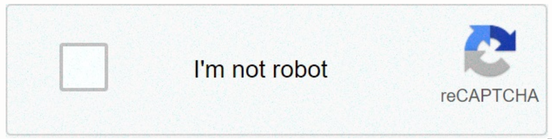

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Asrm guidelines male infertility

Thousands of doctors, nurses, and other reproductive medicine professionals are advancing their careers with the latest news, continuing education, discounts, and network opportunities. Ready to join? | Renew Infertility caused by a problem in the male, for example, inability to ejaculate or insufficient sperm count. Infertility is not just a disease that affects women-men suffering as well. In fact, new studies show that in about 40 percent of male partner infertility couples it is either the only cause or a contributing cause of infertility. Coding Corner Skip Nav Destination PDF Split View Article Content Figuris & Audio Video Tables Additional data Here, we describe the methodology of consensual guidance, summarize the evidence-based recommendations that we have provided to the World Health Organization (WHO) for their consideration in the development of global guidelines and present a narrative analysis of the diagnosis of male infertility in relation to the eight priority questions (problem or population (P), intervention (I), comparison (C) and results (O) (PICO). In addition, we discuss the challenges and research gaps identified during the synthesis of this evidence. The purpose of this paper is to present an evidence-based approach to the diagnosis of male infertility, as related to the eight prioritized PICO questions. The collection of evidence to support the provision of recommendations involved a collaborative process developed by the WHO, namely: identifying priority questions and critical outcomes; obtaining up-to-date evidence and existing guidelines; evaluation and synthesis of samples; and the formulation of draft recommendations to be used to reach consensus with a wide range of global stakeholders. For each draft recommendation, the quality of the supporting evidence was then classified and evaluated for examination within a WHO consensus. The evidence has been summarised and recommendations have been developed to address the diagnosis of male infertility which specifically includes the following: What is the prevalence of male infertility and what proportion of male infertility is attributable? Is it necessary for all infertile men to undergo an in-depth assessment? What is the clinical value (ART/non ART) of the traditional semen parameters? What key factors of male lifestyle impact on fertility (focusing on obesity, heat and tobacco smoking)? Do additional oral antioxidants or herbal therapies significantly influence fertility outcomes for infertile men? What are the evidence-based criteria for genetic screening of infertile men? a history of neoplasia and related treatments in the male impact on (his and his partner) reproductive health and And finally, what is the impact of varicocele on male fertility and not correction of varicoceles improve semen parameters and/or fertility? This analysis of the synthesis of evidence was carried out in a way to be taken into account for diagnosis of male infertility. In 2012, the World Health Organisation (WHO) held a meeting of experts to expand the field of fertility care to develop comprehensive guidelines on infertility. Six sample synthesis groups (ESG) were established. One group was ESG WHO on male infertility: Diagnosis. Following the initial meeting, the main questions of the PICO (problem or population (P), intervention (I), comparison (C) and results (results) (O) were developed and agreed. This included working through the WHO GDG (Development Guidance Group) Committee, as well as through web-based surveys, and through information to the developing country scientists taking an online Geneva Foundation for Medical Education and Research-American Society for Reproductive Medicine- (GFMER-ASRM) WHO evidence based on infertility course. For each PICO question, a systematic analysis of the literature was carried out in accordance with the WHO Handbook for the Development of Guidelines (WHO, 2014). A preliminary analysis of the data was presented to the who/GDG working experts consultation in December 2014, during which changes were made to the various components of some of the PICO questions and additional IOPs were also identified. A comprehensive document including draft recommendations was presented to the WHO/GDG Steering Committee For Guidance and Nomenclature Meeting in September 2015 (Fig. 1). This manuscript provides a narrative review of the evidence synthesized by ESG that helped generate the recommendations (Table I), provides an update of the evidence recommended by expert review, defines some of the challenges in addressing these questions, and discusses current research gaps. It ends by presenting future research opportunities and highlights how they can be achieved. Table IMale Factor Infertility Diagnosis: Summary Recommendations. Clinical questions. RECOMMENDATIONS by evaluating the developed PICO question and the analysis of the associated evidence. The power of evidence. 1. What is the prevalence of male infertility and what proportion of infertility is attributable to the male? It is not possible to determine an impartial prevalence of male infertility in the general population. Very low 2. Is it necessary for all infertile men to undergo an in-depth assessment? The initial assessment for infertility of male factors should include an EP carried out by an examiner with appropriate training and expertise, a reproductive history and at least a properly performed (high-quality) semen analysis. A full assessment by a urologist or other male reproduction specialist should be made if the initial screening assessment demonstrates an abnormal EP, an abnormal male or sexual reproductive history, or an abnormal analysis of seminal is found. Further evaluation of the male partner should also be considered in couples with unexplained infertility and in couples where there is a treated female factor and persistent moderate infertility 3. What is it (ART/non ART) of traditional semen parameters? The evaluation of a combination of several ejaculation parameters is a better predictor of fertility success than a single parameter The high analysis of a single ejaculate is sufficient to determine the most appropriate route of investigation and treatment, although semen analysis could be repeated if one or more High 4 abnormalities are found. What key factors of male lifestyle impact on fertility? The evidence supports a negative effect of obesity on many aspects of health; evidence is contradictory about a potential effect on reproductive function. Males presenting for fertility assessment should be advised on weight loss strategies when the BMI and waist circumference given demonstrate obesity and especially morbid obesity. Moderate There is insufficient evidence to conclude that exposure to heat, be it clothing or due to the position of clothing or body, affects semen quality and/or very low male fertility There is some evidence suggesting a negative effect of smoking cigarettes (tobacco) on semen quality, but not all studies report this. However, since smoking has a negative effect on general health and well-being, it is recommended that men who attempt a pregnancy refrain from smoking Moderate 5. Do additional oral antioxidants or herbal therapies significantly influence fertility outcomes for infertile men? There is insufficient data to recommend the use of additional antioxidant therapies for the treatment of men with abnormal semen parameters and/or low male infertility There is insufficient data to recommend the use of herbal therapies for the treatment of men with abnormal semen parameters and/or very low male infertility 6. What are the evidence-based criteria for genetic screening of infertile men? Cariotype testing should be performed on all men with severe oligozoospermia (<5×106/ml) or NOA before any therapeutic procedure High YCMD testing should be performed on all men with severe oligozoospermia before a therapeutic procedure or NOA before any therapeutic procedure Should be offered to all males with CBAVD or CF High 7. a history of neoplasia and related treatments in the impact of male (his and his partner) reproductive health and fertility options? Every male cancer patient should be provided with information on the impact of his cancer treatment on spermatogenesis and the option of sperm banking Moderate Patients should be advised to use contraception if they do not want to procreate even after periods of azoospermia after radiotherapy, as possible low male recovery cancer patients should be informed that pregnancy outcomes in male cancer survivors partners are good, but a slightly higher risk of congenital abnormalities in their offspring cannot be excluded Low 8. What is the impact of varicocele on male fertility and not correction of varicoceles improve semen parameters and/or fertility? good good Point: Treatment of a clinically palpable varicocele may be offered to the male partner of an infertile couple where there is evidence of abnormal semen parameters and a minimal/unidentifiable female factor, including consideration of age and ovarian reserve Very low point of best practice: IVF with or without ICSI may be considered the primary treatment option when such treatment is necessary to treat a female factor, regardless of the presence of varicoceles and abnormal parameters of semen Point of very low good practice: The experience and expertise of the attending physician, including the evaluation of both partners, together with the available options, should determine the approach to treatment with very low open varicocelein the new tabDownload slideOpregleoutline of the WHO methodology for ESG Male Diagnosis. Flowchart presenting the WHO process for obtaining evidence and formulating and presenting recommendations for male infertility (Diagnostics). This includes steps and methods of summary of samples in accordance with the WHO process. The data in square bracket reflect specific meetings at the WHO in Geneva. PICO: problem or population (P), intervention (I), comparison (C) and results (O). WHO, World Health Organization; ESG, Evidence Synthesis Group. METHODS KEY QUESTIONS PICO The following eight topics were predetermined and identified by the WHO, and were later formulated in PICO questions for systematic analysis, as follows: - What is the prevalence of male infertility and what proportion of infertility in the couple is attributable to the male?- Is it necessary for all infertile men to undergo an in-depth assessment?- What is the clinical value (ART/non ART) of the traditional parameters semen?- What key factors of the male lifestyle have an impact on fertility (focusing on obesity, heat and tobacco smoking)?- Do additional oral antioxidants or herbal therapies significantly influence fertility outcomes for infertile men?- Which are the evidence-based criteria for genetic screening of infertile men?- How does a history of neoplasia and related treatments in the male impact on (him and his partner) reproductive health and fertility options?- What is the impact of varicocele on male fertility and not correction of varicoceles improve material parameters seminal and/or fertility? The methodology for the synthesis of the samples outlined The methodology used to support the provision of recommendations was presented by the WHO (2014), namely: identification of priority questions and critical results; obtaining up-to-date evidence and existing guidelines; evaluation and synthesis of samples; draft recommendations to be used to reach consensus with a wide range of stakeholders. worldwide. For each recommendation, the quality of the supporting evidence would then be classified (very low, low, moderate and high) to be considered for consensus. For example, a high-quality evidence rating means that further research is highly unlikely to change our confidence in the estimation of the By contrast, a very low sample quality rating means that any effect is very uncertain. We have qualified the strength of our recommendations (as strong or weak) based on the consideration of the quality of the evidence. These recommendations were then further assessed through WHO guideline-making processes, which are based on other factors, including stakeholder values and preferences, the extent of the effect, the balance between benefits and damage, the resources used and the feasibility of implementation. In general, whenever possible, the original literature, as well as data from the recently published systematic and Cochrane comments were used. However, due to the diagnostic nature of the questions, a significant amount of literature addressing them does not lend itself to a high level of RCD evidence. Therefore, in addition, the key guidelines and opinions of the Professional Committee were examined in order to contribute to the development of a broader and more comprehensive database, as well as to the development of recommendations, in particular: ASRM — Diagnostic assessment of the infertile man: an opinion of the Committee (2015) (ASRM, 2015a); Statements of good practice by the American Urological Association [AUA] (updated in 2010 and 2011); EDU Guidelines on Male Infertility (Jungwirth et al., 2015); and the Society for Male Reproduction and Urology (2014) Report on Varicocele and Infertility. The data were presented in summary and descriptive form, in tables or narrative in the evidence assessments for each PICO question. If necessary, meta-analysis has been performed. The GRADE frame was applied to the evidence body for each result within each PICO. The WHO then used the worksheets to summarize the volume and quality of the evidence supporting the recommendations, as well as to highlight the values, preferences and judgments made about the strength of the recommendations. The uniqueness of the WHO process was that these balanced worksheets would also be used to note considerations in particular for low- and middle-income countries or settings and to be able to record the reasons for changes to the implicit power of recommendations. The principles or guidelines on best practices must be consensus-based and are also intended to emphasise the importance of respecting reproductive rights and dignity as beneficiaries of healthcare, as well as the need to maintain high ethical and safety standards in clinical practice. These principles, in addition to implementation, monitoring and evaluation strategies, should guide end-users in the process of adapting and implementing any recommendation provided by the WHO to take into account a number of global contexts and settings. Evidence-based analysis and detailed analysis, with grade tables, where possible, for each of the PICO priority, were commissioned and provided by the first WHO author in support of their guidance processes. Then, an WHO assessment of our evidence-based results was carried out, with many parts of the other factors, including the values and preferences of stakeholders, the extent of the effect and the balance between benefits in relation to injury, the use of resources and the feasibility of implementation to better ensure overall applicability. Following the WHO request, a further evaluation of independent experts (2016 and early 2017) will be carried out as a result of these results. Once completed, the WHO will publish their consensus-based guidelines and stakeholders, together with the detailed database (evidence tables, detailed search strategies, balanced worksheets, etc.) and related products (Fig. 1). The current manuscript provides a narrative of evidence. It focuses in particular on areas where evidence is controversial, of a lower quality and more difficult to obtain. It discusses what is missing from the analysis and critically provides a discussion of potential research bottlenecks. The purpose of this manuscript is not to reproduce the original documents submitted to the WHO. Since it was necessary to undergo a global method of prioritization in order to identify the PICO questions that answer, there are inevitably a number of questions in the diagnosis of male infertility that are not addressed by WHO ESG and therefore absent from this manuscript. For example, the effect of paternal age, alcohol and the environment on male fertility (those interested can consult, for example: Age—Eisenberg & Meldrum, 2017; Nybo-Andersen and Urjoj, 2017; Johnson et al., 2015; Ramasamy et al., 2015; Alcohol—Karmon et al., 2017; Jensen et al., 2014; Oil and gas extraction—Balise et al., 2016; Bisphenol A—Mínguez-Alarcón et al. 2016; Outdoor air pollution —Lafuente et al., 2016). Summary of results and narrative review in relation to the eight priority PICI questions Specific recommendations for submission to WHO on the diagnosis of male infertility are included in the text, along with an assessment of the quality of supporting evidence (Table I) and the strengths of recommendations based on the synthesis of our evidence. The final recommendations will result only from an independent review of our business and a review by stakeholder companies, following the evaluation through the WHO Guidance Review Committee. What is the prevalence of male infertility and what proportion of infertility is male attributable? This is a simple and fundamental question. It is essential to know the prevalence of a disease in order to provide resources, estimate impact, make effective economic arguments in the field of health, present rational research questions and manage patients. Investigators studying other diseases often have the incidence of the disease well established in a variety of different populations. However, for male infertility this remarkably simple question is very difficult to respond to. The latest publication shows an estimate of the prevalence of infertility among 15,162 men and women in the United Kingdom (Datta et al., 2016). This was a cross-sectional survey that asked whether ever had a time with a duration of 12 months or more when they and their partner tried for a pregnancy but did not happen. One in eight women (12.5%, 95% CI 11.7–13.1) and one in ten men (10.1%, CI 9.2–11.1) answered this question in the affirmative and thus experienced infertility. This type of study should be repeated in a number of different geographical regions. Addressing the prevalence of male infertility is a difficult one. For example, a difficulty arises from the lack of continuity in the definitions of infertility. In general, infertility is defined as the failure of a couple to become pregnant, despite 12 or more months of unprotected sexual contact. However, some studies, such as Hull et al. (1985) include in their definition couples who become pregnant but miscarry. Other studies include Anderson et al. (2009) and Gurunath et al. (2011) include those seeking medical advice to be able to make a partner pregnant. There is no current method to capture men as individuals or in same-sex relationships who may want a biological child through ART, and who can be found to be infertile. In addition, there is also generally a lack of differentiation between primary and secondary infertility in heterosexual men, and relative rates of primary and secondary infertility vary significantly between studies, especially when comparing clinical-based studies and population-based (see Malekshah et al., 2011 compared to Klemetci et al., 2010). The different definitions used for male infertility and the fact that men are not always evaluated (Pastuszak et al., 2016) may lead to misleading findings of the study. Mehta et al. (2016) have recently documented many of these obstacles when trying to obtain an accurate assessment of the prevalence of male infertility in the US. It is therefore not surprising that there are currently no rigorous systematic reviews or meta-analyses on the epidemiology of male infertility. Agarwal et al. have tried to continue this type of review (Agarwal et al., 2015), but due to the lack of comparable high-quality studies, they have not been able to draw solid conclusions. There are significant variations in the variables evaluated between studies, including but not limited to the age of the participants, the participants themselves (individual men, women or couples), the method of data collection and the measured results. These reserves create inconsistencies in the results of the study, and consequently male infertility studies can generally be divided into two categories: those seeking to determine the prevalence or incidence of infertility among men, or those that focus on the proportion of total infertility that is attributable to the male factor. For example, it is insufficient to simply ask men if they have experienced infertility, this information does not provide a real representation of male factor infertility (as their partner could be the cause of infertility). On the other hand, infertility diagnosed male factor itself often suffers from small sample sizes (Geelhoed et al., 2002) or a biased population-those who consult-that could skew data. Not all couples experiencing infertility choose to consult a doctor and, by couples who do not consult, not all will have experienced more than 12 months of infertility. For example, Louis et al. (2013) reported a higher prevalence of infertility than Anderson et al. (2009) using the same study population because the latter's definition of infertility was limited to men who left for a consultation. Similarly, van Roode et al. (2015) reported a higher prevalence of infertility among 38-year-old men (18.3% vs. 14.4%) when they extended their definition of infertility to include those who sought medical help to generate a pregnancy. Selecting populations of topics is often inherently biased. And in the case of the assessment of male infertility, for example, studies carried out on certain populations, would be military recruits, may not reflect the general population. Large-scale studies of infertility prevalence generally focus on the experience of women of infertility, so it has been reported in demographic surveys, which are based on the use of contraceptives (e.g. Guunath et al., 2011, Mascarenhas et al., 2012) and some large-scale studies are able to gather data on men. Van Roode et al. (2015) reported a big difference in the diagnosis of fertility problems when asking women in a study compared to asking men. Current studies on male infertility often use models of cross-sectional population studies (e.g. Datta et al., 2016 above) or are observational studies of those men who present themselves at infertility clinics. Only one prospective cohort study was identified at birth (van Roode et al., 2015). An additional limitation of the available literature is that some studies are relatively old, such as Hull et al. (1985) and Thoneau et al. (1991); studies that have not been updated in a quarter of a century. There may also be a geographical variation in the incidence of male infertility-a study in France suggested that the male factor alone accounted for 20% of total infertility (Thonneau et al., 1991), while a study in Western Siberia put the figure at 6.4% (Philippov et al., 1998). It is not clear whether they represent actual geographical variations or simply differences in methodology. Suffice it to say that, on the basis of current evidence, some reliable conclusions can be drawn on the epidemiology of male infertility. Several studies have suggested that male factor infertility is the most common single diagnosis among heterosexual couples struggling to become pregnant, but and the diagnosis of male factor varies and several other studies report that female factor infertility is more prevalent. However, all these studies highlight the need for further research. A simplistic and commonly used approach to assessing male infertility was the examination of semen parameters in population and determine the frequency of semen abnormalities in relation to standard ranges (Cooper et al., 2010, Virtanen et al., 2017). A multitude of studies have done so and have also used this information in an attempt to address changes in semen quality over time (Virtanen et al., 2017). The advantage of these studies is that they can provide comparable data, but only if the populations are well characterised first and, secondly, the laboratory methods used to determine the quality of semen are robust and consistent in all study sites (see Björndahl et al., 2016). However, the main disadvantage of this approach is that the parameters of the semen itself are not equivalent to the definition of infertility/fertility (MacLeod, 1950; Guzik and al., 2001; Cooper et al., 2010). As such, the current analysis focused on the proportion of heterosexual men experiencing a delay (extended time) in inducing pregnancy (Fig. 2). Opened in the new tabDownload slidePrevalence of male infertility. Prevalence of male infertility in general population surveys. Male infertility was generally defined as that of men who report infertility experience (generally >12 months in duration). In short, we strongly recommend, due to the very low quality of evidence, that it is currently not possible to determine an impartial prevalence of male infertility in global, regional or national populations, including neglected individual populations. In addition, it is currently not possible to determine what proportion of infertility in heterosexual couples is attributable to the male partner (Table I). A number of topics have been identified for future research. There is a need for large population-based studies to determine the prevalence of male infertility in the general male population, whether in a relationship or not. Ideally, population-based cohort studies in several different geographical regions should be carried out with consistent definitions of infertility and comparable models of clinical trials. Is it necessary for all infertile men to undergo an in-depth assessment? Medical conditions in men may be the cause of infertility (such as hypogonadotropic, hypogonadism or bilateral cryptorchidism) or associated with infertility (tumor testis in men with normal sperm analysis). The justification for the man's assessment and the extent of this assessment depend on the objectives of the assessment. More medical statements of good practice (AUA, 2011; ASRM, 2015a) suggests that the objectives of the man's assessment are to identify: the conditions that can be corrected; irreversible conditions for which ART would be needed using the male partner's sperm; irreversible conditions for which sperm male will not be available or appropriate and may require consideration of donor sperm or adoption; serious medical conditions that may cause or present male infertility and which could affect the health of the man and require medical treatment; And And causes of male infertility that could affect the success of treatment or the health of the offspring if ART is used. Assessments of infertile male populations identified patients in each of these categories highlighting the need for male evaluation (Nieschlag and Behre, 2001; Tournaye et al., 2016; Olesen et al., 2017; Punab et al., 2017, Pastuszak et al., 2016). An initial assessment of the male consists of three main components: history, physical examination (PE) and semen analysis. There is general agreement on the importance of obtaining a reproductive history (including a sexual history) and semen analysis. ASRM (ASRM, 2015a) suggests that reproductive history should include: frequency and coital timing; duration of infertility and previous fertility; childhood diseases and developmental history; systemic medical diseases (such as diabetes mellitus and upper respiratory diseases); previous surgery; medicines and allergies; sexual history (including sexually transmitted infections); and exposures to gonadotropins (including environmental and chemical toxins and heat). However, a point of discussion is the need, timing of investigations and indications for the EP; and is in this area where the current guidelines appear to be inconsistent. The AuA and ASRM declarations of practice recommend an initial assessment of all males of infertile couples, consisting of a detailed reproductive history and semen analysis. For example, ASRM states that at the very least, the initial assessment of the screening of the male partner of an infertile couple should include a reproductive history and an analysis of at least one semen sample (ASRM, 2015a). ASRM then recommends that men with risk factors in their reproductive history or abnormal semen parameters be referred to a male reproductive specialist for a more in-depth assessment including an EP. In particular, both organizations (ASRM and AUA) recommend considering a full male assessment (including EP) in those couples with unexplained infertility or those who remain infertile after correcting female factors. The European Urology Association (EAU) states that a medical history and EP are standard assessments for all men (Jungwirth et al., 2015). Others suggested a full assessment of all men in infertile relationships (Honig et al., 1994; Kolettis and Sabanegh, 2001; Olesen et al., 2017; Punab et al., 2017), which includes an EP. The question is: What diagnostic strategy is optimal? A significant number of identified male factors are associated with abnormalities found through semen analysis. However, etiology remains to be quantified robustly, especially in the light of the causes of infertility, such as congenital malformations, acquired forms of infertility, infection, to have an erection or ejaculation, various syndromes, as well as metabolic and endocrine disorders. Sexual dysfunction may be associated with normal semen parameters, but may be identified by a In addition, there are a number of genetic syndromes that predispose or cause male infertility some of which are associated with abnormal semen parameters. An initial assessment of the man consisting of a reproductive history, a simple analysis of the EP and semen could identify the majority of these cases, however, these assessments must also be sensitive to different cultural practices and different regional etiologies, e.g. HIV, genital tuberculosis (TB) in endemic areas of TB, lifestyle, environmental and work hazards. Significant medical conditions were reported in 1.1-6% of men who presented for infertility assessments and a number of these men had abnormal semen parameters. Importantly, however, there is limited data on the incidence of significant medical conditions that predispose men to infertility. A number of older data reported that 0.16% of men had significant medical conditions, but normal semen parameters indicate that conditions will be missed by limiting a male assessment to a reproductive history and semen analysis (Honig et al., 1994). Therefore, there are several approaches that can be used consisting of the following possibilities. One approach is that all under-fertile men should have an initial assessment with history, EP by an examiner with appropriate training and expertise, and a semen analysis. Importantly, this will raise the missed conditions by excluding an EP and is in line with the EUA guidelines (Jungwirth et al., 2015). Alternatively, the initial assessment consists of the detailed reproduction history and semen analyses; in this scenario, only if either it is abnormal not the male suffers a more thorough history and an EP. However, men with significant medical conditions will be missed by this approach. Overall, there are, on a global scale, a number of advantages and few disadvantages to include an EP carried out by an examiner with appropriate training and expertise in this initial assessment. For example, in low- and middle-income countries, where visits to health care professionals infertility will be narrower due to factors such as geography and costs, it is less likely that a man will return to the clinic, even if the results of a semen test are abnormal. Interestingly, both ASRM and EAU ASRM do not recommend endocrine testing as a first-line primary investigation. For example, ASRM (2015a) suggests endocrine testing in men with abnormal semen parameters (especially when sperm concentration I < 10 million/ml), impaired sexual function or clinical findings suggesting specific endocrinology. And after affirming some experts believe that all infertile men deserve an endocrine evaluation (Ventimiglia et al., 2016; Olesen et al., 2017). What is important is that the key recommendations are checked in different populations to determine how robust they are and, if necessary, such recommendations are modified. Interestingly, Ventimiglia et al. have recently examined ASRM ASRM for endocrine evaluations in a cross-sectional study of 1056 infertile men to predict hypogonadism. Using the same database, the authors developed a regression-based logistic diagram, including the volume of testicles measured during physical examination, BMI and azoospermia to predict total testosterone levels of <3 ng/dl. Although, their diagram had a higher predictive accuracy (68%) than ASRM guidelines (58%), concluded, based on their statistical analyses, that their diagram was also not reliable enough to predict hypogonadism. These examples underline the importance of validating recommendations in a variety of populations. In short, we strongly recommend, on the basis of a moderate quality of evidence that: - The initial assessment for infertility of male factors should include an EP carried out by an examiner with appropriate training and expertise, a reproductive history and at least a properly performed (high quality) semen analysis.- A full assessment by a urologist or other male reproductive specialist should be carried out if the initial screening assessment demonstrates an abnormal PE, an abnormal male reproductive or sexual history or abnormal semen analysis is found.- Further assessment of the male partner should also be considered in couples with unexplained infertility and in couples with a treated female factor and persistent infertility (Fig. 3 , Table I). Open in the new tabDownload slideFlowchart summary of the algorithm for diagnosing male infertility. As detailed in section PICO 2 (Does all infertile men need to undergo an in-depth assessment?) first-line investigations should include physical examination, history and semen analysis. The anomalies in these lead to further investigation. YCMD, Y chromosome microdelete; CFTR, TRANSMEMBRANARY CF CONDUCTION REGULATOR. There are significant areas for future research. For example, what constitutes the most appropriate PE and this provides significant additional information for male health in general, does not carry out a PE improve male engagement in diagnosis and treatment, which is cost-effectiveness of making an EP on all men who attend an infertility clinic instead of doing an EP only after abnormal findings in semen analysis and/or an abnormal reproduction and sexual history, can a globally validated questionnaire/list of topics for reproduction and sexualhistoric be used (which includes low-income settings) to identify people at risk of male infertility, and is the result better with earlier diagnosis and is a less expensive treatment with earlier diagnosis? What is the clinical value ART) of the traditional parameters of semen? Specifically, I asked two clinical questions. This first question was whether the predictive value of semen analysis for reproductive outcome is better using a combination of several parameters compared to a single semen analysis parameter, and the second was whether an assessment of a single ejaculate versus two ejaculates is for referral to the investigation and treatment of infertility. A fundamental challenge in literature analysis is the quality of laboratory tests that are often carried out using suboptimal methods (Keel, 2004; Björndahl et al., 2016). This is illustrated by data from three recent national quality control programmes in Belgium, Germany and Italy (Maldidis et al., 2012; Filimberti et al., 2013; Punjabi et al., 2016) documenting that, in general, a number of laboratories do not adhere to WHO methods for semen analysis. The lack of adherence to properly recommended and standardised methods significantly undermines the potential diagnostic value. Effective strategies for addressing this issue remain a topic of significant debate (e.g. Carrell and De Jonge, 2016). The analysis of studies to address this PICO question was limited to those published after 1 January 2000, based on two key assumptions. Firstly, there was a very slow increase in compliance with WHO recommendations for semen analysis. The fourth edition was published in 1999, and several publications before that shows evidence of significant and clear compliance with the recommended techniques (see Tomminson et al., 1999). Secondly, the assessment of the prognostic value of semen analysis depends on the quality of available clinical interventions. Therefore, historical data for THE success of IN ART are not relevant to the treatments available in recent years, as ART techniques have improved significantly (Wade et al., 2015). Another major challenge that has been recognised for over 70 years is substantial overlap in the distribution of semen analysis results in fertile men and men in infertile couples (MacLeod, 1950; Guzik and al., 2001; Cooper et al., 2010). This means that comparing the semen parameters of a patient with the distribution of results for fertile men is not sufficient in itself to determine whether the patient is fertile or infertile (Björndahl, 2011). In addition, semen analysis is only part of human investigation and a number of other attributes contribute to its fertility potential. As regards the first question, is the predictive value of semen analysis for the reproductive outcome better using a combination of several parameters compared to a single semen analysis parameter? The studies were considered eligible if they submitted primary data on predictive values (or quota rates (OR)) on multiple or unique analysis parameters. Four studies provided data on multiple parameter assessments (Zinaman et al., 2000; Guzik and al., 2001; Jendrzejczak et al., 2008; van der Steec et al., 2011, total n = 5022) and 10 studies focused on unique ejaculateas as predictors of fertility. Studies identifying a single parameter of semen with significant predictive fertility power are relatively common, but discriminatory power is very often low, for example, expressed as the characteristic curve/area of receptor operation below (ROC–ASC) close to 0.500 or OR including 1.00 in 95% CI. By contrast, studies that investigated several parameters, which more reflect testicular production/function and maturation, e.g. Guzick et al. (2001) and Jestrzejczak et al. (2008), present or predictive values, which are comparable to laboratory diagnostic tools in other areas of modern clinical medicine (Boyd, 2010). As such, the conclusion of this analysis was that the examination of several parameters was more predictive. In short, we strongly recommend, on the basis of a high quality of evidence, that the evaluation of a combination of several ejaculation parameters is a better predictor of fertility success than a single parameter (Table I). The second fundamental question is frequently asked, but rarely answered: Is an assessment of a single ejaculate versus two ejaculates sufficient for referral to infertility and treatment? This was considered important globally due to the low level of male involvement to address reproductive health issues in many settings. As above, the analysis was limited to studies published after 1 January 2000, mainly due to the assumed developments in quality in laboratory andrology. In this analysis, the studies were eligible only if they provided adequate information to establish the reliability of the data obtained from the semen analysis and submitted primary data on the usefulness of the repeated analyses (e.g. intraclass correlation coefficient (CCI), where an ICC close to 1.00 indicates high reliability between a pair of assessments). Only five studies (Francavilla et al., 2007; Stokes-Riner et al., 2007; Mishail et al., 2009; Leushuis et al., 2010; Christman et al., 2013 total n = 6482) provided information that could be used to support or reject a recommendation on the analysis of a single counter of two ejaculates (see Additional data for a detailed analysis of studies). The analysis, which included measures, would be the ICC, demonstrates the reliability of a single ejaculate for reference to the infertility investigation and the treatment leading to the conclusion that the examination of a single ejaculate is sufficient. This conclusion is consistent with the recommendations of asRM and the EAU. For example, ASRM (2015a) states that, at the very least, the initial screening... should include the analysis of at least one semen sample and the EAU states that if the results of the semen analysis are normal according to WHO criteria, a test is sufficient (Jungwirth et al., 2015). The question is whether there is a sub-group of men being investigated for infertility that requires a repeated analysis of semen. If so, which group would that be? It is most likely that men with ejaculation have results between very good and very poor, i.e. those in the intermediate range (Guzick et al. 2001). Guzick et al. (2001) presented a model in which patients were divided into three categories: poor, intermediate and good ejaculation outcomes. Creating three men's groups infertility may seem somewhat hypothetical. However, there is considerable overlap of the results of the ejaculated analysis from fertile and infertile men, and the intermediate range largely corresponds to this mixed group. For men with results in the intermediate group, a repeated analysis could provide additional information – confirming previous results or indicating a less or more severe problem. It is therefore logical to use a boundary area between good and very poor results (Guzick et al. 2001; Björndahl, 2011) and may restrict the repetition of the analysis to this mixed group. However, a recommendation that the analysis of a single ejaculate is sufficient to determine the most appropriate course of investigation and treatment is a controversial strategy. In some cases, this seems contrary to conventional clinical practice in which a multitude of well-documented variables are known to affect semen analysis, thereby reducing the clinical value of a single ejaculate. In addition, the analyses of a single ejaculate are contrary to previous standard OMS recommendations. However, a main reason for the variability of semen parameters is that some laboratories do not comply with the standard whorecommendations (Maldidis et al., 2012) and that key parameters, e.g. abstinence, do not control the standard recommendations of the test. Importantly, most of them can be mitigated by adopting and adhering to the appropriate WHO practices and procedures (WHO, 2010). However, the adoption of a strategy for the analysis of a single ejaculate should be accompanied by a detailed cost-benefit analysis to examine whether and at what stage the additional assessment of semen is appropriate, in particular in the limit area. It is also important to point out that this recommendation applies only to referral for the investigation and treatment of infertility and is not relevant, for example, if the purpose of a study is to establish a real value of sperm production or sperm production rate, for example, if a single ejaculate is not sufficient (Amann and Chapman, 2009). In short, we strongly recommend that, on the basis of high-quality evidence, it be established that the analysis of a single ejaculate is sufficient to determine the most appropriate route of investigation and treatment, although the semen analysis could be repeated if one or more abnormalities are found (Table I). There are a number of areas that are significant for the future. First, for example, large multi-centre studies are needed to examine predictive values in semen analysis to identify men who could contribute to spontaneous pregnancy, ART pregnancy, fertilisation failure, pregnancy loss/spontaneous abortion, time to pregnancy (TTP) and life span. Secondly, a fundamental to the development of new therapies or diagnostic tests for male infertility is the limited understanding of the formation, maturation and physiological functioning of normal and dysfunctional spermatozoa. There is an urgent requirement to understand these cellular, cellular, biochemical and genetic mechanisms to formulate appropriate diagnostic tests and rational therapy for men. What key factors of male lifestyle impact on fertility? This is, and is likely to remain, a topical issue. The analysis focused on obesity, smoking and heat exposure. Does obesity influence semen parameters? Obesity is a global health problem. It impacts not only cardiovascular disease, but also on many other related health disorders. Obesity can negatively affect male reproduction through endocrinological, thermal, genetic and sexual mechanisms (Reis & Dias, 2012). As such, obesity should be considered as a potential causal factor in male infertility. However, two key meta-analyses published in this area show conflicting data (MacDonald et al., 2010; Sermonidade et al., 2013), the latter concluding: overweight and obesity have been associated with an increased prevalence of azoospermia and oligozoospermia. In addition, there are a number of cross-sectional and longitudinal studies (MacDonald et al., 2013; Eisenberg et al., 2014 and Andersen et al., 2015) who reported some negative associations between semen parameters and obesity. A cross-sectional study of new Zealand males (2013) showed that morphology was the only parameter that correlated with BMI (MacDonald et al., 2013). A longitudinal study of American males reported an increase in OR for decreasein ejaculation volume and total sperm count associated with obesity (Eisenberg et al., 2014). In addition, SA for a lower concentration of sperm and total sperm count increased with waist circumference. A cross-sectional study of Norwegian men found a significant decrease in all standard semen quality markers with increasing BMI. BMI has also been negatively associated with reproductive hormones (Andersen et al., 2015). A cross-sectional study of 4,400 men attending infertility clinics in the U.S. reported a significant negative relationship between obesity and semen parameters (Bieniek et al., 2016). In addition, the incidence of azoospermia and oligozoospermia was more prevalent in obese men. Data from the CHAPS-UK study found no evidence for a BMI effect on motile concentration (Povey et al., 2012) or sperm morphology (Pacey et al., 2014). ASRM concluded in the obesity and reproduction document: an opinion of the commission's 2015 opinion committee that obesity in men may be associated with impaired reproductive function (ASRM, 2015b). Based on the number of papers that can be included in each meta-analysis paper (n = 31 and 25 for MacDonald et al., 2010 and Sermondade et al., 2013) and the conflicting results, together with the results of cross-sectional studies and a reasonable conclusion is that well-controlled, population-based additional studies are needed before stronger conclusions can be reached on the potential impact of obesity on semen parameters. The methods used to assess obesity should also be standardized. Obesity studies should measuring reproductive hormones as the only meta-analysis paper (MacDonald et al., 2010) that included hormonal parameters concluded There was a strong negative relationship for testosterone, SHBG and free testosterone with increased BMI. In a recent cross-sectional study (Andersen et al., 2015) the correlation between the three hormones and obesity was affirmed. Studies on the impact of nutritional weight loss interventions on reproductive health are lacking. Bariatric surgery reports exist, however the results are mixed and access is often restricted according to socio-economic status. In short, the evidence supports a negative effect of obesity on many aspects of health, and the evidence is contradictory about a potential effect on reproductive function. Therefore, we strongly recommend, on the basis of a moderate quality of evidence, that men who present themselves for fertility assessment be advised on weight loss strategies when data on BMI and waist circumference demonstrate obesity and especially morbid obesity (Table I). Does heat exposure adversely affect semen parameters and/or male fertility? Perhaps surprisingly, the quality of evidence linking heat to human male infertility is relatively poor. Data from animals, mainly through experimental manipulation of the testicles, strongly suggest an adverse effect of heat on spermatogenesis and subsequent fertility (Durairajanayagam et al., 2015). In addition, it is well established that cryptorchidism is associated with abnormal spermatogenesis that can be attributed, at least in part, to the thermal exposure of the testicles to the base body temperature (Hutson et al., 2013). A key question is: When the testicles are in the scrotum, does heat exposure negatively affect semen parameters and male fertility? Many studies link certain activities to the increase in scrotal temperature (e.g. use of saunas, hot baths), but do not follow this with information about the effect on semen parameters (Durairajanayagam et al., 2015). Of the studies investigating the effect of temperature on semen parameters, fewer still provide indicators of fertility outcomes, such as live birth rate or TTP. Only Thonneau et al. (1997) evaluated TTP, and this study alone, with a small sample size, was insufficient to draw solid conclusions about the effect of heat exposure on fertility. The reported reduction in semen parameters caused by heat is often small and it is not clear what effect, if any, this would have on biological fertility. For example, Hjolllund et al. (2000) reported a lower average sperm concentration in men with higher scrotal temperatures, but this was (over 15 × 106/ml, WHO, 2010). In addition, some studies did not measure scrotal temperature, attributing a difference between semen parameters to an activity without providing evidence that there was an increase in testicular temperature (e.g. a study of taxi drivers Figà-Talamanca et al., 1996). No RTTs were found and almost all collected retrospectively. Previous studies often suffer from small sample sizes (e.g. Garolla et al., 2013) and from factors of confusion, such as lifestyle factors (e.g. Figà-Talamanca et al., 1996). Very few of the studies have used control groups, which further complicates interpretation. No systematic analyses or meta-analyses were performed, which is probably due to significant variation in the study design. Available studies use different participant ages, different results, subjective definitions of heat exposure and even different criteria for semen analysis (Zorgniotti & Seaflon, 1988 and Cherry et al., 2014). Some studies have investigated the effect of occupational heat exposure on male fertility, e.g. welders. The evidence that this activity affects male fertility is low and extreme heat exposures, such as this, do not represent normal thermal exposures of the general population (caused by the wearing of different types of underwear, sedentary position, etc.). Povey et al. (2012) and Pacey et al. (2014) concluded that there was no significant effect on lifestyle factors, including exposure to heat, semen parameters, and others have also failed to find a significant effect, e.g. Støy et al. (2004) and Eisenberg et al. (2015), although Priskorn et al., (2016) reported a negative association between watching television for 5 hours/day and sperm concentration, but there was no measurement of heat exposure. Suffice it to say that further work is needed to elucidate the effects of heat exposure on male fertility. Ideally, scrotal temperature, semen parameters and a measure of fertility outcomes, such as live births, should be measured in prospective cohort studies. Studies should use comparable semen analysis measures, methods of measuring scrotal temperature and definitions of infertility in order to make comparisons. This would allow for a systematic review or meta-analysis of the evidence. In short, we strongly recommend, on the basis of a very low quality of evidence, that there is insufficient evidence to conclude that exposure to heat, whether in clothing or due to body position, affects semen quality and/or male fertility (Table I). Does smoking of cigarettes (tobacco) adversely affect the parameters of semen and/or male fertility? Most of the published literature on smoking cigarettes (tobacco) and male fertility only examines the effect of smoking on semen parameters. The quality of recent evidence linking smoking to the decrease in semen quality is moderate, a systematic review and meta-analysis of 46 cross-sectional studies (Li et al., 2011) found that smoking was associated with reductions in all semen parameters. A further meta-analysis of the 2010 literature, which analysed 20 studies with 5865 participants (Sharma et al., 2016), also concluded a significant negative effect of cigarette smoking on all semen parameters. A prospective cohort study was identified, which the effect of the state of smoking on the quality of semen (Yang et al., 2015). This study reported a significant reduction in total sperm count (P = 0.012) and concentration (P = 0.023) after multivariate analysis. Several cross-sectional and case-control studies found different effects of smoking on semen quality. For example, Jeng et al (2014) reported a decrease in the proportion of sperm with normal morphology in those who smoked >10 cigarettes/day (P = 0.04), while Povey et al. (2012) found no significant effect of smoking on sperm concentration motile and Pacey et al. (2014) found no significant effect on sperm morphology. Several studies have reported an association between smoking and changes in blood hormone levels. For example, Jeng et al. (2014), Al-Matubsi et al. (2011) and Lotti et al. (2015) reported increased serum testosterone in smokers compared to non-smokers. The definitions of smoking status vary from study to study, with some studies failing to define the participants they have classified as smokers (Caserta et al., 2013) and some studies that use cotinin levels to assess the state of smoking, rather than the number of cigarettes smoked per day. Lotti et al. (2015) considered those who smoked for <1 year to be never smokers. Studies have also varied on how they treated with ex-smokers- in some studies only those who have smoked today have been smokers and in others, anyone who has exceeded 1-pack-year at any time of their lives have been moderate smokers (Anifondis et al., 2014). In some cases, the smoking status was divided into light, moderate and heavy, and again, these definitions were inconsistent. These inconsistencies made it difficult for Li et al. (2011) to establish a dose-dependent smoking trend and a low semen quality. Much of the current evidence comes from men presenting at infertility clinics, and may not represent the effect of smoking on semen quality and/or fertility in the general population. Also, the status of smoking was generally self-reported. This could introduce bias to evidence-based. There are few studies that examine the effect of smoking on fecundity indicators, such as TTP. A retrospective cohort study, Mutsaerts et al., (2012) found that paternal smoking had no effect on TTP. ASRM (2012a) concluded that there is insufficient evidence of the association between smoking and male infertility, despite the fact that smoking has been shown in many studies to affect semen quality, however, a review of this recommendation is to be published in the near future. Systematic review and meta-analysis are necessary to investigate the effect of smoking on hormones in the blood, as well as fecundity measures, would be TTP. However, this assessment would require a greater number of well-designed, prospective cohort studies with consistent definitions of smoking status. Participants could be stratified into smoking levels, which could be evaluated by biochemical methods to reduce self-reporting biases. The results should include parameters of semen, as well as measures of fecundity and fertility, such as TTP and live birth rate. In short, we strongly recommend based on a moderate quality of evidence that there is some evidence suggesting a negative effect of smoking cigarettes (tobacco) on semen quality/male fertility, but not all studies report this. However, since smoking has a negative effect on general health and well-being, it is recommended that men who try to abstain from smoking (Table I). After previously mentioned the effect of lifestyle (and environmental factors) affecting male infertility is likely to remain a rapidly developing and topical problem. There are a large number of significant areas for future research. First, large-scale multi-centre multi-centre studies comprising a variety of geographical locations are necessary to examine the effects of lifestyle (e.g. obesity, heat exposure, smoking, recreational and medical drug use, high-intensity sports) and environmental factors (e.g. occupational exposures, endocrine disrupting chemicals (EDCs)/toxins) on spermatogenesis, semen analysis, results of male fertility and fertility, including the health of subsequent progeny. Do additional oral antioxidants and herbal therapies significantly influence fertility outcomes for infertile men? There is a significant body of data to support the concept that oxidative stress plays a key role in sperm dysfunction and male infertility (Aitken et al., 2014). Therefore, the antioxidant treatment of infertile man can improve semen quality and/or fertility. However, the key question is: Is there any data to support this? Two approaches were used to address this question: the use of a recent review of Cochrane (updated; Showell et al., 2014); and primary analysis, including the analysis of literature on herbal therapies. The Cochrane Review (Showell et al., 2014) examined the use of antioxidants. Forty-eight published studies were included in the systematic review, 37 studies included in the meta-analysis. In short, only 7/48 studies reported the clinical pregnancy rate, of which only four continued to report live births. The authors recommended that up to birth live and clinical pregnancy rate are strongly reported by all infertility studies, it is not possible to draw clear conclusions about the use of antioxidants for infertile men. In addition, they concluded that low quality evidence from only four small RRCs suggested that antioxidant supplementation in infertile men may improve live birth rates. Data on other adverse effects were missing. Importantly, they suggested that in large well-designed randomized placebo-controlled trials are needed to clarify these results. Our primary analysis of literature came to a conclusion similar to that of the Cochrane analysis (Showell et al., 2014), as very few additional studies were examined (e.g. Raigani et al., 2014). Far fewer studies have examined the use of herbal therapies (Y virilin, Saffron, Addyzoa). Two thirds of studies showed some improvement in semen parameters and one study reported a positive effect on sperm membrane integrity (Omu et al. 1998). Two studies have shown improvements in sperm DNA integrity after herbal therapy (Omu et al. 2008; Raigani et al. 2014). After the use of herbal therapies only one of the three (33.3%) studies have reported a positive influence on pregnancy rates. Adverse reactions were reported in 16.6% of the studies, and most of them were mild to moderate. However, it is worth noting the study Safarinejad et al. (2011) in which a large number of patients had adverse haematological reactions during

treatment with the compound Linn Crocus sativus (Saffron). An inevitable conclusion was that the methodological quality of most studies in the literature on antioxidants and herbal therapies to treat male infertility is poor. In addition, the heterogeneity of the selected studies makes meta-analysis difficult. A further complication is that oxidative stress measurement techniques, antioxidant capacity and/or DNA damage are not standardized between all studies. In addition, there is often a lack of clear preselection of a subgroup for testing, for example, confirmed high-reactive oxygen species/DNA damage, reduced antioxidant capacity. Taking these factors into account, oral antioxidant therapy can improve the seminal oxidative condition in infertile men, either by decreasing oxidative stress or by increasing total antioxidant capacity, but the evidence is of poor quality. In some cases, positive relationships are manifested by improvements in semen parameters, most often sperm motility. This may explain higher pregnancy rates after antioxidant therapy compared to placebo, but further detailed studies are needed. Studies evaluating herb supplementation constitute only a small part of the available literature. For these studies, the heterogeneity of the studies does not allow a solid conclusion. Suffice it to say, there is no high quality data to support the use of a single antioxidant or a specific combination of antioxidants. Furthermore, it is not possible to recommend an effective treatment regimen. In short, we strongly recommend based on low quality evidence that there is insufficient data to recommend the use of additional antioxidant therapies for the treatment of men with abnormal semen parameters and/ or male infertility. In addition, we strongly recommend on the basis of the very low quality of evidence that there is insufficient data to recommend the use of herbal therapies for the treatment of men with abnormal semen parameters and/or male infertility (Table I). significant areas for future research; there is an absolute and urgent requirement for large, well-designed placebo-controlled randomized trials with primary TTP results and live births (including the health of these births) reported in well-characterized groups to examine, for example, the effects of dietary supplementation, vitamins and herbal remedies. Plants. are the evidence-based criteria for genetic screening of infertile men? Determining whether an infertile man receives a genetic evaluation depends on the etiology of reproductive compromise and severity. A detailed and comprehensive EP history, along with adjuvant tests such as semen analysis, hormonal tests and occasionally biopsy testis, help clarify the diagnostic category of which the patient belongs and, as a useful consequence, help to determine genetic studies that may be fruitful. For example, if a man has a reproductive history consistent with a known cause of the resulting spermatogenic failure, such as chemotherapy, bilateral mumps, orchita with resulting atrophy or current use of anabolic steroids, and is currently severely oligozoospermic or azoospermic, it can be assumed that these are the immediate reasons for reduced/absent spermatogenesis and no genetic evaluation should be performed. Recommendations focused on the analysis of mutations by Cariotype, Y Microelets and Cystic Fiber (CF). Y chromosome microlets and cariotype in men with spermatogenic dysfunction No cochrane evaluations have been identified. The primary evidence was from studies conducted by Rozen et al. (2012) and Krausz et al. (2014) and from the declarations of practice of ASRM (2012b), AUA (2011) and EAU (Jungwirth et al., 2015). Based on the evidence, we recommended that in men who have a history, PE and hormonal tests consistent with severe oligozoospermia or non-obstructive azoospermia (NOA), both a cariotype and Y chromosome microdelete test should be offered. Cariotype: Men with sperm count <5 million/ml have a much higher rate of autosomal abnormalities than fertile populations (around 4%) while the highest frequency is found in NOA men (mostly Klinefelter syndrome). Klinefelter syndrome [47,XXY including variants (48,XXXY) and MALE XX (SRY+ and SRY−)] is the most common of sexual chromosomal aneuploids. Translocations can be found in a relatively small percentage of men with severe oligozoospermia and azoospermia (Yatsenko et al., 2010). The benefits of knowing if there is a chromosomal abnormality are in planning for therapy and in the future follow-up of the patient. As such, cariotype analysis should be performed before the use of ejaculated sperm in combination with ICSI or before the extraction of test sperm (TESE). A priori knowledge of a chromosomal translocation, depending on its exact nature, can significantly alter the thought process and therapeutic strategy of a future ICSI cycle by using PGS to allow the transfer only of balanced or normal embryos while discarding those who are chromosomally unbalanced (e.g. Dul et al., 2012). In short, we strongly recommend, on the basis of high-quality evidence, that be performed on all males with severe oligozoospermia (<5 × 106/ml) or NOA before any therapeutic procedure (Table I). Chromosome Y-chromosomal Y-chromosomal test: The molecular geography of the Y chromosome is such that microdeletions (not recognized by cytogenetic methods) may occur which partially or completely eliminate the azoospermia factor (AZF) or the AZFb/c region of the genome and, consequently, any necessary spermatogene important genes that are in these ranges. Frequency data compiled by Rozen et al. (2012) shows an overall incidence of Y microdeletes in the AZFc region in 1/27 men, which varied according to the Y haplotype. The importance of testing Y microdelete in the severe oligozoospermic or azoospermic male prior to any treatment (ICSI using ejaculated sperm or TESE) is for the prognosis and consideration of PGD. For example, the data show that when a complete azFa, AZFb or AZFb/c microdeletion is present (~1–2% incidence of each in NOA man) no sperm will be found on the TESE. When there is no possibility that sperm will be present, it is useless and painful for the male to be operated on and, in the last circumstance, for the female partner to have an ovarian stimulation unnecessarily. Men with AZFc microdeletes can produce sperm capable of fertilization, embryonic development and long-term pregnancy (Oates et al., 2002). An AZFc micro-publication leads to a quantitative reduction in spermatogenesis with the maintenance of sperm quality and function. All born males will directly inherit the AZFc micro-delegation. Pe scurt, recomandăm cu tărie, pe baza unei dovezi de înaltă calitate, ca testarea microdeleției cromozomiale Y (YCMD) să fie efectuată pe toți bărbații cu oligozoospermie severă (<5 ×= 106/ml)= or= noa= prior= to= any= therapeutic= procedure= (table= i).= cf-mutation= analysis= in= men= with= congenital= bilateral= absence= of= the= vas= deferens= or= clinical= cf= no= cochrane= reviews= were= identified.= the= primary= evidence= was= from= studies= by= yu= et= al.= (2012),= xu= et= al.= (2014)= and= lommatzsch= and= aris= (2009),= and= practice= statements= from= asrm= (2012b),= aua= (2011)= and= eau= (jungwirth= et= al.,= 2015).men= with= clinical= cf= (pulmonary= and= pancreatic= dysfunction)= will= also= have= absence= of= the= vasa= and= seminal= vesicles= bilaterally= and= will,= consequently,= have= a= low= volume,= low= ph ,= and= an= azoospermic= ejaculate.= the= incidence= in= males= of= northern= european= heritage= is= 1:2000.= an= equal= frequency= of= men= with= low= volumes,= acid= ph,= azoospermia= will= have= congenital= bilateral= absence= of= the= vas= deferens= (cbarvd)= with= little= respiratory= or= pancreatic= disease,= the= vast= majority= of= who= will= posses= mutations/androgenic= abnormalities= in= both= maternal= and= paternal= cf= alleles.= when= one= presents= with= respiratory= tree= (including= sinuses)= and/or= pancreatic= disease,= simply= absence= of= the= vas= deferens= or= somewhere= clinically= between= these= phenotypical= extremes= depends= upon= exactly= which= in= the= alleles= are= inherited.= there= are=>1985 mutații recunoscute în gena CF regulator de conducție transmembrană (CFTR) (Rostosis Cystic Mutation Database: The Hospital for Sick Children, </5> </5> and Genomics Biology. Toronto: 1989 [Accessed: August 2014]. Available at: The CFTR gene has 27 exons covering 250 kb of chromosome 7 (7q31) and encodes a 6.5 kb mRNA, and the final protein contains 1480 amino acids. Certain mutations, would be c.1521_1523delCTT (inherited name: F508del), seriously affect the amount or functional quality of the CFTR protein determined by that allel. Other anomalies, such as the 5 T polymorphism of intron 8 (5 T), only slightly affect the amount or functional quality of the CFTR protein determined by that alleal. It is the combination of the two that correlates with the severity of the expression of the disease. If a person is homozygous for c.1521_1523delCTT, for example, s/he will have problematic respiratory and pancreatic diseases manifested and diagnosed in childhood. However, if a male inherited the 5 T allell and c.1521_1523delCTT on the opposite alleand is therefore a compound heterozygous, lung and pancreatic function may be clinically normal and CBAVD is the only recognised phenotypic consequence. The absence of bilateral vasal is then the most sensitive indicator of an abnormality of the BIALlelic CF gene, since there is differential expressiveness and sensitivity to CFTR in different epithelial tissues. In addition, it was postulated that the severity of the phenotype can be modified by polymorphisms in independent genes, such as TGFB1 (transformer growth factor) and EDNRA (type A endothelial receptor) (Havasi et al., 2010). In a recent meta-analysis by Yu et al. (2012) in patients with CBAVD, 78% had at least one mutation identified, 46% had two mutations identified and 28% had a single mutation identified. The most common association of heterozygous mutations was F508del/5T (17% of CBAVD cases) and F508del/R117H (c.350G > A; 4% of CBAVD cases). The poly-thymidine tract in intron 8 has three alleles consisting of 5, 7 and 9 thymidines that are found in 5, 85, and 10% of the general population, respectively. In the presence of 5T, exon 9 sepising is reduced and, consequently, the expression of the CFTR is reduced along the entire length. Because 5T acts as a mutation when trans (on the opposite allover) to a defined CFTR mutation, e.g. F508del, the poly-T tract in inintron 8 should be defined in cases of CNAVD. Analysis of the Poli-T tract is often only a reflex test when R117H is detected (Chen and Prada, 2014). However, many of the studies in meta-analysis Yu et al. (2012) were conducted in the early years after the discovery of the association of mutations CBAVD and CF, when only a small cohort of mutations was known and sought after (Anguiano et al., 1992). The more comprehensive the test, the more patients will have the second abnormality identified. Although a genetic basis of the CFTR mutation underlying most Cases of CBAVD was a statistical certainty, this meta-analysis provides well-defined summary values in all likelihood, will be modified upwards in the coming years, as the CFTR and more fully is made for men with CBUVD. The distribution of CFTR mutations and polymorphism differs depending on the ethnic/geographical origin of the patient/population studied. After being reviewed by Lommatzsch and Aris (2009), F508del is the most common mutation leading to CF worldwide, but varies in its frequency by ethnicity/geographical location: 70-80% in patients with FC in northern Europe, 50% in patients with FC in southern Europe, 48% in African-Americans, 46% in Hispanic Americans, 30% in Ashkenazi Jews, 18% of patients with Tunisian CF and rarely in Native Americans. In addition, in the Jewish population Ashkenazi c.3846G > A (inherited name W1282X) is the most common mutation found (frequency of 48%). Meta-analysis by Xu et al. (2014), which specifically analysed F508del, 5T and M470V, supports the above findings, concluding that there are significant associations between F508del and CBAVD (P < 0.001, OR = 22.20, 95% IC = 7.49–65.79), 5T and CNAVD (P < 0.001, OR = 8.35, 95% IC = 6.68–10.43). In CF or CBHAVD situations, it is always necessary to check the female partner for cf gene abnormalities so as to make an appropriate risk assessment of any offspring inheriting one of the two paternal mutations and maternal mutation and presenting with clinical CF or, at the very least, CBAVD if male. In addition, the benefit of testing the male with CbAVD helps provide information to its siblings who have a 75% chance of harboring at least one (or possibly both) mutations inherited by the patient from their parents. Finally, patients may have mild cf symptoms, such as sinusitis or bronchitis, which have not previously been recognized as being related to the CF mutation and which, with a full understanding of their genetic basis, can be treated therapeutically in a different way. Not all CBAVDs appear to be caused by/associated with CFTR mutations and abnormalities, and these cases may be secondary to a distinct genetic etiology that affects the development of mesonephric ducts. The final phenotypic product may be CBAVD and unilateral renal agenesis as described as mcCallum et al. (2001). Therefore, in cases of CBAVD where CFTR mutations are not identified, renal ultrasound is indicated. In short, we strongly recommend, on the basis of the high quality of the evidence, that an appropriate analysis of the CFTR mutation should be provided to all males with CBAVD or CF (Table I). There are significant areas for future research into the genetic screening of the infertile male. For example, what are the long-term health outcomes of children born to infertile men, can cost-effective tools be developed for genetic screening in men (cariotype, micro Y deletions and analysis of CF mutations) in low-income environments, and what is the genetic basis for unilateral vessel absence associated with unilateral renal agenesis? a history of neoplasia and related treatments in the male impact (his partners) reproductive health and fertility options? In a number of aspects, this has been a address. Although there have been several reviews in the area, for example Tournaye et al. (2014) and Samplaski and Nangia (2015), as well as key recommendations from national companies, for example the American Society of Clinical Oncology (ASCO) (Loren et al., 2013), therapeutic agents and treatment regimens are continuously evolving. In addition, there were limited data on the key aspects of the problem, such as counseling on the post-treatment contraception window and the health of both juvenile cancer survivors and adults. However, overall, the recommendations of the main medical societies in Europe and the USA have coherence: the European Society of Medical Onclology (Peccatori et al., 2013) and ASCO (Loren et al., 2013). For example, the storage of semen samples is the main option to preserve the fertility of men (and boys who produce semen in ejaculate) who are undergoing chemotherapy/radiotherapy regimens (Loren et al., 2013; Peccatori et al., 2013). As such, overwhelming evidence suggests that all patients should be provided with information about the impact of their cancer treatment on spermatogenesis and the option of sperm banking. If regimens are of a high or lower probability of long-term fertility impairment, given the variability of the individual response to treatment and the potential for relapse, the evidence would recommend that sperm cryopreservation should always be taken into account and services available and accessible. Counselling should include, also, the fact that there is little chance of recovery from azoospermia after 10 years of radiotherapy (Sandeman, 1966), total irradiation of the body (Rovó et al., 2006) or chemotherapy (Meistrich et al., 1992, Heinekens et al., 1996), however, contraception should continue to be taken into account if paternity is not desired. However, active pregnancy testing during cancer treatment should be avoided if an accidental pregnancy occurs during cancer treatment, this should not be automatically considered an indication for elective discontinuation. The pregnant couple should be given appropriate counselling and fetal diagnostic interventions, e.g. a minimal ultrasound assessment of the foetus (De Santis et al., 2008). Although the fertility of male cancer survivors is reduced, the registry data identified subgroups dependent on the type of cancer, age at onset, treatment method and dose, whose fertility is not different from the general population (Tournaye et al., 2014). Pregnancy outcomes, such as pre-term birth, low birth rate and miscarriages, appear to be comparable to the general population, but there are conflicting data on the risk of malformations (Ståhl et al., 2011). In general, a coordinated approach between professionals in the health involved in the treatment of cancer and specialists in reproductive medicine is highly recommended, although unfortunately it has not always been achieved. In short, we strongly recommend that, based on the moderate quality of the that every male cancer patient should be provided with information on the impact of his cancer treatment on spermatogenesis and the option of sperm banking. In addition, we strongly recommend on the basis of the low quality of evidence that: patients should be advised to use contraception if they do not want to procreate even after prolonged periods of azoospermia after radiotherapy, since recovery is possible; male cancer patients should be informed that pregnancy outcomes in partners are good, but a slightly higher risk of congenital abnormalities in their offspring cannot be excluded (Table I). There are significant areas for future research. For example, there is insufficient data to advise men on the post-treatment contraception window and a lack of systematic data on the risk of birth defects following accidental conception during treatment. It must also be determined whether there are effects in the second generation of cancer survivors following cancer treatment; there are no risk data for partners or chickens from semen chemotherapeutic agents. What is the impact of varicocele on male fertility and not correction of varicoceles improve semen parameters and/or fertility? For this question and following discussions with this expert working group and the WhoDG leadership, a recommendation was made to use the ASRM Practice Committee; Society for Male Reproduction and Urology (2014). Report on varicocele and infertility: an opinion of the committee (level IV of evidence). Since the methodology used to prepare this report was not equivalent to the assessment of the WHO GRAD, the conclusions cannot be suggested as a recommendation, but as an opinion based on a review of the literature. As such, these are suggested as points of good practice, namely:- Treatment of a clinically palpable varicocele may be offered to the male partner of an infertile couple where there is evidence of abnormal semen parameters and a minimal/unidentified female factor, including consideration of age and ovarian reserve.- IVF with or without ICSI may be considered the primary treatment option when such treatment is necessary to treat a female factor, regardless of the presence of varicocele and abnormal parameters of semen.- The experience and expertise of the attending physician, including the evaluation of both partners, together with the available options, should determine the approach to varicocele treatment. An analysis by Shridharani et al., (2016) presents a detailed assessment of the recommendations of the EAU, ASRM and AUA on varicocele. The differences between their recommendations and the complexity of conducting a prospective long-term study that would definitively answer this question clearly indicate that significant additional research is needed to guide clinical management. Challenges and future research opportunities It was probably an inevitable conclusion that, in carrying out these analyses, there will be identified behind the literature. It would be surprising if this was not Case. However, what was surprising was the substantial nature of the lags where effectively little or sometimes no research was carried out. Of an additional note was sometimes the low quality of available evidence. Such a combination makes it difficult to formulate informed evidence-based decisions for the diagnosis of the man (see Table I for the summary). However, instead, a number of issues have been identified with clear and significant opportunities for the way forward. Key themes in developing these recommendations Areas for focus research We present key areas for focus research that require investigation. In general, a high priority area for research has been to gain a better understanding of the production, formation and functioning of a human sperm. There is an urgent requirement to understand these cellular, molecular biochemical and genetic mechanisms to formulate appropriate diagnostic tests, to develop rational therapy for men and to understand how external factors, would be the environment, negatively or positively influence these processes. Not surprisingly, this is not unique to our discipline. For example, a new strategy for understanding neurodegeneration with a main focus on cell formation and function is now strongly supported as being absolutely essential for accelerating progress for understanding neurodegenerative disorders (Kosik et al., 2016). Although research into understanding the functioning of human sperm has progressed significantly over the past 10 years, there is still the need to catch up and then keep up with the knowledge base in other cellular systems. A number of robust diagnostic tools for sperm function are unlikely to be developed without further detailed understanding of the normal and dysfunctional cell's work. In addition, without this knowledge, the complementary development of a drug(s) that a man can take or have added to in vitro sperm to improve sperm function will continue to remain evasive. Premature introduction of putative but unproven diagnostic and/or therapeutic tools in clinical practice in ART may prevent, rather than long-term progress in the field (Harper et al., 2012, 2017; Spencer et al., 2016). Another priority thematic area for research was the examination of the long-term health outcomes of children born to men with compromised fertility (including those treated with ART), regardless of the nature of the compromising event(s) (e.g. genetic, environmental, iatrogen and/or occupational). In addition, this analysis should assess the effects in different geographical locations. In addition to the research themes that accompany each question, we have identified other areas that need to be addressed. De what is the impact of age on male fertility? What are the underlying causes of male-related iVF-ICSI treatment? Which gene (or epigenetics) defects in men can predict ART results? What are they the most effective educational initiatives to improve the understanding of male infertility? What are the attitudes of men and women (in different geographical locations) towards the investigation of male fertility? Of course, in presenting this analysis, a multitude of research questions was generated. Requirement to obtain solid data A coherent theme was the emphasis on the quality of the evidence available to support any recommendations. The criteria used can be presented in two formats, not mutually exclusive: Traditionally, the quality of the samples is represented by the use of a range of different levels. However, it is clear that a considerable degree of research related to the diagnosis of male infertility does not easily fall into these categories. The evidence is sometimes observational and cannot be easily analysed. With regard to the scientific and clinical evaluation of diagnostic methods, i.e. methods that measure the characteristics of individuals, RCT scans are usually not appropriate. First, there is no inclusion of a separate group to be used as a control, i.e. a group that did not obtain the treatment investigated. In assessing a diagnostic method, the control of the diagnostic method can be obtained with another independent method or from the final clinical outcome. From this point of view, the highest level of evidence cannot be easily obtained by an RCT. One of the problems was the robustness of the studies and therefore the general applicability. The robustness of the evidence base in reproductive medicine was discussed (Evers, 2013, Barratt, 2016a, 2016b; Glujovsky et al., 2016) and is, of course, not just a theme in reproductive medicine (Baker, 2016). Solid methods must be developed and used at a later date. One example where we have probably made relatively little progress is the technical challenges of semen analysis. However, with greater appreciation for the difficulties in this arena (Carrell and De Jonge, 2016) it is now likely that the WHO is likely to produce a 6th version of the semen assessment manual. The evidence based on the current manual (5th version) is at least 10 years from the date and a lot has changed. However, there are areas of good practice: the guidelines of the European Academy of Andrology and recommendations for quality control of the Y chromosome microdelete test (Krausz et al., 2014) are commonly used. Robustness also applies to the verification of key recommendations from, for example, professional companies (see Ventimiglia et al., 2016). In the future, we must remember the lessons of the past and ensure that the evidence base, including the use of sound tools, is significantly improved. Theme of International Infertility Studies is a global and significant health problem. A coherent theme is the requirement for national and international efforts, with large-scale multi-central studies geographical locations. Considerable regional variations in key male reproductive health indices (Skakkebaek et al., 2016) have been reported, but they are often on a relatively local scale. It is essential to understand potential variations in sentinel markers of male reproductive health in other countries/regions, as well as in global resource environments, in order to inform about subsequent policies and practices. Context of resource establishment A key theme is the issue of global implementation of diagnostic tools and therapeutic procedures, especially in low-resource environments. Basic procedures require resources and some recommendations, although very simple procedures (e.g. sperm banking before potential cancer therapy sterilization) may be feasible in most settings, but unfortunately they may not be in some areas without specialized storage facilities. General summary: the road to a healthy future for male infertility There are significant advances in male reproductive health from developments in in vitro spermatogenesis to dissecting the functioning of mature spermatozoa. However, progress in this arena is relatively slow. The robustness of data is sometimes desired and therefore the ability to provide the strongest evidence-based guidance has proven to be a challenge. We have provided recommendations based on available evidence. However, as we look to the future, it is necessary to understand why data happened to be limited and not available, in order to inform the direction of future initiatives and efforts that could lead to more studies that produce solid evidence from men living in medium, medium and small backgrounds. What is the scale of the problem of male infertility and its consequences? It is fundamental to know the prevalence of a disease in order to provide resources, estimate impact, make effective economic arguments in the field of health, present rational research questions and manage patients. However, there is a lack of clinical data on the scale of reproductive health and infertility problems in men globally in all health economies. The best estimates on infertility in demographic health studies use the heterosexual woman because she self-reports a problem with becoming pregnant, which still involves a diagnosis of female infertility (due to minimal reporting of any female clinical diagnosis), or possibly an assumption of an infertile relationship; and, together with an even greater lack of male diagnosis and infertility management in low- and middle-income countries, any values of male infertility prevalence based on demographic health reports or from small private clinics are, at best, very much extrapolated, and (Mascarenhas et al., 2012). Consequently, there is limited information on the fundamental key markers, such as the socio-economic impact that infertility and other diseases or disorders can have on the individual and society a whole. Underlining the importance of the male partner's commitment to assessing the infertile couple and educating the public about male infertility should improve the couple's care and expand our knowledge of the scale of the problem. Moreover, there is an urgent need to determine the potential consequences of male infertility. This is a wide area of investigation that should extend beyond the limits of the couple and their immediate relationships to investigate, for example, the relationship of infertility with other diseases and what impact this has on the disease. There is growing evidence (although currently mainly in animals) of the potential transmission to the next generation of harmful insults to the male germline through epigenetic mechanisms (Siklenka et al., 2015). This may become particularly relevant with the effect of significant potential changes in external environments on the fidelity of the germ line and also the likely future use of more immature gametes (Tanaka et al., 2015) and even in vitro. Funding science to match the scale of the problem The lack of data in key areas reflects the general lack of high-quality national and international funding flows in the long term to support reproductive medicine, in particular male infertility. Although this has been discussed previously, it remains a fundamental deadlock for further progress and a critical issue (Evers, 2013; Barratt, 2016a, 2016b). THE WHO has not published evidence-based guidelines in this area, and the previous infertility/fertility manual for the management of infertile male based on current practice since then has been published in 1992. This effectively means ~25 years without an update on best practices and never any official guidelines for adoption and adaptation at the country level. This is an unacceptable situation, as the lack of universal international guidelines does not help to advance the field of male infertility or male reproductive health in general. However, these new evidence-based guidelines for the male are expected to act as a platform for studies that contribute to the raising of the male reproductive health profile. In essence, it is necessary to present stronger arguments to national and international agencies in order to contribute to the impetus of the research order and, subsequently, to place reproductive medicine, with a demonstrated impact on couples and individuals, at the forefront of the funding landscape. Coupling EDC with male reproductive health may provide an example. In this area, strong scientific, socio-economic and political arguments have been constantly gathered to support research into what has been called an epidemic of health problems (Hauser et al., 2015; Skakkebaek et al., 2016; Trasande et al., 2016). The pregnancy of the disease (through EDC) was estimated and an impact assessment was carried out (e.g. Olsson, 2014; Hauser et al., 2015). For example, it is estimated that EDC may substantially for male reproductive disorders and diseases equivalent to a staggering cost of EUR 15 billion in the European Union (Hauser et al., 2015), although these figures are subject to considerable debate (e.g. Olsson, 2014; Woodruff, 2015). This type of analysis must be developed and continuously fine-tuned for male reproductive health as a whole where additional support for basic science and clinical basis of male infertility must be achieved. We also need to realise that this support must include educating future students (some of whom will be consumers and other leaders in the field), underlining the importance of studying reproductive health in the school/higher education system (Finney and Brannigan, 2017). Developing and triage of arguments for decision-makers is a complex and ongoing challenge. Male reproductive health needs first of all a series of tough documents that provide evidence based on the importance and challenges of our discipline. However, this is only the beginning of the process, as the delivery of these recommendations requires a multitude of discussions with international agencies, politicians and key decision-makers. Evidence alone does not determine action – after it is illustrated by the challenges of implementing regional policy, let alone global, to address the increase in CO2 emissions from the atmosphere (Malakoff, 2017). We need to need a whole range of skills to produce policies, and the scientific evidence itself is insufficient for major policy changes (see Cairney, 2012, 2017). Mentioning the obvious – evidence-based guidelines requires high-quality evidence, which will only be obtained with adequate funding, which will lead to this data being obtained. Without solid data from all segments of society, the state of male reproductive health will remain invisible and men's reproductive health needs will remain neglected in the near future. Additional data Additional data is available online at Human Reproduction Update. Carla Stek confirmations from ASRM for literature search and data analysis; Fraser Stuart Barratt University of Edinburgh, Edinburgh, Scotland and Niels Jørgensen, University Department of Growth and Reproduction, Rigshospitalet, GR-5064, Blegdamsvej 9, DK-2100 Copenhagen, Denmark for discussions on the incidence/prevalence of male infertility. The authors also want to acknowledge the contributions of Dr. A La Barbera (ASRM) and Professor A Pacey (University of Sheffield) for discussions and recommendations of revised documents. The authors' roles were members of the Evidence Synthesis Group (see above) and were responsible for the synthesis and presentation of literature. All authors contributed to the synthesis of literature, the writing and Funding for literature analysis was mainly provided by the WHO Programme for Human Reproduction (WHO Department for Health and Reproductive Research, HRP (UNFPA/UNICEF/WHO/World Bank research, development and research in the field of human reproduction)). ClRB is funded by the UK Medical Research Commission and NHS Scotland. RMcL is funded as a main research fellowship of Australian #1022327 NHMRC. Disclaimer: Although data acquisition and analysis was partially sponsored by the WHO, this manuscript is not an official WHO document. 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