Hypogonadism and metabolic syndrome. *J Endocrinol Invest* 2011; 34: 557–67.
32 Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, *et al*. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009; 120: 1640–5.
33 Miccoli R, Bianchi C, Odoguardi L, Penno G, Caricato F, *et al*. Prevalence of the metabolic syndrome among Italian adults according to ATP III definition. *Nutr Metab Cardiovasc* Dis 2005; 15: 250–4.
34 Salonia A, Capogrosso P, Bianchi M, Ventimiglia E, Clementi MC, *et al*. Prevalence and clinical meaning of metabolic syndrome in European Caucasian men presenting for primary couple's infertility. *J Urol* 189: e938.
35 Gimenes F, Souza RP, Bento JC, Teixeira JJ, Maria-Engler SS, *et al*. Male infertility: a public health issue caused by sexually transmitted pathogens. *Nat Rev Urol* 2014; 11: 672–87.
36 Muller M, Grobbee DE, den Tonkelaar I, Lamberts SW, van der Schouw YT. Endogenous sex hormones and metabolic syndrome in aging men. *J Clin Endocrinol Metab* 2005; 90: 2618–23.
37 Svartberg J, von Muhlen D, Sundsfjord J, Jorde R. Waist circumference and testosterone levels in community dwelling men. The Tromso Study. *Eur J Epidemiol* 2004; 19: 657–63.
38 Mohr BA, Bhasin S, Link CL, O'Donnell AB, McKinlay JB. The effect of changes in adiposity on testosterone levels in older men: longitudinal results from the Massachusetts Male Aging Study. *Eur J Endocrinol* 2006; 155: 443–52.
39 MacDonald AA, Herbison GP, Showell M, Farquhar CM. The impact of body mass index on semen parameters and reproductive hormones in human males: a systematic review with meta-analysis. *Hum Reprod Update* 2010; 16: 293–311.
40 Camacho EM, Huhtaniemi IT, O'Neill TW, Finn JD, Pye SR, *et al*. Age-associated changes in hypothalamic-pituitary-testicular function in middle-aged and older men are modified by weight change and lifestyle factors: longitudinal results from the European Male Ageing Study. *Eur J Endocrinol* 2013; 168: 445–55.
41 Robeva R, Tomova A, Kirilov G, Kumanov P. Anti-Mullerian hormone and inhibin B levels reflect altered Sertoli cell function in men with metabolic syndrome. *Andrologia* 2012; 44 Suppl 1: 329–34.
42 Morgante G, Tosti C, Orvieto R, Musacchio MC, Piomboni P, *et al*. Metformin improves semen characteristics of oligo-terato-asthenozoospermic men with metabolic syndrome. *Fertil Steril* 2011; 95: 2150–2.