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Primary, secondary and compensated hypogonadism: a novel risk stratification for infertile men

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SUMMARY

Recently, the cohort of men from the European Male Ageing Study has been stratified into different categories distinguishing primary, secondary and compensated hypogonadism. A similar classification has not yet been applied to the infertile population. We performed a cross-sectional study enrolling 786 consecutive Caucasian-European infertile men segregated into eugonadal [normal serum total testosterone (≥3.03 ng/mL) and normal luteinizing hormone (≤9.4 mU/mL)], secondary (low total testosterone, low/normal luteinizing hormone), primary (low total testosterone, elevated luteinizing hormone) and compensated hypogonadism (normal total testosterone; elevated luteinizing hormone). In this cross-sectional study, logistic regression models tested the association between semen parameters, clinical characteristics and the defined gonadal status. Eugonadism, secondary, primary and compensated hypogonadism were found in 80, 15, 2, and 3% of men respectively. Secondary hypogonadal men were at highest risk for obesity [OR (95% CI): 3.48 (1.98–6.01)]. Primary hypogonadal men were those at highest risk for azoospermia [24.54 (6.39–161.39)] and testicular volume <15 mL [12.80 (3.40–83.26)]. Compensated had a similar profile to primary hypogonadal men, while their risk of azoospermia [5.31 (2.25–13.10)] and small testicular volume [8.04 (3.17–24.66)] was lower. The risk of small testicular volume [1.52 (1.01–2.33)] and azoospermia [1.76 (1.09–2.82)] was increased, although in a milder fashion, in secondary hypogonadal men as well. Overall, primary and compensated hypogonadism depicted the worst clinical picture in terms of impaired fertility. Although not specifically designed for infertile men, European Male Ageing Study categories might serve as a clinical stratification tool even in this setting.

INTRODUCTION

Male hypogonadism is a common finding in infertile men (Jungwirth *et al.*, 2016). Although it has been clearly defined as a clinical entity in the general population, several phenotypes can be observed among hypogonadal men (Basaria, 2014; Jungwirth *et al.*, 2016), each one reflecting an underlying pathological feature. More precisely, hypogonadism is characterized by the testicular failure to produce testosterone (T), either for a central disorder (hypothalamus or pituitary) or a primary deficiency. The phenotype picture of these two clinical entities are very similar; the main difference is that in primary hypogonadism spermatogenesis tends to be impaired to a greater degree than Leydig cell function, whereas both functions are impaired to the same degree in men with secondary hypogonadism (Basaria, 2014). Remarkably, a progressive decline in T and sperm production usually occurs with age, such that men in their eighth decade have mean circulating total T (tT) and free T levels of 35 and 50%, lower than young men in their 20s respectively (Vermeulen *et al.*, 1999).

Recently, using data from the cohort of 40–79 years old men from the European Male Ageing Study (EMAS), Tajar *et al.* (2010) stratified individuals into four different categories of gonadal status where primary, secondary and compensated hypogonadism were distinguished by luteinizing hormone (LH) and tT measurements, specific risk factors and associated symptoms. More specifically, they outlined the issue of compensated hypogonadism, which occurs in men with normal tT levels combined with higher LH values, particularly in the ageing

population, thus representing a further clinical subgroup of hypogonadism.

A similar hormonal milieu stratification has not yet been applied to the infertile population which, conversely, shares a number of similarities with the aged counterpart, beginning with a more frequently impaired overall health status (Salonia *et al.*, 2009; Eisenberg *et al.*, 2015; Ventimiglia *et al.*, 2016a). Likewise, no previous clinical evidence has considered the potential impact of different forms of hypogonadism on the general health status, the hormonal milieu and the overall reproductive function of men presenting for couple's infertility. These observations prompted us to investigate the prevalence of different forms of hypogonadism and the eventual association of clinical, semen and hormonal parameters in a homogeneous cohort of Caucasian-European men presenting for couple's infertility. As a final point, we sought to revaluate our findings in terms of male infertility in consideration of previously published data concerning the general aging male population (Tajar *et al.*, 2010), in order to discuss the infertility workup in light of this new categorization.

MATERIALS AND METHODS

Study population

The analyses of this cross-sectional study were based on a cohort of 786 consecutive Caucasian-European men assessed at a single academic centre for couple's infertility (non-interracial infertile couples only) between September 2006 and September 2014. Patients were enrolled if they were ≥18 and ≤80 years old and had either male factor infertility (MFI) or mixed factor infertility (MxFI). MFI was defined after a comprehensive diagnostic evaluation of all the female partners. According to the World Health Organisation (WHO) criteria, infertility was defined as not conceiving a pregnancy after at least 12 months of unprotected intercourse regardless of whether or not a pregnancy ultimately occurs (WHO, 2015). Men were included in the study when having at least one pathologic semen parameter according to the WHO criteria at two separate semen analyses.

Secondary infertility is defined according to the inability to conceive following a previous pregnancy (WHO, 2015). Patients were assessed with a thorough self-reported medical history including age and co-morbidities. Weight and height were measured for each patient, calculating body mass index (BMI), further treated as a categorical variable using the NIH definitions of 'normal' (from 18.5 to 24.9), 'overweight' (from 25 to 29.9) and 'obese' (30+) (WHO/Europe, n.d.). Testes volume was assessed in each case using a Prader orchidometer by an expert academic uroandrologist (AS). Varicocoele was clinically detected in each and further confirmed by ultrasound examination (*Jungwirth et al.*, 2016). Health-significant co-morbidities were scored with the Charlson Comorbidity Index (CCI; Charlson *et al.*, 1987). We used the *International Classification of Diseases, 9th revision* in which coding algorithms were used to define the 17 co-morbidities that constitute the most widely used CCI score.

Venous blood samples were drawn from each patient between 7 AM and 11 AM after an overnight fast. Follicle-stimulating hormone (FSH), LH and 17-beta-estradiol (E2) were measured using a heterogeneous competitive magnetic separation assay (Bayer Immuno 1 System; Bayer Corp., Tarrytown, NY, USA). Inhibin B (InhB) was measured by an enzyme-linked immunosorbent assay (Beckman Coulter AMH Gen II ELISA, Brea, CA, USA). Total testosterone levels were measured via a direct chemiluminescence immunoassay (ADVIA Centaur; Siemens Medical Solutions Diagnostics, Deerfield, IL, USA). Sex hormone-binding globulin 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 (Bhasin *et al.*, 2010). Patients underwent at least two consecutive semen analyses, evaluated according to the World Health Organisation (2010) criteria. Data collection was carried out following the principles outlined in the Declaration of Helsinki; all patients signed an informed consent agreeing to deliver their own anonymous information for future studies. The study was approved by our local ethical committee.

Statistical methods

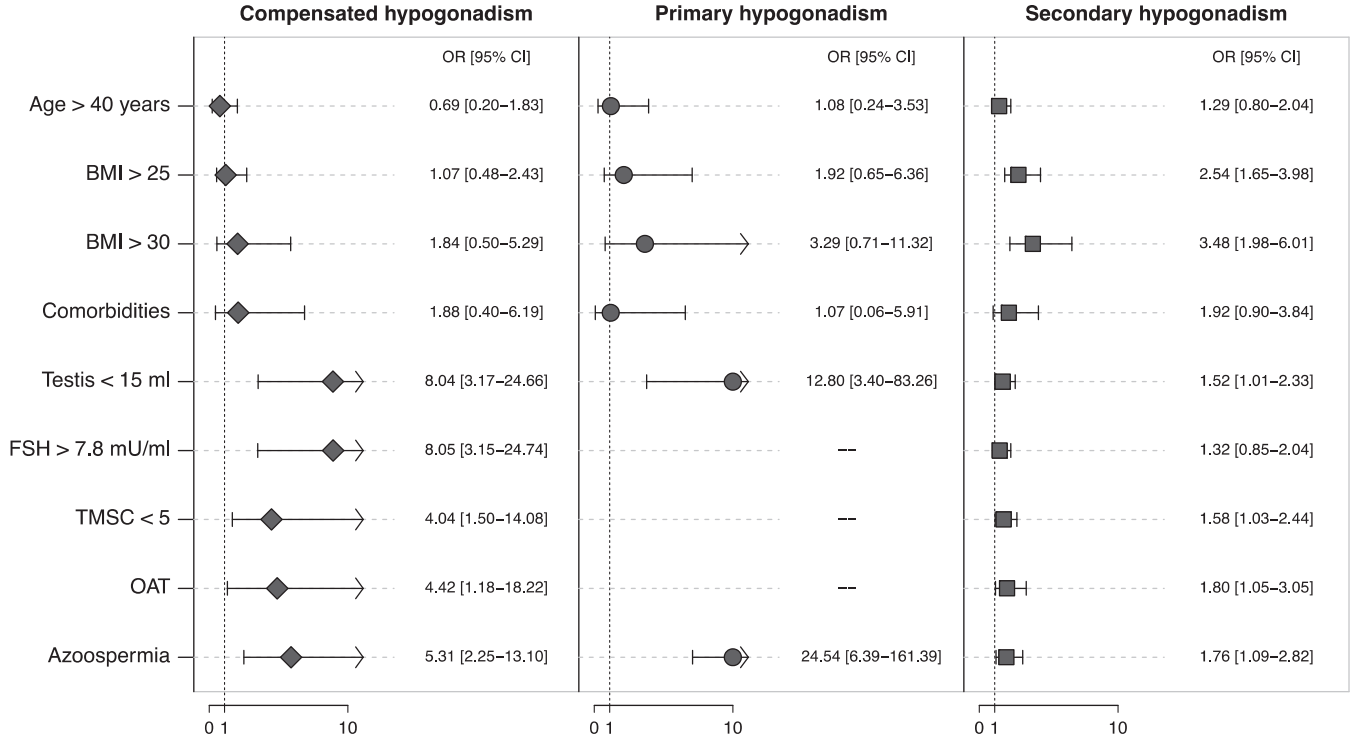
Descriptive statistics tested the associations between clinical characteristics, laboratory values and semen parameters in different groups of hypogonadal patients; four groups of individuals were defined according to Tajar *et al.* (2010): eugonadal [normal tT (≥3.03 ng/mL) and normal LH (≤9.4 mUI/mL)], secondary hypogonadism [low tT (≤3.03 ng/mL) and low/normal LH (≤9.4 mUI/mL)], primary hypogonadism [low tT (≤3.03 ng/mL) and elevated LH (≥9.4 mUI/mL)] and compensated hypogonadism [normal tT (≥3.03 ng/mL) and elevated LH (≥9.4 mUI/mL)] hypogonadism.

Data are presented descriptively as medians and interquartile ranges. Statistical tests were performed using R version 3.3.0 (The R Foundation for Statistical Computing, 2016). Logistic regression models tested the multivariate likelihood for each hypogonadal category of having the following outcomes of decreased reproductive health: oligoasthenoteratozoospermia (OAT, i.e. sperm concentration, progressive motility and normal morphology simultaneously below standard values according to the WHO 2010 criteria; Jungwirth *et al.*, 2016), total motile sperm count (TMSC) $< 5 \times 10^6$ spermatozoa (Hamilton *et al.*, 2014), azoospermia (i.e. absence of spermatozoa in the semen), mean testicular volume < 15 mL (Lipshultz *et al.*, 2009; Lotti & Maggi, 2015), FSH > 7.8 mU/mL (Barbotin *et al.*, 2015). Secondary outcomes for our analysis were older age at presentation (>40 years), BMI > 25 kg/m^2, BMI > 30 kg/m^2 and presence of co-morbidities (i.e. CCI > 0). Whenever possible, covariates included known risk factors for decreased reproductive health: age, BMI, CCI, primary vs. secondary infertility, length of infertility, varicocoele, cryptorchidism and karyotype abnormalities. The adjusted odds ratios were then represented in a forest plot (Fig. 1).

RESULTS

Table 1 lists the characteristics and the descriptive statistics of the entire cohort of patients according to their gonadal status. Overall, hypogonadism was observed in 155 (20%) patients. Of all, eugonadism, secondary, primary and compensated hypogonadism were found in 631 (80%), 114 (15%), 14 (2%) and 27 (3%) men respectively. Median age did not vary markedly with gonadal status in our cohort. All groups showed median BMI values above the overweight range, with primary and secondary hypogonadal men having the highest rates of obesity (both 21%). More than 80% of men with either primary or compensated

Figure 1 Forest plot with the multivariable adjusted OR (95% CI) for each analysed outcome according to the specific gonadal group. The reference group (OR = 1) is represented by eugonadal men. Age > 40 years was adjusted for length of infertility. BMI > 25 and 30 kg/m^2 were adjusted for patient age and Charlson Comorbidity Index (CCI). Co-morbidities were adjusted for age and BMI. Testicular volume < 15 mL, FSH > 7.8 mU/mL, OAT, TMSC < 5 and azoospermia OR were adjusted for age, CCI, primary vs. secondary infertility, length of infertility, varicocoele, cryptorchidism and karyotype abnormalities. BMI, body mass index; Co-morbidities: CCI > 0; FSH, follicle-stimulating hormone; OAT, oligoasthenoteratozoospermia; TMSC, total motile sperm count.



hypogonadism had a testicular volume < 15 mL; moreover, primary and compensated hypogodanal men displayed the highest values of FSH, the lowest of InhB, with 100 and 81% of them having FSH ≥ 7.8 mU/mL respectively. Considering semen parameters, azoospermia was more commonly diagnosed in primary (86%) and compensated (63%) hypogonadal men. Analysis of covariance (ANCOVA) assessment of differences among groups is reported in Table S1.

Figure 1 portrays the forest plot with the multivariable adjusted OR (95% CI) for each analysed outcome according to the specific gonadal group. The referral category is represented by eugonadal men (OR = 1). Primary hypogonadal men were those at highest risk for azoospermia [24.54 (6.39–161.39)] and testicular volume < 15 mL [12.8 (3.4–83.26)]. ORs for FSH > 7.8 mU/mL, OAT and pathological TMSC could not be estimated in this category as 100% of these men had a pathological outcome (Table 1). Compensated had a similar profile to primary hypogonadal men, however their risk of azoospermia [5.31 (2.25–13.1)] and small testicular volume [8.04 (3.17–24.66)] was lower; moreover, they were at higher risk for having FSH values > 7.8 mU/mL [8.05 (3.15–24.74)], OAT (4.42 (1.18–18.22)] and TMSC < 5 × 10^6 spermatozoa [4.5 (1.69–15.6)] compared to eugonadal men. The risk of testicular volume < 15 mL [1.52 (1.01–2.33)], OAT [1.8 (1.05–3.05)], pathological TMSC [1.58 (1.03–2.44)] and azoospermia [1.76 (1.09–2.82)] was increased in secondary hypogonadal men, however in a milder fashion than both primary and compensated ones. Importantly, the highest risk of obesity was observed in secondary hypogonadism [3.48 (1.98–6.01)].

DISCUSSION

We investigated whether different forms of hypogonadism can be distinguished among infertile men according to the stratification described by Tajar *et al.* (2010) in the EMAS cohort, comparing our findings to those observed in the general ageing EMAS population, reconsidering both hypogonadism and infertility workup in light of this new categorization. Moreover, we tested if the analysed categories had a possible prognostic impact in terms of seminal alterations.

Hypogonadism was present in 20% of this cohort of infertile men, with a distribution among subcategories closely resembling that seen in the general middle-aged population studied in the EMAS cohort (Tajar *et al.*, 2010). Moreover, what clearly emerges from our study is how the applied hormonal clustering is able to prognostically stratify the infertile patients. This should not be self-evident, because we applied categories previously identified and validated in an older and unselected sample including both fertile and infertile men (Tajar *et al.*, 2010). Consistent with this, several clinically relevant differences emerge when comparing our categories to EMAS' ones. First, if the EMAS found relevant differences in terms of age among the analysed gonadal group, when applying the same categories to infertile men, the median age was rather homogeneous and certainly it did not vary drastically according to the gonadal status. When focusing on infertile men, one should always remember that we are dealing with a very peculiar subset of individuals from the general population, usually younger and less healthy (Salonia *et al.*, 2009). Moreover, among infertile men, those with the lowest values of sperm concentration appear at higher risk of

Table 1 Descriptive statistics in the study populations. Columns portray men according to their gonadal status

	Overall	Eugonadism	Compensated	Primary	Secondary
N	786	631	27	14	114
Age (years), median (IQR)	36 (33–40)	36 (33–40)	38 (35–40)	38 (34–40)	37 (34–40)
Age > 40 years, *n* (%)	162 (21)	127 (20)	4 (15)	3 (21)	28 (25)
BMI (kg/m^2), median (IQR)	25 (23–27)	25 (23–27)	27 (23–27)	26 (23–28)	27 (25–30)
Weight status					
Normal weight	374 (48)	324 (51)	12 (44)	5 (36)	33 (29)
Over weight	337 (43)	263 (42)	11 (41)	6 (43)	57 (50)
Obesity	75 (10)	44 (7)	4 (15)	3 (21)	24 (21)
Overweight or obesity, *n* (%)	412 (52)	307 (49)	15 (56)	9 (64)	81 (71)
Obesity, *n* (%)	75 (10)	44 (7)	4 (15)	3 (21)	24 (21)
CCI, median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
CCI					
0	732 (93)	593 (94)	24 (89)	13 (93)	102 (89)
1	30 (4)	22 (3)	0 (0)	0 (0)	8 (7)
≥2	24 (3)	16 (3)	3 (11)	1 (7)	4 (4)
Co-morbidities, *n* (%)	54 (7)	38 (6)	3 (11)	1 (7)	12 (11)
Smokers, *n* (%)	233 (30)	185 (29)	11 (41)	5 (36)	32 (28)
Mean testicular volume, median (IQR)	16 (12–20)	18 (13–22)	10 (7–12)	6 (3–8)	15 (11–20)
Testicular volume < 15 mL, *n* (%)	274 (35)	193 (31)	22 (81)	12 (86)	47 (41)
FSH (mU/mL), median (IQR)	5 (3–10)	5 (3–9)	21 (15–30)	28 (24–41)	6 (3–11)
FSH > 7.8 mU/mL, *n* (%)	261 (33)	182 (29)	22 (81)	14 (100)	43 (38)
LH (mU/mL), median (IQR)	4 (3–6)	4 (3–5)	12 (11–17)	14 (13–18)	3 (2–5)
Total testosterone (ng/mL), median (IQR)	5 (3–6)	5 (4–6)	5 (4–6)	3 (2–3)	3 (2–3)
Calculated free testosterone (pg/mL), median (IQR)	90 (71–120)	98 (78–124)	83 (67–113)	49 (33–54)	64 (52–77)
SHBG (nmol/L), median (IQR)	30 (23–40)	32 (25–41)	38 (33–50)	34 (25–48)	19 (16–27)
E_2 (pg/mL), median (IQR)	30 (24–40)	30 (24–41)	36 (41–42)	36 (25–42)	26 (24–34)
Inhibin B (pg/mL), median (IQR)	106 (47–166)	118 (63–173)	8 (6–44)	7 (6–7)	89 (32–124)
Semen volume (mL), median (IQR)	3 (2–4)	3 (2–4)	2 (2–3)	2 (1–3)	3 (2–4)
Sperm concentration (10^6 spermatozoa),[a] median (IQR)	18 (5–46)	19 (5–46)	9 (3–21)	1 (1–1)	15 (4–40)
Progressive motility[a] (%), median (IQR)	24 (9–36)	25 (10–37)	15 (1–20)	6 (3–9)	16 (6–34)
Sperm normal morphology[a] (%), median (IQR)	3 (0–12)	3 (0–12)	2 (0–4)	3 (2–4)	3 (0–10)
Infertility					
Primary	709 (90)	570 (90)	26 (96)	14 (100)	99 (87)
Secondary	77 (10)	61 (10)	1 (4)	0 (0)	15 (13)
Azoospermia, *n* (%)	190 (24)	126 (20)	17 (63)	12 (86)	35 (31)
OAT,[a] *n* (%)	158 (27)	124 (25)	6 (60)	1 (50)	27 (34)
TMSC < 5 × 10^6,[a] *n* (%)	254 (43)	208 (41)	6 (60)	2 (100)	38 (48)
Varicocoele, *n* (%)	411 (52)	334 (53)	10 (37)	6 (43)	61 (54)
Cryptorchidism,[b] *n* (%)	89 (11)	60 (10)	8 (30)	2 (14)	18 (17)
Karyotype abnormalities, *n* (%)	28 (4)	17 (3)	3 (16)	5 (42)	3 (3)
Time of infertility (months), median (IQR)	18 (12–30)	18 (12–30)	24 (12–36)	18 (12–24)	18 (12–31)

BMI, body mass index; CCI, Charlson Comorbidity Index; E_2, 17-beta-estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; OAT, oligoasthenoteratozoospermia; SHBG, sex hormone-binding globulin; TMSC, total motile sperm count; IQR, interquartile range. [a]Data obtained on 596 non-azoospermic men. [b]Bilateral in 32 men (19 eugonadal, 5 compensated, 1 primary and 7 secondary hypogonadal men).

having a deteriorated health status (Eisenberg *et al.*, 2015; Ventimiglia *et al.*, 2015), particularly in the case of azoospermic men (Lotti *et al.*, 2016); in this context, our findings suggest that having a perturbed gonadal status does not apparently increase the risk of having a CCI > 0. However, the CCI does take into account a limited set of co-morbidities, for instance, excluding even hypertension (Charlson *et al.*, 1987).

The basic step of the male infertility workup is represented by physical examination (Tournaye *et al.*, 2016), which provide valuable information regarding patient metabolic status and the health of his reproductive system. More specifically, in our study, we inquired how patients' BMI and testicular volume, both easily obtainable at the first infertility evaluation, were influenced by the gonadal status. Concerning the first point, each analysed group displays median BMI values in the overweight range, with all the three hypogonadal subgroups showing doubled, if not tripled, rates of obesity when compared to eugonadal patients. Secondary hypogonadal men were those at highest risk for obesity (Fig. 1), as was previously shown in the EMAS cohort (Tajar *et al.*, 2010). The link between obesity, metabolic syndrome and low tT levels has become more and more clear during the last years (Lotti *et al.*, 2013; Michalakis *et al.*, 2013; Ventimiglia *et al.*, 2016c,d), and BMI appears to be one of the most powerful predictors of biochemical hypogonadism in the infertility setting (Ventimiglia *et al.*, 2016a). Moreover, these findings are consistent with the picture of secondary hypogonadism, which is indeed the subpopulation showing higher BMI and prevalence of obesity. Therefore, encouraging a secondary hypogonadal man to lose weight could lead to an increase in gonadotropins and tT levels (Travison *et al.*, 2007; Grossmann, 2011; Camacho *et al.*, 2013).

On the other side, a smaller testicular volume is associated to spermatogenic dysfunction and to a higher probability of having tT < 3 ng/mL (Arai *et al.*, 1998; Rastrelli *et al.*, 2013; Ventimiglia *et al.*, 2016a). Compensated and, above all, primary hypogonadal men were not only those with the lowest median testicular volumes but also had the highest risk of having a testicular volume < 15 mL, which has already being associated with a certain degree of spermatogenic dysfunction (Lipshultz *et al.*, 2009). Even men with secondary hypogonadism had a slightly higher

risk compared to eugonadal men. This would potentially suggest how compensated hypogonadism might show, despite normal tT values, an already impaired testicular function resembling what happens in primary hypogonadal men.

Considering the endocrine compartment, while very high FSH values are not surprising in primary hypogonadal men (Jungwirth *et al.*, 2016), four men out of five in the compensated group had a FSH value above 7.8 mU/mL, previously demonstrated as a very informative threshold in predicting impaired spermatogenesis (Barbotin *et al.*, 2015). Our findings on FSH go along with those regarding inhibin B, with very low values in both primary and compensated hypogonadal men. In spite of an endocrine compartment still capable of maintaining an appropriate T production in men with compensated hypogonadism, the exocrine compartment appears severely compromised in these men. This is consistent with the previously analysed clinical feature indicating how compensated hypogonadism more closely resembles primary rather than secondary.

The descriptive and prognostic relevant differences observed in terms of semen parameters among the analysed subgroups are one of the major finding of this study. Primary hypogonadal men are the worst performers, with the highest risk of azoospermia, whereas compensated and secondary hypogonadal men showed a milder degree of spermatogenesis impairment. When focusing on non-azoospermic men, compensated and secondary hypogonadal ones were once again at higher risk when compared to eugonadal ones for having both OAT and, more importantly, TMSC < 5 million spermatozoa, recently emerged as a very accurate measure of the male fertility potential (Hamilton *et al.*, 2014); the compensated subgroup was the most suffering of the two of them considering sperm production. Of importance, these data testify how the EMAS categories are able to identify different subgroups of infertile patients. These findings are not unique, because recent evidence showed no difference in testosterone levels among infertile men with isolated vs. multiple seminal parameters (Lotti *et al.*, 2016), and enhance the importance of overall gonadal status assessment (i.e. testosterone along with gonadotropins in every patient). Combing hormonal and seminal data not only gives us a thorough overview of the reproductive health in the infertile individual according to his specific gonadal status, but also outlines a possible diagnostic/prognostic role for the EMAS categories. In concordance with this, the highest proportion of karyotype abnormalities was found among primary and compensated hypogonadal men (Ventimiglia *et al.*, 2016b).

Although developed in the general population and with the specific purpose of targeting late onset hypogonadism, the EMAS categories have proven a good discrimination potential when applied to infertile men. Hormonal profile is easy to obtain during the earlier steps of the infertility workup, and therefore the currently employed classification constitutes an easy way to implement the diagnostic process and patient counselling.

However, several important limitations concerning the use of this classification in the infertility setting are worth mentioning. The inability of fathering children is mainly related to an impairment of the exocrine testicular function (Tournaye *et al.*, 2016), often partnered or directly driven by the endocrine compartment; the EMAS categories were instead developed relying on LH and tT values, without taking into account the fertility status of the study participants. In this study, we focused on tT and LH values and their derived definition of hypogonadism: if on the one hand it is of major importance that hypogonadism should be regarded as a clinical syndrome rather than a biochemical diagnosis, on the other hand, until male infertility-related hypogonadism will gain its own nosological dignity, this issue remains unfortunately unaddressed. The concept of clinical syndrome in the infertile men is obviously intertwined with paternity outcomes; semen parameters are the most informative available predictors of paternity considering the male counterpart, but unfortunately share important limitations (Tournaye *et al.*, 2016). Indeed, the major challenges in defining the infertility-related hypogonadism are represented by the younger age of infertile men and the still poor knowledge we have in the field of male infertility pathogenesis. A paradigm shift from T to reproductive health, including both exocrine and endocrine testicular functions, is definitely demanded at this regard, without losing sight of the general health status as well. A definition of the infertility-related male hypogonadism based on FSH levels and impaired spermatogenesis would perhaps be more suitable for this specific subset of male individuals rather than employing LH and tT on their own.

Our study is not devoid of further limitations. First, the analyses were cross-sectionally implemented and a comparison with a same-race, age-matched cohort of fertile individuals is lacking. Second, the analyses offer no data regarding the potential molecular alterations in terms of spermatogenesis, which might be of importance in investigating the eventual impact of the hormonal milieu on semen health. Until wider and more comprehensive studies, focusing on paternity outcomes, and including fertile individual as well will not be available, defining infertility-related hypogonadism will still remain a far from ending work in progress.

CONCLUSIONS

Overall, we found a high prevalence of hypogonadism among infertile patients, closely resembling epidemiological data found in cohorts of older individuals not specifically screened for infertility. Primary and compensated hypogonadism depicted the worst clinical picture in terms of impaired fertility, with primary hypogonadal men having a 24-fold increased risk of azoospermia and a 13-fold increased risk of small testicular volume compared to eugonadal men. Compensated hypogonadism emerged to be a clear condition of testicular dysfunction (fivefold increased risk of azoospermia, fourfold increased risk of low total motile sperm count, eightfold increased risk of low testicular volume), in spite of normal *T* values. Although not specifically designed for infertile men, EMAS categories might serve as a clinical stratification tool in infertile men.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. ANCOVA/chi-square statistics in the study populations.