Review Article
Male reproductive health and infertility

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Is It Time for Andrology and Endocrinology Professionals in Assisted Reproduction Centers?

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Epidemiologists indicate that about half of the couple's infertility cases are due to a male factor. Despite this, the role of andrologists or endocrinologists in assisted reproductive technique (ART) centers is still underestimated. According to our literature review, this reduces the chance of a thorough clinical evaluation of the male partners, which, sometimes consists only in a mere semen analysis, usually performed by laboratory technicians. A more complete diagnostic process could lead to the identification of potentially treatable causes of infertility, the recognition of diseases that require immediate treatment, and to the discovery of genetic diseases and, therefore, transmissible to the offspring. It can also increase the success rate of ART resulting in less psychological and financial burden for both public health resources and infertile couples. The presence of medical personnel with andrological and endocrinological skills in the ART centers represents the first step in creating 'precision medicine'. We hope that the guidelines of the various scientific societies will clearly contemplate this possibility.

Keywords: Andrology; Endocrinologist; Guidelin; Male infertility; Reproductive techniques, assisted

INTRODUCTION

Couple infertility has a worldwide prevalence of 15%–20% and is defined when a couple fails to achieve pregnancy after 12 months or more of regular unprotected sexual intercourse [1]. It is estimated to affect 40.5 million couples [1]. This prevalence is expected to further increase [2]. Once the diagnosis of couple infertility has been established, the therapeutic options include, according to the principle of graduality, medical and/or surgical treatment and, in case of failure, assisted reproductive technique (ART). These are divided into first, second, and third-level techniques.

First-level techniques (intrauterine insemination, IUI) include intracervical or supracervical insemination and are generally used for the male infertility factor (slight alteration of sperm parameters, sexual dysfunction, *etc.*). The second-level techniques include *in vitro* fertilization (IVF) with embryo transfer and intracytoplasmic sperm injection (ICSI). Third-level techniques include male gamete recovery from the gonads by surgical techniques and subsequent ICSI. The latter techniques are used in case of moderate-severe alteration of sperm parameters or female infertility factors as cervical factor, or to prevent infectious diseases which could be transmitted during conception.

The definition of male factor infertility lies in the seminal fluid characteristic, which must be performed

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according to the criteria of the World Health Organization (WHO), recently updated by the sixth edition of the relative manual [3]. However, the recent modifications of this manual with the elimination of the threshold values underline that the laboratory evaluation of the human semen is not sufficient to indicate the potential fecundity of the male partner. The evaluation of the sperm characteristics of the seminal fluid cannot, therefore, be separated from the andrological and endocrinological evaluation of the male partner by a physician with experience in this field. Similarly, the evaluation of the female partner by a gynecologist and an endocrinologist is necessary to discover the causes of infertility and to evaluate the ovarian reserve. This narrative review article aims at highlighting the role of andrology and endocrinology professionals to improve the performance of ART centers. To accomplish this, we will discuss the prevalence and etiology of the male factor infertility, debate the current success rate of ART, review the weight of the male factor in the ART outcome, taking into consideration the role of azoospermia and of varicocele. Finally, we will provide an overview of the international guidelines of ART, to examine what it is currently suggested about the seminological and endocrinological procedures, as well as regarding the presence of an andrologist or an endocrinologist in ART centers.

PREVALENCE AND ETIOLOGY OF MALE FACTOR INFERTILITY

Male infertility is a frequent pathological condition and represents the primary or contributing factor in about 50% of couples seeking for fertility [4]. These data seem to be progressive, as male infertility is increasing in recent years associated with a progressive decline of sperm parameters. A 2017 metanalysis of 185 studies conducted from 1973 to 2011, analyzing a total of 42,935 semen sample revealed a progressive decline in sperm count and progressive sperm count. These data suggest that public research must study the reasons of this decline to better understand physiopathological mechanism and prevent or cure them [5].

The analysis of seminal fluid represents the first step in the diagnostic characterization of male infertility: this can show alteration of conventional sperm parameters and bio-functional sperm parameters, which could also reflect the presence of mitochondrial disfunction, sperm apoptosis, abnormal chromatin compactness, or DNA fragmentation [6-8].

Interestingly, the analysis of seminal fluid is also important as its quality may provide an indicator of health. Different studies affirmed how men with compromised semen parameters have higher rate of morbidity and mortality and suggest how semen analysis could be an early marker for some type of cancer [9-11]. This points toward the importance of an accurate evaluation of the infertile male patient.

The etiology of male infertility is classified into pretesticular, testicular, and post-testicular causes. A schematic summary of causes in male infertility is provided in Supplement Table 1 [12]. A particular mention goes to the possible risk factors, some of which are the result of improper lifestyle habits ranging from unfit nutrition, poor physical activity, use or abuse of voluptuous substances that can cause damage to endocrine gonadal function and gametogenesis (Supplement Table 2) (Ministero della Salute Italiano, 2012).

SUCCESS RATE OF ASSISTED REPRODUCTIVE TECHNIQUES

In ART centers, during the infertility diagnostic work-up, the male partner does not receive the same attention as the female partner and is often seen by personnel not qualified for this task [13]. Evaluation of the male partner should be part of the clinical management of the couple in ART centers, but usually the personnel counseling the infertile patients is represented by gynecologists and embryologists who do not have adequate skills for diagnosis and treatment. However, the diagnostic process of the male partner begins late or only after embryo development or implantation failure. Furthermore, with the advent of ART the clinical management of the male partner has been further neglected [13]. A recent study from our group, conducted on 320 infertile Italian couples, showed that more than half (56%) of them underwent ART (ICSI) although the male partner had a potentially treatable cause (oligoasthenoteratozoospermia with follicle-stimulating hormone levels <8 IU/L, mono or bilateral varicocele, and urogenital infections) and the female partner was at a young age (<35 y) [14].

In view of the widespread and not always justified use of ART for couple infertility, examining the success rate of Italian, European and American ART centers is important to understand whether the current practice is effective or not.

The activity of the Italian ART centers updated to 2019 is summarized in Supplement Table 3. Overall, the success rate of ART seems to be poor, without any improvement in the period 2014–2019, at least in Italy. Particularly, the live birth rate per number of cycles started annually ranges from 15.3% (2015) to 16.5% (2014) for the second and third levels (Table 1) [15], and from 7.0% (2014) to 8.4% (2018) for the first level (Table 1) [16,17]. These data suggest the need for an in-depth analysis of the procedures followed in the ART centers for their possible implementation.

The European Society of Human Reproduction and Embryology (ESHRE) registry reports 39 countries collecting data for the year 2018, with a total number or 1,422 clinics offering Medical Assisted Reproduction (MAR), accounting for more than 1 million (1,007,598) treatment cycles. These include 162,837 IVF, 400,375 ICSI, and 309,475 Fresh Embryo Transfer. The data show an overall success rate of 23%–25% with IVF or ICSI in 2017–2018 (Table 2) [16,17]. If we observe data stratified for age distributions of women treated with IVF and ICSI, we see an age-dependent decline of preg-

Table 1. Summary of the use of first, second and third level procedures in assisted reproductive techniques in Italy in 2014–2019 [15]

	2014	2015	2016	2017	2018	2019
First-level techniques[a]						
Number of couples treated	14,967	14,545	13,798	12,423	11,426	10,985
Number of cycles started	23,903	23,062	21,767	19,431	17,774	16,586
Number of pregnancies	2,399	2,466	2,429	2,078	1,952	1,767
% pregnancies per cycle started	10.0	10.7	11.2	10.7	11.0	10.7
% of pregnancies lost to follow-up	18.2	16.8	15.0	13.9	11.7	11.2
Number of deliveries	1,530	1,649	1,629	1,396	1,369	1,249
Number of live birth	1,683	1,807	1,791	1,519	1,493	1,365
Number of live birth/number of cycles started (%)	7.0	7.8	8.2	7.8	8.4	8.2
Second and third level techniques[b]						
Number of couples treated	55,859	59,747	63,724	65,943	66,083	67,633
Number of cycle started	67,054	72,048	75,889	78,457	79,735	82,476
Number of pregnancies	13,642	14,391	15,405	16,793	17,042	17,787
% of pregnancies lost to follow-up	10.8	11.3	10.2	11.9	9.7	10.6
Number of deliveries	9,252	9,512	10,386	11,094	11,428	11,754
Number of live birth	11,037	11,029	11,791	12,454	12,646	12,797
Number of live birth/number of cycle started (%)	16.5	15.3	15.5	15.9	15.9	15.5

[a]Data include intrauterine insemination and male gamete donation.
[b]Data include fresh techniques, thawing of embryos and oocytes, and donation of male and female gametes.

Table 2. Statistics of the use of first and second-third level procedures in assisted reproductive techniques in Europe in 2017–2018 [16,17]

	2017		2018	
	Second and third-levels techniques[a]		Second and third-levels techniques[a]	
	IVF	ICSI	IVF	ICSI
Number of cycles started	562,223		487,406	
Number of aspiration	151,250	367,796	153,648	363,611
% pregnancies per aspirations	26.8	24.0	25.5	25.5
% deliveries per aspirations	20.5	17.7	19.6	16.7
Number of transfers	389,434		364,574	
Number of deliveries	91,024		91,427	
% of deliveries per transfers	23.0		25.0	

ICSI: intra cytoplasmatic sperm injection, IVF: *in vitro* fertilization.
[a]Including IVF and ICSI but not Fresh Embryo Transfer.

Table 3. Aspirations, pregnancy and delivery rates by age distribution of women treated with IVF and ICSI in 2018 in Europe [18]

	IVF			ICSI		
	Age of women (y)			Age of women (y)		
	<34	35–39	≥40	<34	35–39	≥40
Aspirations (%)	44.6	37.0	18.3	41.9	37.1	20.9
Pregnancy rates (%)	30.8	25.4	13.6	27.9	22.3	11.2
Delivery rates (%)	25.1	19.0	7.8	22.1	16.1	6.3

ICSI: intra cytoplasmatic sperm injection, IVF: *in vitro* fertilization.

Table 4. Statistics of the use of first and second-third level procedures in assisted reproductive techniques in USA in 2019 stratified for maternal age [19]

	Age of woman (y)				
	<35	35–37	38–40	41–42	>42
Number of cycle starts	46,853	28,642	27,832	13,979	9,629
Cryopreservation rate (%)	85.6	80.2	72.1	62.8	47.5
% of cycles with no transfer	21.3	33.0	47.3	62.0	72.8
Number of retrievals	44,619	26,603	24,981	12,220	7,958
Cancelled cycles (%)	4.8	7.1	10.2	12.6	17.4
Retrievals with no embryos suitable for transfer (%)	5.7	10.7	18.4	28.1	36.7
Mean number of embryos transferred	1.2	1.2	1.4	1.6	2.1
Number of retrievals	44,619	26,603	24,981	12,220	7,958
Number of transfers	36,888	19,196	14,671	5,313	2,621
Live birth per transfer (%)	51.7	47.3	41.9	30.8	14.3
Implantation rate (%)	52.9	47.3	37.9	24.0	9.9

nancy and delivery rates for IVF and ICSI cycles. Data are summarized in Table 3 [18].

In the United States (US) for the year 2019, the data collected by the American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology (SART) account for 298,689 total cycles (Final National Summary Report for 2019, SART). More reassuring rates are shown by their report, which stratify the pregnancy outcome for maternal age (Table 4) [19]. Thus, there would seem to be a clear difference in the success rate between Italy (7%–17%), Europe (23%–25%), and US (10%–53%).

PREVALENCE OF THE MALE FACTOR IN THE ACCESS TO ART AND WEIGHT OF THE MALE FACTOR IN THE OUTCOME

ART has opened a new era in fertility treatment, granting for biological offspring in couples whose fertility was compromised. Current evidence considers ICSI mandatory in case of azoospermia, absolute asthenozoospermia and globozoospermia [20], while it is recommended in case of severe oligoasthenozoospermia or in case of sperm DNA fragmentation (SDF) [21-23]. Evidence is not against or pro IVF or ICSI in case of moderate oligoasthenozoospermia and when anti-sperm antibodies are found [24-26].

Nearly all patients with male factor infertility are treatable with ART, but up to 75 % of men with a male factor will have identifiable or treatable conditions that affect their fertility [27]. Therefore, specific investigations should be assessed prior to applying more invasive techniques. Furthermore, treatment of potentially curable causes of infertility (such as varicoceles, anti-sperm antibodies, infections, and obstructive azoospermia [OA]), should be pursued as it has been demonstrated in designed studies to have a fundamental role in the management of male infertility [27,28].

It is difficult to establish the real prevalence male infertility and its causes among couples accessing ART centers, as male fertility factors are often misrecognized or misdiagnosed [29]. The lack of surveillance on male factor infertility among ART fertility centers is reported by the National Assisted Reproductive Technology Surveillance System (NAASS): even in the most recent years (2016), male factor was non stratified on the causes, but only reported whether present/absent, following social constructs for which fertility is related to female partner [13].

These data raise the importance of collecting information about health of both partners, to better identify the etiology of male infertility, and to provide better therapeutic options in terms of costs, ethic, and risks for the couple [29]. Failure to diagnose and treat the cause of male infertility can first lead to a delayed diagnosis of potentially treatable diseases, in the recognition of genetically and therefore potentially transmissible diseases, and in the identification of diseases that can worsen over time. Furthermore, although the biotechnology involved in ART has achieved great development and precision, the use of these procedures in the presence of an unrecognized male factor of infertility have still a high risk of ART failure. This can also lead to the use of more invasive techniques with a consequent increase in costs for both public health and for couples. Finally, the failure of one or more ART cycles is associated with psychological and emotional distress for the couple, as well as the possible loss of confidence in both the procedure and the staff of the ART centers [27].

The underestimation of the male factor for which the couple access to ART centers and the increase of ICSI technique we are assisting to in these years, may suggest that this use is sometimes exceeded, without clear indication or evidence of advantages. Boulet and colleagues in a study of 2015 [30] described that use of ICSI in the last decades has increased compared to IVF, but this finding was not associated with higher prevalence of infertile couples with severe male factor infertility and with better pregnancy outcomes. Then, given its increased chance of fertilization in presence of a male factor infertility, ICSI should be proposed only in couples with severely impaired sperm parameters. However, it is often used even in the presence of borderline or non-pathological sperm parameters, without clear indication or evidence of practice this technique in case of non-male infertility factor [14]. ICSI use was not associated with improved post-fertilization reproductive outcomes, compared with conventional IVF, irrespective of male factor infertility diagnosis and despite the progressively increased use of the technique, which should have led to better outcomes [30-32]. Findings of the study of Boulet et al [30] suggest that compromission of the natural selection which derives from ICSI-obtained pregnancies, could lead to significant decrease in implantation, pregnancy, live birth though the techniques are associated with improved fertilization rate. This has been confirmed also elsewhere [33].

A study from Shuai et al [25] explored these concerns, finding no differences between IVF and ICSI in fertilization, implantation, and pregnancy rates in couples undergoing ART with men diagnosed with moderate impairment of sperm parameters. Similar findings were reported in another study where, compared to IVF, ICSI did not increase live birth rate in couples undergoing ART with a male partner with normal sperm parameters [34].

Due to these data, the ASRM recommended against the massive use of ICSI in couples undergoing to ART without confirmed male factor infertility [35].

Criticism to the use or abuse of ICSI lies in the chance of transmission of genetic defects, which seems to be higher in ICSI compared to conventional IVF. Several studies reported increased incidence of chromosomal abnormalities, autism, intellectual disabilities, imprinting disorders, and epigenetic modifications rather than child born after IVF, thought it must be assumed whether these data are associated with the real cause of infertility or to the technique itself [36]. Current data highlight the importance of epigenetic modifications in IVF/ICSI cycles and the implication of using abnormally methylated sperm from infertile patients on the offspring health [37].

To better understand the weight of male factor infertility and the role of its treatment in the outcome of ART, following we will take into consideration three specific conditions: azoospermia, varicocele and elevated SDF.

1. Influence of male factor of infertility on ART: role of azoospermia

Azoospermia is found in 1% of men and can be distinguished into OA, which accounts for approximately 40%, and non-obstructive azoospermia (NOA), which is the highest percentage.

The advent of ICSI realized the desire of parenting in male with these severe defects [38,39]. The option for men with azoospermia comprehend sperm retrieval with microsurgical techniques as TESA, from the testis, and PESA, from the epididymis, followed by ICSI. The outcomes of sperm retrieval depend on the type of azoospermia [28] and are higher in those with OA, for which the method is simply and successful regardless the cause of obstruction [24]. ICSI using testicular or epididymal sperm aspirated from men with OA are comparable. Conversely, the chances of achieving a live birth by ICSI are significantly reduced in couples whose male partner have NOA. In these cases, efficacy rate of the gamete retrieval is lower (approximately 50%), with no differences between the different etiologies.

A retrospective study of Pallavi et al [40], compared the outcomes of ICSI with surgically retrieved sperm of azoospermic men (obstructive or nonobstructive) with ejaculated sperms in men with severe oligospermia. It was found that ICSI outcome, fertilization rate, implantation rates and clinical pregnancy rates were comparable in both the groups, showing that minimally invasive techniques can be successfully performed to retrieve sperm for ICSI in the treatment of azoospermic men and that the outcomes can be auspiciously compared with that of ICSI using ejaculated sperm [40].

Similar data come from the retrospective analysis of Rai et al [41], evaluating the outcome of IVF with surgically retrieved sperm from azoospermic men. The analysis was conducted on 100 cycles with surgically retrieved sperm, and compared them with ejaculated sperms cycles. Outcome in the two groups were similar in terms of fertilization rate, embryo quality and pregnancy rate. The data also revealed similar outcome between the use of epididymal or testicular sperm, confirming that surgical sperm retrieval is achievable and that it is a successful procedure [41].

2. Influence of male factor of infertility on ART: role of varicocele

Varicocele is the abnormal dilation of the pampiniform plexus of veins within the scrotum: it is considered the most common correctable cause of male infertility as about 35% of men with primary infertility experience varicocele, and 81% of men with secondary infertility are found with clinical varicocele [42].

Medical or surgical reparation of varicocele should be recommended when slow testicular growth or impaired semen quality are observed in adolescents or in male partners of a couple seeking for fertility [43].

The American Urological Association's guidelines for Varicocele and Infertility recommend treatment for a varicocele only if the clinical varicocele is palpable, the couple has known infertility, the female partner is normal or has a potentially treatable cause of infertility and the male partner has abnormal sperm parameter(s), while treatment of subclinical varicocele is not recommended as it has been shown that it is not related to improvement of sperm parameters or pregnancy outcomes [44].

A meta-analysis evaluating both randomized controlled trials and observational studies on a population of infertile men with clinically palpable unilateral or bilateral varicocele and impaired sperm parameters who had undergone surgical correction, showed an increase in sperm concentration and motility, thus concluding that surgical correction of varicocele considerably raises semen parameters in infertile men with palpable varicocele and abnormal seminal fluid [45].

Similar data were confirmed in a meta-analysis of 2013 suggesting that varicocelectomy should be offered as first line treatment in sub-fertile men with NOA and clinical varicocele, as it is associated with improved sperm parameters and outcome of sperm retrieval [46].

Daitch et al [47] reported higher pregnancy rate and live birth in 34 men who underwent varicocelectomy prior to IUI, compared to those without varicocele treatment, though sperm motility was not different between treated and untreated group. Cayan et al [48] evaluated how varicocelectomy modifies semen quality in terms of total motile sperm count and observed an increased number of spontaneous pregnancy rate and an overall reduction of the need of the technique with couples supposed for IVF or ICSI achieving spontaneous pregnancy or IUI pregnancy after correction of varicocelectomy. Another important study conducted by Booman et al [49] in 2008 retrospectively evaluates 118 couples whose male partner was affected by varicocele and asthenozoospermia. The varicocelectomy group (n=69) demonstrated significant improvement in total sperm count, with higher pregnancy rates both after IUI (74% *vs.* 36%) and after IVF/ICSI (32% *vs.* 11%) compared to the untreated group [49]. Ashkenazi et al [50], in study of 1,089 were the first to suggest an improvement in IVF outcomes in patients undergone varicocele repair. Esteves et al [51] examined IVF/ICSI outcomes of 80 couples whose male partner underwent surgical correction of varicocele, showing that pregnancy rate and live birth rate were higher in treated group. Gokce et al [52], reported significantly increased values for clinical pregnancies and live birth rate in 168 oligozoospermic men candidate to ART who underwent surgical correction of varicocele, compared to 138 untreated patients.

Contrasting results came from the studies of Pasqualotto et al [53] in 2013 compared 169 couples, in which the male partner underwent varicocelectomy before ICSI, with 79 couples who did not undergo varicocelectomy, finding no significant differences in sperm concentration, motility, morphology, spontaneous implantation, pregnancy, and miscarriage rates. A significant difference between the two groups was found on fertilization rate, as it was higher in the treated group (73.2%) compared to the untreated one (64.9%, p=0.0377) [53]. Zini et al [21] evaluated 610 infertile males of whom 363 underwent varicocelectomy, and 247 were untreated. They reported lower sperm concentration and motility in the surgical group, compared with the observation one. Utilization of ART was significantly higher in the untreated group compared with the surgical group, but overall pregnancy rates (spontaneous plus assisted pregnancies) in the observation and surgical group were not significantly different. However, data are not confrontable as couples who responded positively to varicocelectomy were excluded from the analysis since this resulted in early spontaneous pregnancy without ART [21]. Data coming from original studies on this issue are summarized in Table 5 [21,47-49,52-54].

All together, these data indicate the importance of a proper management of varicocele in couples undergoing ART.

3. Influence of male factor of infertility on ART: SDF

In recent years, research interest has focused on SDF and its influence on reproductive outcomes. Damage to the spermatic genetic material has an independent role in male infertility, as it compromises the fertilizing potential of the male gamete and reduces reproductive outcomes. Infertile men with idiopathic infertility have high SDF values more frequently [23].

SDF tests assess and quantify the breakage of DNA strands inside the sperm head. The most used assay to test SDF is TUNEL assay, which detects single-stranded and double-stranded DNA breaks; male infertility is identified with a DNA Fragmentation Index (DFI) >17% [23].

Evidence demonstrates the effect of a high SDF on poor outcome following stimulated IUI, impaired embryo development, miscarriage rates and risk of pregnancy loss after both IVF and ICSI and poorer outcomes even after naturally conceived pregnancies

Table 5. Original studies evaluating the effects of varicocele repair on ART

Study	Year of publication	Number of participants (treated+untreated)	Type of ART	Results in treated group
Daitch et al [47]	2001	58 (34+24)	IUI	≈ Total motile count ↑ Pregnancy rate ↑ Live birth rate
Cayan et al [48]	2002	540 (393+147)	IUI	↑ Total motile count ↑ Pregnancy rate both spontaneous of after IUI
Boman et al [49]	2008	118 (69+49)	IUI/IVF+ICSI	↑ Total motile count ↑ Pregnancy rate
Esteves and Schneider [54]	2011	242 (80+162)	IVF/IVF+ICSI	↑ Pregnancy rate ↑ Live birth rate ↓ Miscarriage rate ↑ Total motile count
Gokce et al [52]	2013	306 (168+138)	ICSI	↑ Sperm parameters ↑ Pregnancy rate ↑ Live birth rate ↓ Miscarriage rate
Pasqualotto et al [53]	2012	248 (169+79)	ICSI	↑ Fertilization rate ≈ Spontaneous implantation ≈ Pregnancy rate ≈ Miscarriage rate
Zini et al [21]	2008	610 (363+247)	IUI/IVF+ICSI	≈ Pregnancy rate

ART: assisted reproductive technique, ICSI: intra cytoplasmatic sperm injection, IUI: intra uterine insemination, IVF: *in vitro* fertilization.

[21,55,56], though the fertilization rate does not seem influenced by elevated SDF.

It is still debated whether a high SDF constitutes an indication for the repair of varicocele. Recent evidence demonstrates that the surgical repair of clinical varicocele improves sperm parameters, decreases seminal OS and SDF, by reducing seminal OS [57], but more research is necessaire to determine the real impact of SDF correction on conception and implantation rate.

In a study including 49 infertile men with clinical varicocele and oligozoospermia, the DFI decreased significantly after correction of varicocele from 35.2% to 30.2% (p=0.019). After varicocelectomy, 37% of the couples conceived spontaneously and 24% achieved pregnancy with ART. In couples who did not conceive spontaneously or with ART the mean DFI was significantly higher [58].

In 2012 La Vignera et al [59] evaluated the effect of varicocelectomy on 30 infertile men with III grade varicocele. Analysis included assessment of SDF and concomitant estimation of OS/sperm function markers. After correction of varicocele, improvements were seen in conventional sperm parameters (higher sperm density, progressive motility, and normal forms compared with pre-intervention) and in bio-functional parameters that are indirect markers of OS in spermatozoa [59].

These and other studies were object of a careful evaluation from Roque and Esteves [60], who, in a 2018 review, confirm the efficacy of varicocelectomy to reduce SDF and thus potentially improve fertility.

There is limited consensus in literature about the different SDF test, the interpretation of results and how to restore a good sperm DNA integrity, so that evaluation of SDF is not always included in the routine evaluation of infertile couples yet.

ROLE OF ANDROLOGIST AND ENDOCRINOLOGIST PROFESSIONALS IN ART CENTERS ACCORDING TO INTERNATIONAL GUIDELINES

Several guidelines from different societies of reproductive medicine have been currently released. To examine the indications for evaluating the male partner, the suggested diagnostic procedure, and the role of andrologist/endocrinologist professionals in ART centers, we carefully reviewed each of them. The result of this

Table 6. Summary of andrological diagnostic process of the most important scientific societies of gynecology or reproductive medicine

Guidelines (country)	Year	Sperm analysis	Clinical andrological-endocrinological counseling	Genetic counseling			Is the presence of an endocrinologist-andrologist required in the Center?
				Karyotype analysis	Y chromosome microdeletions	*CFTR* mutations	
CFAS (Canada) [61]	2007	Yes	No	Yes	Available, not routine	Yes	Andrological laboratory
ESHRE (Europe) [62]	2015	Yes	No	Non mentioned in the document			No
FSA (Australia) [66]	2017	Non mentioned in the document	Non mentioned in the document	Non mentioned in the document			Continuous medical training in endocrinology of reproduction required
NICE (England) [63]	2017	Yes	No	Yes	Available, not routine	No	No
ISS (Italy) [64]	2019	Yes	For diagnosis of infertility When the third level techniques are planned	Yes	Yes	Yes	No
ASRM (USA) [65]	2022	Yes	No	Non mentioned in the document			No

ASRM: American Society for Reproductive Medicine, *CFTR*: cystic fibrosis transmembrane conductance regulator gene, CFAS: Canadian Fertility and Andrology Society, ESHRE: European Society of Human Reproduction and Embryology, FSA: Fertility Society of Australia, ISS: Istituto Superiore di Sanità, NICE: National Institute for Care and Health Excellence.

research is shown in Table 6 [61-66].

The Canadian Fertility and Andrology Society guidelines [61] report the importance of performing clinical and genetic counseling in all patients with severe oligozoospermia or azoospermia. The document states that professionals employed in ART centers operate in the field of embryology and andrology. However, there is no comprehensive education program in Canada that provides specific training in the field, and often the minimum requirement is a laboratory science or technology degree. In particular, the organization of Canadian ART centers distinguishes between clinical embryologists and laboratory andrologists. The first is requested to have technical experience in micromanipulation procedures on human oocytes, cryopreservation and thawing of human embryos, oocyte and sperm specimens, preparation of human sperm samples for therapeutic procedures, IVF, and embryo transfers. Laboratory andrologists have no responsibility for embryology and are in charge of quality control and research testing of human sperm samples, preparation of human sperm specimens for therapeutic procedures, and cryopreservation of human sperm samples which contribute to the continuous improvement of laboratory services, procedures, and standards.

The guidelines of the ESHRE [67] contain indications on the collection of seminal fluid for the patient and for the laboratory technician. The figures employed in this process are laboratory directors, laboratory supervisors, and clinical embryologists. The qualifications required for laboratory management are qualifications and expertise in clinical embryology and biological/medical sciences, with a minimum of 6 years of documented experience in human embryology. The laboratory supervisor requires at least a biomedical science qualification, three years of documented experience in human embryology, and preferably ESHRE certification as a clinical embryologist. The clinical embryologist must have a degree in biomedical sciences. In all three positions employed in diagnostics, it is striking that the presence of physicians with an andrological or endocrinological background is not contemplated.

The guidelines of the Fertility Society of Australia [66], published in 2017, focus on the need for the ART center to have staff with endocrinological and andrological skills to meet the reproductive health needs of male patients and their partners. Women undergo clinical evaluation for reproductive or gynecological health problems or those resulting from ART treatment; men undergo clinical evaluation for coexisting reproductive health and related problems. The medical director of the center, responsible for clinical management, must be a recognized specialist in gynecology or a physician with at least five years of experience in the management of patients with infertility. The scientific director must have a higher degree in reproductive biology, with skills and/or specialist training in reproductive physiology, cell biology, and biochemistry, and a minimum of four years of ART clinical laboratory. Hence, training is required to manage clinical embryology or the clinical andrology laboratory but, again, the qualification of an andrologist or endocrinologist is not expected.

The guidelines of the National Institute for Care and Health Excellence (NICE) [63], published in 2013 and revised in 2017, recommend that the semen analysis follows the WHO fifth edition for macroscopic and microscopic parameters. It does not recommend the routine evaluation of anti-sperm antibodies because there is no evidence that treatment improves fertility. If semen evaluation is abnormal, a second semen sample, collected at least three months later is indicated for an accurate evaluation (so that the sperm life cycle is complete), except when severe oligozoospermia or azoospermia is found. In these cases, the second assessment can be performed as soon as possible. For couples approaching ICSI, genetic counseling is indicated to establish a diagnosis and any therapeutic implications. The analysis of the karyotype of the male partner is necessary in cases of NOA or severe deficiency in the quality of the seminal fluid. Y-chromosome microdeletions are not used as a routine test.

The Italian guidelines [68] require the presence of a specialist in Andrology (or in Endocrinology or Urology both with andrological training) in the following cases: certification of the state of male infertility and the consequent need for undergo ART and when third level procedures are necessary (testicular sperm retrieval, evaluation of the adequacy of surgical or endoscopic procedures for the treatment of ongoing genital pathology and sperm recovery). The Italian document also provides that the Director of the ART center is a medical doctor who specialized in gynecology. This figure is then flanked by biologists, biotechnologists, or physicians with experience in reproductive medicine. In the case of sperm banks, the person responsible may be an endocrinologist, an andrologist, a urologist with andrological skills, or a biologist with expertise in reproductive medicine. Genetic investigations are necessary in cases where a specific etiology is suspected (*e.g.*, congenital mono or bilateral agenesis of the vas deferens, in cases where the indication for ICSI is due to severe oligoasthenoteratozoospermia or azoospermia).

The recently published guidelines of the ASRM [65] define the diagnostic and preparatory process for ART, providing information on the analysis of the male factor of infertility. The first and indispensable step is represented by the analysis of the semen, according to what is stated in the WHO manual, fifth edition, evaluating both the macroscopic and microscopic parameters. Other indications contained in the document are the preparation of seminal fluid for the techniques and the cryopreservation of the semen. The ASRM issues strategies also the training of the personnel assigned to the analysis laboratory, with a continuous training program. It is notable that a medical degree with laboratory experience or a doctorate in laboratory science, chemistry, or physics is required for andrology and endocrinology assessments, but not a specialty in andrology, endocrinology, or embryology. In fact, laboratory analyses are performed by personnel who possess the skills for the technical execution of the test, but not the clinical knowledge useful if not necessary for its more correct interpretation.

CONCLUDING REMARKS

In conclusion, epidemiologists indicate that about half of the couple's infertility cases are due to a male factor. Despite this, the role of andrologists or endocrinologists in ART centers is still underestimated. This reduces the chance of a thorough clinical evaluation of the male partners, which, sometimes consists only in a mere semen analysis, usually performed by laboratory technicians. On the other hand, a more complete diagnostic process could lead to the identification of potentially treatable causes of infertility, the recognition of diseases that require immediate treatment, and to the discovery of genetic diseases and, therefore, transmissible to the offspring. The presence of medical personnel with andrological and endocrinological skills in the ART centers represents the first step in creating 'precision medicine' even in reproductive medicine, in which both partners of the infertile couple must undergo specific clinical management according to their characteristics. Andrology had moved from the time when the definition of oligozoospermia was not well defined, genetic knowledge was scarce, and most decisions were based on simple laboratory analyses even without adequate standardization, to the contemporary era in which the understanding of the finely-tuned molecular mechanisms of spermatogenesis and the function of spermatozoa are becoming more and more precisely delineated thanks to the growing knowledge of genomics, transcriptomics, and proteomics of spermatozoa [69,70]. Therefore, the time has come to include personnel specialized in andrology and endocrinology among the staff of the ART centers, to correctly identify the cause of male infertility and to increase the success rate of ART. We hope that the guidelines of the various scientific societies will clearly contemplate this possibility.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: RC, AEC. Data curation: MM. Formal analysis: MM, RC. Investigation: MM. Methodology: MM, RC. Project administration: AEC. Supervision: SLV, RAC. Validation: RAC, RC. Visualization: SLV. Writing – original draft: MM. Writing – review & editing: RC, AEC.

Supplementary Materials

Supplementary materials can be found *via* https://doi.org/10.5534/wjmh.220253.

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