Thieme

Diagnosis and Treatment Before Assisted Reproductive Treatments. Guideline of the DGGG, OEGGG and SGGG (S2k Level, AWMF Register Number 015-085, February 2019) – Part 2, Hemostaseology, Andrology, Genetics and History of Malignant Disease

Diagnostik und Therapie vor einer assistierten reproduktionsmedizinischen Behandlung. Leitlinie der DGGG, OEGGG und SGGG (S2k Level, AWMF-Registernummer 015-085, Februar 2019) – Teil 2, Hämostaseologie, Andrologie, Humangenetik und Z. n. onkologischen Erkrankungen

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Key words
infertility, preconception counselling, genetics, andrology, oncology, guideline

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ABSTRACT

Introduction Supporting and counselling couples with fertility issues prior to starting ART is a multidisciplinary diagnostic and therapeutic challenge. The first German-language interdisciplinary S2k guideline on "Diagnosis and Therapy Before Assisted Reproductive Treatments (ART)" was published in February 2019. The guideline was developed in the context of the guidelines program of the German Society of Gynecology and Obstetrics (DGGG) in cooperation with the Swiss Society of Gynecology and Obstetrics (SGGG) and the Austrian Society of Gynecology and Obstetrics (OEGGG).

Aim In one third of cases, the cause of involuntary childlessness remains unclear, even if the woman or man have numerous possible risk factors. Because the topic is still very much taboo, couples may be socially isolated and often only present quite late to a fertility center. There is no standard treatment concept for these patients at present, as there are currently no standard multidisciplinary procedures for the diagnostic workup and treatment of infertility. The aim of this guideline is to provide physicians with evidence-based recommendations for counselling, diagnosis and treatment.

Methods This S2k guideline was developed on behalf of the Guidelines Commission of the DGGG by representative members from different professional medical organizations and societies using a structured consensus process.

Recommendations This second part of the guideline describes the hematological workup for women as well as additional diagnostic procedures which can be used to investigate couples and which are carried out in cooperation with physicians working in other medical fields such as andrologists, geneticists and oncologists.

ZUSAMMENFASSUNG

Einleitung Die Begleitung von Paaren mit unerfülltem Kinderwunsch vor einer ART ist eine multidisziplinäre diagnostische und therapeutische Herausforderung. Im Februar 2019 erschien die erste deutschsprachige interdisziplinäre S2k-Leitlinie für die „Diagnostik und Therapie vor einer assistierten reproduktionsmedizinischen Behandlung (ART)". Die Leitlinienerstellung erfolgte im Rahmen des Leitlinienprogrammes der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe (DGGG) in Kooperation mit der Schweizer Gesellschaft für Gynäkologie und Geburtshilfe (SGGG) und der Österreichischen Gesellschaft für Gynäkologie und Geburtshilfe (OEGGG).

Ziel Ein Drittel der Ursachen für Kinderlosigkeit bleibt unklar, auch wenn es eine Vielzahl an möglichen Risikofaktoren aufseiten der Frau und des Mannes gibt. Aufgrund der immer noch vorhandenen Tabuisierung des Themas sind die Paare teilweise sozial isoliert und wenden sich oftmals erst spät an ein Kinderwunschzentrum. Derzeit besteht kein einheitliches Behandlungskonzept, da keine fächerübergreifenden Handlungsanweisungen zur Diagnostik und Therapie der Infertilität vorliegen. Ziel der Leitlinie ist es, dem behandelnden Arzt/Ärztin im Rahmen der Beratung, diagnostischen Abklärung und Behandlung evidenzbasierte Empfehlungen anzubieten.

Methoden Diese S2k-Leitlinie wurde durch einen strukturierten Konsens von repräsentativen Mitgliedern verschiedener Fachgesellschaften im Auftrag der Leitlinienkommission der DGGG entwickelt.

Empfehlungen In diesem 2. Teil der Publikation der Leitlinie wird neben der hämostaseologischen Abklärung der Frau die weitere Abklärung des Paares in Zusammenarbeit mit anderen Fachdisziplinen wie Andrologen, Humangenetikern und Onkologen beschrieben.

I Guideline Information

Guidelines program of the DGGG, OEGGG and SGGG

For information on the guidelines program, please refer to the end of the guideline.

Citation format

Diagnosis and Treatment Before Assisted Reproductive Treatments. Guideline of the DGGG, OEGGG and SGGG (S2k Level, AWMF Register Number 015-085, February 2019) – Part 2, Hemostaseology, Andrology, Genetics and History of Malignant Disease. Geburtsh Frauenheilk 2019; 79: 1293–1308

Guideline documents

The complete long version together with a slide version of this guideline and a list of the conflicts of interests of all authors involved are available in German on the homepage of the AWMF: https://www.awmf.org/leitlinien/detail/ll/015-085.html

Guideline authors

See ▸ **Tables 1** and **2**.

PD Dr. Helmut Sitter (AWMF-certified guideline advisor/moderator) was responsible for moderating the guideline.

▶ **Table 1** Lead author and/or coordinating lead author of the guideline.

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▶ **Table 2** Contributing guideline authors.

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II Guideline Application

Purpose and objectives

The purpose of this guideline was to standardize the diagnosis and treatment before ART, based on the available evidence in the current literature and national/international guidelines.

The guideline was developed using common, consistent definitions and based on objectivized evaluation modalities and standardized diagnostic and therapeutic protocols.

Targeted areas of patient care

- Outpatient care
- Primary care and specialist medical care

Target user groups/target audience

The recommendations of the guideline are aimed at gynecologists, general practitioners and specialists working in the fields of urology, andrology, genetics, psychotherapy, clinical pathology, hemostaseology, and internal medicine as well as other professionals who provide care to couples with fertility issues.

Additional target groups (for information purposes):

- Nursing staff
- Family members

Adoption and period of validity

The validity of this guideline was confirmed by the executive boards/heads of the participating professional societies/working groups/organizations/associations as well as by the boards of the DGGG, the DGGG Guidelines Commission and the SGGG and the OEGGG in January 2019 and was thus approved in its entirety. This guideline is valid from 1st February 2019 through to 31st January 2022. Because of the contents of this guideline, this period of validity is only an estimate.

III Methodology

Basic principles

The method used to prepare this guideline was determined by the class to which this guideline was assigned. The AWMF Guidance Manual (version 1.0) has set out the respective rules and requirements for different classes of guidelines. Guidelines are differentiated into lowest (S1), intermediate (S2) and highest (S3) class. The lowest class is defined as a set of recommendations for action compiled by a non-representative group of experts. In 2004, the S2 class was divided into two subclasses: a systematic evidence-based subclass (S2e) and a structural consensus-based subclass (S2k). The highest S3 class combines both approaches.

This guideline was classified as: **S2k**

Grading of recommendations

Grading of evidence based on the systematic search, selection, evaluation and synthesis of the evidence base which is then used to grade the recommendations is not envisaged for S2k-level guidelines. The various individual statements and recommendations are differentiated only by syntax, not by symbols (▶ **Table 3**).

▶ **Table 3** Grading of recommendations.

Strength of recommendation	Syntax
strong recommendation, highly binding	must/must not
regular recommendation, moderately binding	should/should not
open recommendation, not binding	may/may not

Statements

Expositions or explanations of specific facts, circumstances or problems which are not direct recommendations for action included in this guideline are referred to as “statements”. It is **not** possible to provide any information about the grading of evidence for these statements.

Achieving consensus and strength of consensus

At structured NIH-type consensus-based conferences (S2k/S3 level), authorized participants attending the session voted on draft statements and recommendations. The process was as follows. A recommendation was presented, its contents were discussed, proposed changes were put forward, and finally, all proposed changes were voted on. If a consensus was not achieved (> 75 % of votes), another round of discussions was held, followed by a repeat vote. Finally, the extent of consensus was determined based on the number of participants (▶ **Table 4**).

▶ **Table 4** Classification showing extent of agreement underpinning consensus-based decisions.

Symbol	Strength of consensus	Extent of agreement in percent
+++	Strong consensus	> 95 % of participants agree
++	Consensus	> 75–95 % of participants agree
+	Majority agreement	> 50–75 % of participants agree
–	No consensus	< 50 % of participants agree

Expert consensus

As the name already implies, this refers to consensus decisions taken with regard to recommendations/statements where no prior or systematic search of the literature (S2k) was carried out or for which evidence is lacking (S2e/S3). The term “expert consensus” (EC) used here is synonymous with terms used in other guidelines such as “good clinical practice” (GCP) or “clinical consensus point” (CCP). The strength of the recommendation is graded as previously described in the chapter “Grading of recommendations”, i.e., purely semantically (“must”/“must not” or “should”/“should not” or “may”/“may not”), without the use of symbols.

IV Guideline

1.1 Special aspects for patients with a prior history of oncologic disease in childhood, adolescence or adulthood

As women with a history of oncologic disease face many unanswered questions with respect to their future fertility which may significantly affect their quality of life [6], professional and possibly interdisciplinary counselling is necessary. Professionals working in associated medical fields (e.g. oncologists, radiotherapists, geneticists, etc.) should be consulted where necessary, ideally before the start of pregnancy.

Consensus-based recommendation 3.9.E51	
Expert consensus	**Strength of consensus +++**
Patients with a history of oncologic disease who want to have children must be given counselling by an interdisciplinary team.	

1.1.1 Importance of pregnancy for underlying malignant disease

The patient's general condition, life expectancy, potential necessity to adapt an existing maintenance regimen and the possible impact of ovarian stimulation or possible pregnancy on the prognosis of the primary disease must all be considered along with the opinions of professionals working in associated medical fields about specific types of oncologic disease.

Consensus-based recommendation 3.9.E52	
Expert consensus	**Strength of consensus +++**
Patients wanting to have children with distant metastatic oncologic disease must only start reproductive medical treatment after ART has been approved by an interdisciplinary team on a case-by-case basis.	

It is also important to consider the risk of ovarian metastasis when cryopreserved ovarian tissue resected prior to oncological treatment is transplanted back into the patient after the end of treatment. The risk of metastasis varies considerably according to the underlying tumor type (▶ **Table 5**), meaning that for certain tumor entities such as leukemia. transplantation can currently not be considered a safe option [23]. For details, please refer to the German-language AWMF guideline "Fertility Preservation and Oncologic Disease," register number 015-082 [22].

Consensus-based recommendation 3.9.E53	
Expert consensus	**Strength of consensus +++**
When planning the transplantation of cryopreserved ovarian tissue into patients with a history of oncologic disease, part of the tissue must be examined histologically to exclude ovarian metastasis. Patients must also be informed in detail about the risk of possible metastasis prior to transplantation, the associated risk of inducing recurrence as well as the limited available data about these issues.	

Consensus-based recommendation 3.9.E54	
Expert consensus	**Strength of consensus +++**
Autologous ovarian transplantation should only be carried out if the patient wants to have children. The patient's partner must also first undergo an andrological examination prior to ovarian transplantation. Fallopian tube patency must be checked as part of the preparation for transplantation. Where possible, ovarian transplantation must be done on the side with a patent fallopian tube.	

▶ **Table 5** Risk of ovarian metastasis depending on the primary tumor entity (modified [22]).

High risk	Moderate risk	Low risk
▪ leukemia ▪ neuroblastoma ▪ Burkitt's lymphoma ▪ ovarian tumors	▪ stage IV breast cancer ▪ invasive lobular subtypes ▪ colon cancer ▪ endometrial cancer ▪ gastric cancer ▪ cervical adenocarcinoma ▪ non-Hodgkin's lymphoma ▪ Ewing's sarcoma	▪ stage I–III breast cancer ▪ invasive ductal subtypes ▪ squamous cell carcinoma of the cervix ▪ Hodgkin's lymphoma ▪ osteosarcoma ▪ extragenital rhabdomyosarcoma ▪ Wilms tumor

After transplantation of cryopreserved ovarian tissue, signs of hormone activity usually appear within 2–4 months after surgery. The following approach should be followed to avoid unnecessary stress for the patient: if her period starts in the first 4 months after transplantation, the patient must make an appointment with her treating physician. Hormone levels (E2, LH, FSH, poss. progesterone, poss. AMH) should then be determined. If the patient has still not had a period at 4 months after transplantation, then she should present to a fertility center for further examination (see above). If hormone activity is detected, then intervention may be postponed for a further two months to see whether the patient starts her period in these two months. If no hormonal activity is detected after 8 months, transplantation of further ovarian tissue (if available) should be considered [4].

1.1.2 Significance of underlying malignant disease for potential pregnancy

Consensus-based recommendation 3.9.E55	
Expert consensus	**Strength of consensus +++**
Patients with a possible genetic predisposition to develop cancer must be offered genetic counselling.	

Consensus-based recommendation 3.9.E56	
Expert consensus	**Strength of consensus ++**
Disease-specific pregnancy risks must be discussed beforehand with patients who have a history of oncologic disease.	

1.2 Hematological factors

Not just pregnancy [32] but also ovarian stimulation [12] carried out in the context of fertility treatment is accompanied by an activation of the female coagulation system. The changes which occur in this context include increased coagulation and reduced fibrinolysis; they are comparable, in principle, with changes which occur naturally during pregnancy [9, 11, 26] and are associated with an increased risk of thrombosis.

Basically, there are two areas which need to be taken into account when investigating hematological factors: the importance of avoiding complications and aim to increase the live birth rate (LBR). As regards avoiding complications, it appears to be important whether the patient has a positive personal or familial history of VTE or not.

1.2.1 Diagnostic workup

Consensus-based recommendation 3.10.E57	
Expert consensus	**Strength of consensus +++**
Asymptomatic women must not be screened for thrombophilia. Patients with a positive personal or familial history of thromboembolic events should be investigated for thrombophilia to evaluate their individual risk of thrombosis.	

1.2.2 Treatment

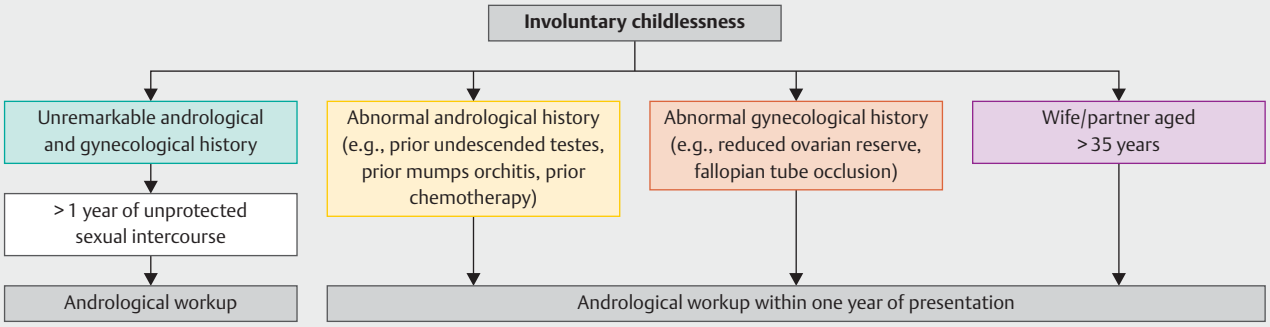
Anticoagulation for the prophylaxis of thrombosis

Consensus-based recommendation 3.10.E58	
Expert consensus	**Strength of consensus +++**
Asymptomatic women must not routinely be given anticoagulation during ART to prevent thrombosis. If the patient has a positive personal or familial history of thrombophilia or thromboembolic disease, the patient's management must be adapted to take account of the patient's additional risk.	

▶ **Table 6** shows a possible approach to be taken during ovarian stimulation of a patient with confirmed thrombophilia; this approach is similar to the management procedures used for pregnant women. Patients who have had a prior thrombotic event should be managed by an interdisciplinary team.

▶ **Table 6** Possible approach in cases with confirmed maternal thrombophilia (taken from AWMF 2018, adapted from the ACOG bulletin as well as the German-language S3-guideline "Prophylaxis Against Venous Thromboembolism (VTE)", AWMF Guideline Register No. 003/001).

Clinical constellation	Possible approach
Confirmation of low-risk thrombophilia (heterozygous factor V Leiden mutation or prothrombin mutation, protein C or S deficiency) with no prior history of thromboembolic events (VTE)	Clinical monitoring or administration of heparin in prophylactic doses (if additional risk factors are present)
Confirmation of low-risk thrombophilia (heterozygous factor V Leiden mutation or prothrombin *[G20210A]* mutation, protein C or S deficiency) with positive familial history but no personal history of thromboembolic events	Clinical monitoring or administration of heparin in prophylactic doses if additional risk factors are present
Confirmation of low-risk thrombophilia (heterozygous factor V Leiden mutation or prothrombin *[G20210A]* mutation, protein C or S deficiency) with prior history of thromboembolic events but with no ongoing long-term anticoagulation	Clinical monitoring or administration of heparin in prophylactic doses
Confirmation of high-risk thrombophilia (antithrombin deficiency; combined heterozygous status for prothrombin *[G20210A]* and factor V Leiden mutation; homozygous prothrombin and factor V Leiden mutation) without prior history of thromboembolic events	Administration of heparin in prophylactic doses
Confirmation of high-risk thrombophilia (antithrombin deficiency; combined heterozygous status for prothrombin *[G20210A]* and factor V Leiden mutation; homozygous prothrombin and factor V Leiden mutation) with prior history of thromboembolic events but with no ongoing long-term anticoagulation	Administration of heparin in prophylactic, intermediate or adjusted doses
Prior history of two or more thromboembolic events with no long-term anticoagulation, irrespective of thrombophilia status	Administration of heparin in prophylactic or therapeutic doses
Prior history of two or more thromboembolic events with long-term anticoagulation, irrespective of thrombophilia status	Administration of heparin in therapeutic doses



▶ **Fig. 1** Indications for an andrological diagnostic workup. [rerif]

Consensus-based recommendation 3.10.E59	
Expert consensus	**Strength of consensus +++**
No anticoagulation must be given if the sole purpose is to improve the pregnancy and live birth rate.	

1.3 Andrological diagnosis and treatment before starting assisted reproductive treatment

1.3.1 Andrological diagnostic workup

1.3.1.1 Indications for an andrological workup

Andrological examinations aim to identify possible causes of fertility disorders, determine their severity and find out if they can be treated (▶ **Fig. 1**).

1.3.1.2 Guidelines and national regulations

The extent and type of required clinical andrological examinations have been specified in the WHO manuals "WHO Manual for the Standardized Investigation, Diagnosis and Management of the Infertile Male" [29] and the "WHO Manual for the Standardized Investigation and Diagnosis of the Infertile Couple" [30]. In addition, there is also an international European guideline "Male Infertility" by the European Association of Urology (EAU) [17].

Consensus-based recommendation 3.11.E60	
Expert consensus	**Strength of consensus +**
Before starting any assisted reproductive treatment, the man must be examined by an andrologist.	

Consensus-based recommendation 3.11.E61	
Expert consensus	**Strength of consensus +++**
Andrological examinations must include the man's personal and familial medical history as well as the couple's medical history and must include their sexual medical history, a physical examination, an ejaculate analysis, and, if necessary, an ultrasound examination of the scrotal organs as well as hormone, cytogenetic and molecular genetic examinations.	

1.3.1.3 Lifestyle und male fertility

Overweight

Consensus-based recommendation 3.11.E62	
Expert consensus	**Strength of consensus ++**
Overweight men should be advised to lose weight.	

Nicotine

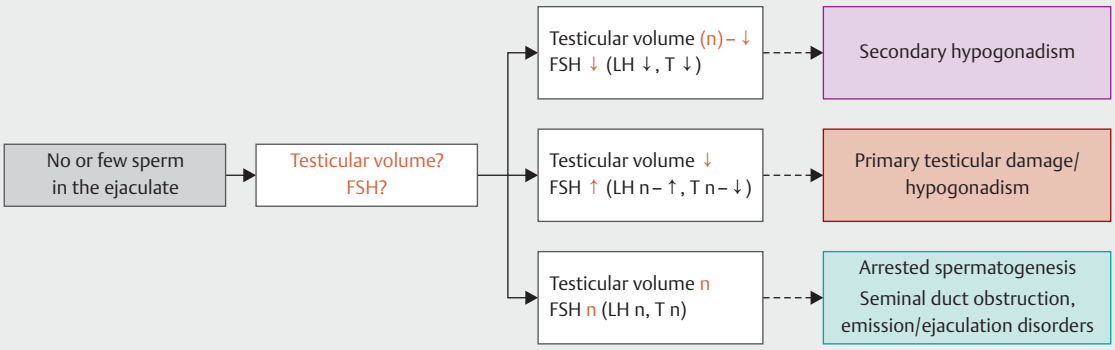
Consensus-based recommendation 3.11.E63	
Expert consensus	**Strength of consensus +++**
Men must be advised to quit smoking.	

Alcohol

Alcohol can have a negative effect on sperm quality through its impact on the pituitary-gonadal axis and its direct injurious effect on the germinal epithelium and Leydig cells [3]. It is not possible to provide unambiguous data about a dose-response relationship.

Consensus-based recommendation 3.11.E64	
Expert consensus	**Strength of consensus +++**
Men must be asked whether they take drugs and advised not to use drugs.	

Consensus-based recommendation 3.11.E65	
Expert consensus	**Strength of consensus +++**
Further investigations must be carried out if the andrological workup shows that the patient has a history of taking anabolic steroids or physical examination or laboratory tests show that the patient takes anabolic steroids.	



▶ **Fig. 2** Diagnostic information obtained from examinations of the basal endocrine system in the context of further diagnostic examinations. [rerif]

Diet and sperm quality

The available studies indicate the necessity of a balanced and healthy diet [19].

Foods which are rich in omega-3 fatty acids, antioxidants such as vitamin E, vitamin C, beta-carotene, selenium, zinc, cryptoxanthin or lycopene, other vitamins such as vitamin D or folic acid and have low levels of saturated fatty acids appear to be associated with a better sperm quality. A diet based on the consumption of fish, seafood, chicken, cereals, vegetables and fruits, low-fat dairy products and low-fat milk appears to be associated with a better sperm quality than a diet consisting predominantly of ready meals, soya, potatoes, full-fat dairy products, cheese, coffee, alcohol, sugary drinks and sweets [31].

The available studies do not provide evidence-based dietary recommendations for men with involuntary childlessness.

1.3.1.4 Clinical examinations, diagnostic apparatus and laboratory workup in andrology

Significance of diagnostic procedures

A comprehensive workup is required if the patient's medical history, initial physical examination or sperm analysis indicate abnormalities or if the couple is diagnosed with idiopathic infertility or if infertility persists despite treatment of the underlying gynecological factor. The evidence level for this approach is stated to be "moderate".

Consensus-based recommendation 3.11.E66	
Expert consensus	**Strength of consensus +++**
Examination of the ejaculate must be carried out in accordance with the 2010 WHO guidelines. The quality of the tests determining sperm concentration, motility and morphology must be verified and documented through regular participation in external and internal quality assurance programs.	

Microbiological examinations

Consensus-based recommendation 3.11.E67	
Expert consensus	**Strength of consensus +++**
Microbiological examination of the ejaculate must be carried out if > 1×10^6/ml peroxidase-positive cells are detected in the ejaculate.	

Examination of post-orgasmic or post-ejaculatory urine sediment

Consensus-based recommendation 3.11.E68	
Expert consensus	**Strength of consensus +++**
Post-ejaculatory urine sediment must be examined if there is no ejaculation despite orgasm or the ejaculate volume is significantly decreased and the patient's medical history indicates the possibility of partial or complete retrograde ejaculation. It is important to first exclude problems in obtaining the ejaculate.	

Endocrine examinations

The importance of investigating basal hormone levels to evaluate fertility is because of the information this workup can provide about possible causes of reduced sperm quality and whether these causes are treatable (▶ **Fig. 2**).

Consensus-based recommendation 3.11.E69	
Expert consensus	**Strength of consensus +++**
The endocrine workup of men with involuntary childlessness must also address any issues in the patient's medical history, his physical examination and the findings of an examination of the ejaculate.	

Consensus-based recommendation 3.11.E70	
Expert consensus	**Strength of consensus +++**
The basic endocrine examination of male patients must include FSH and testosterone; further endocrine tests will be necessary if the basic examination shows abnormal findings.	

Consensus-based recommendation 3.11.E71	
Expert consensus	**Strength of consensus +++**
Further diagnostic investigations must be carried out if the patient's medical history or any findings during his physical examination indicate possible hypogonadism.	

Secondary hypogonadism is particularly important from a therapeutic point of view. Hypothalamic damage with reduced secretion of GnRH leading to a lack of stimulation of the pituitary gland or dysfunction of the pituitary gland itself results in a lack of stimulation of the testes due to low gonadotropin levels. Pituitary gland damage may be caused by pituitary tumors such as prolactinoma. Kallmann syndrome and congenital hypogonadotropic hypogonadism are typical examples of hypothalamic damage. In cases with decreased LH and FSH levels, it may be necessary to specifically re-examine the patient's medical history (use of testosterone or anabolic steroids?). In addition, prolactin levels should be determined and further diagnostic tests should be carried out if prolactin levels are increased (e.g. diagnostic imaging, investigation of other pituitary hormones).

The GnRH test (LHRH test) or GnRH pump test are useful to differentiate whether reduced gonadotropin serum concentrations are due to hypothalamic or pituitary disorders. An increase in gonadotropin levels after external GnRH stimulation indicates the presence of a hypothalamic disorder; if there is no increase in gonadotropin serum concentrations after external GnRH stimulation then the cause of the disorder is located in the pituitary gland.

Genetic diagnostic workup

See chapter on Genetic Factors.

Diagnostic testicular biopsy

If the findings on testicular ultrasound result in a diagnosis of testicular microlithiasis or a suspicion of a testicular pathology in a patient with oligozoospermia, then a diagnostic testicular biopsy may be indicated, particularly if additional risk factors are present (undescended testicles, testicular tumor) [34]. Infertile men have a significantly higher incidence of germ cell tumors compared to the general male population [5, 28]. Multiple sampling should always be done during diagnostic testicular biopsy to increase diagnostic certainty [13, 18]. Different scoring systems are available to evaluate spermatogenesis [7].

Consensus-based recommendation 3.11.E72	
Expert consensus	**Strength of consensus +++**
Purely diagnostic testicular biopsies must not be carried out if there is no suspicion of testicular pathology.	

Consensus-based recommendation 3.11.E73	
Expert consensus	**Strength of consensus +++**
A histological biopsy must be carried out when sampling testicular tissue for spermatozoa extraction to obtain more information about the cause of azoospermia/disordered spermatogenesis and to detect any testicular germ cell neoplasia in situ (GCNIS).	

1.3.2 Causes and treatment approaches for male infertility disorders

Consensus-based recommendation 3.11.E74	
Expert consensus	**Strength of consensus +++**
Treatable disorders should be treated before deciding that ART is indicated. Any gynecological findings must be carefully considered before making the decision to treat andrological factors (▶ **Fig. 3**).	

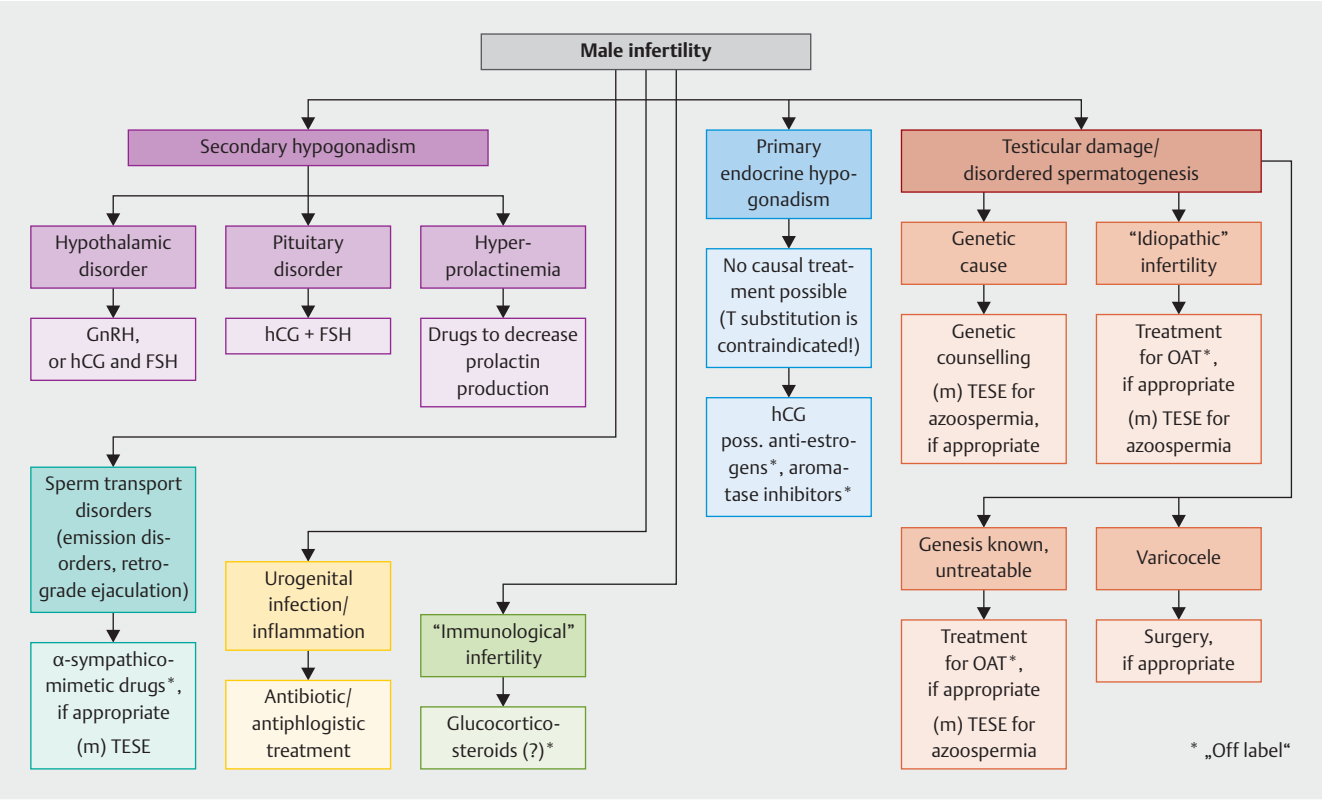
Consensus-based recommendation 3.11.E75	
Expert consensus	**Strength of consensus +++**
If secondary hypogonadism with azoospermia is present, causal therapy must be attempted before carrying out testicular biopsy with TESE/ICSI or ICSI for cryptozoospermia or severe oligozoospermia, unless the gynecological findings require a different chronological approach.	

Consensus-based recommendation 3.11.E76	
Expert consensus	**Strength of consensus +++**
The surgical treatment for azoospermia must be guided by the cause of the azoospermia and must differentiate between obstructive and non-obstructive causes.	

Consensus-based recommendation 3.11.E77	
Expert consensus	**Strength of consensus +++**
Depending on the cause of the obstructive azoospermia, the patient must be offered reconstructive microsurgery or surgery to obtain spermatozoa. Priority should be given to reconstructive surgery rather than procedures purely designed to extract sperm.	

Consensus-based recommendation 3.11.E78	
Expert consensus	**Strength of consensus ++**
A genetic workup must be done to obtain a differential diagnosis for non-obstructive azoospermia before carrying out surgical sperm extraction, as this could have consequences for the success of surgical treatment (see Chapter 3.12.1.1).	

Consensus-based recommendation 3.11.E79	
Expert consensus	**Strength of consensus +++**
Surgical sperm extraction procedures must be combined with the option of sperm cryopreservation.	



▶ **Fig. 3** Andrological treatment algorithm. [rerif]

Consensus-based recommendation 3.11.E80	
Expert consensus	**Strength of consensus +++**
Endocrine disorders associated with azoospermia must be treated prior to performing surgical sperm extraction, if the pathology permits.	

Consensus-based recommendation 3.11.E81	
Expert consensus	**Strength of consensus +++**
Microsurgical or multifocal testicular tissue retrieval for TESE must be carried out in patients with non-obstructive azoospermia.	

Infections and inflammations of the genital tract

Various aspects must be borne in mind when investigating potential urogenital infections in men with involuntary childlessness prior to starting ART:

- the impact of infections on sperm quality and male fertility
- transmission of the infection to the female partner
- contamination of culture media and oocytes during the ART procedure

Consensus-based recommendation 3.11.E82	
Expert consensus	**Strength of consensus ++**
Relevant bacterial infections of the seminal ducts must be treated with antibiotics (both partners must be treated, if necessary).	

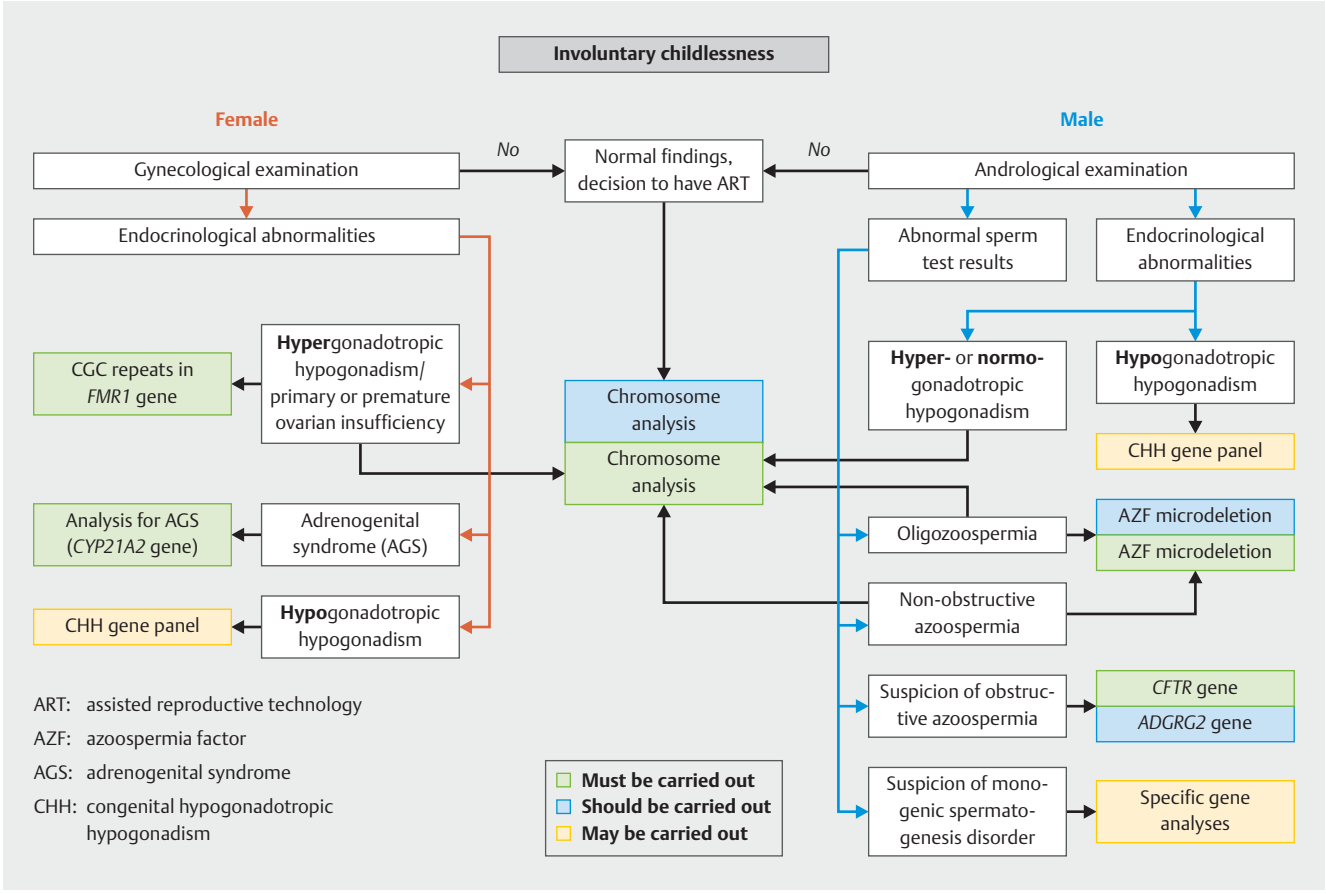
1.3.2.1 Immunological infertility

Consensus-based recommendation 3.11.E83	
Expert consensus	**Strength of consensus +++**
The confirmation of sperm autoantibodies in the ejaculate is an immunological infertility factor, and ART may be indicated.	

1.3.3 Reproductive biology and diagnostic and therapeutic aspects before starting assisted reproductive treatment

1.3.3.1 Significance of sperm DNA fragmentation assay

Consensus-based statement 3.11.S1	
Expert consensus	**Strength of consensus +++**
Although the analysis of DNA fragmentation in spermatozoa could potentially be a useful clinical biomarker, the conclusive predictive value of this test for IVF and/or ICSI treatment is still unclear. Nevertheless, carrying out sperm DNA fragmentation analysis in addition to standard sperm analysis to determine sperm DNA integrity can lead to a more comprehensive understanding of the man's reproductive health.	



▶ **Fig. 4** Algorithm for the genetic workup of couples before starting ART. [rerif]

1.3.3.2 Significance of sperm enrichment procedures

Consensus-based statement 3.11.S2	
Expert consensus	**Strength of consensus +++**
A sperm enrichment procedure may provide information about the behavior of the ejaculate sample in the female genital tract.	

Consensus-based recommendation 3.11.E84	
Expert consensus	**Strength of consensus +++**
A sperm enrichment procedure must be carried out before every ART to obtain a better assessment of the necessary therapy.	

1.3.3.3 Procedure for immotile sperm

Consensus-based statement 3.11.S3	
Expert consensus	**Strength of consensus +++**
It is useful to determine the percentage of vital but immotile sperm beforehand. It may serve as a diagnostic analysis for further treatment options, e.g. TESE before starting ART treatment or the use of non-depleting vitality tests on the day of ICSI.	

Consensus-based recommendation 3.11.E85	
Expert consensus	**Strength of consensus +++**
In patients with immotile sperm, a diagnostic vitality test to determine the number of vital but immotile sperm should be carried out before starting ART.	

1.4 Genetic factors

1.4.1 Diagnosing genetic factors

Genetic disorders (chromosome changes and monogenic disorders) are responsible for around 10–20% of male and 5–10% female cases of infertility or subfertility. Before starting ART, the patient's detailed personal and familial medical history should be taken, for example in the context of genetic counselling, with a view to identifying potential hereditary disorders. Particular attention must be paid to a possible familial aggregation of possible genetic developmental disorders, infertility or hormonal imbalances. If there are indications of an underlying genetic disease in the family, it is usually necessary to carry out a molecular genetic workup of an affected person before persons at risk can be tested. ▶ **Fig. 4** shows an algorithm for the genetic workup of couples before starting assisted reproductive treatment.

Consensus-based recommendation 3.12.E86	
Expert consensus	**Strength of consensus +++**
A detailed personal and familial medical history of the couple wanting to have children must be taken with a view to identifying potential genetic risk factors. Genetic counselling must be offered by a genetic specialist in accordance with national guidelines prior to carrying out a genetic workup.	

1.4.1.1 Male genetic factors

According to the WHO guideline [3], no genetic testing is required if the spermatogenesis disorder has a known non-genetic cause (prior chemotherapy, use of anabolic steroids).

If an additional genetic workup is required, it is useful to differentiate between non-obstructive azoospermia or oligozoospermia and obstructive azoospermia:

Non-obstructive disorders of spermatogenesis

i. Y-chromosomal microdeletions

Y-chromosomal microdeletions are the second most common genetic cause of disorders of spermatogenesis and play a significant role in the chance of success of testicular biopsies. Y-chromosome microdeletions are found in less than 2% of infertile men in Germany and Austria. The overwhelming majority, accounting for around 80% of cases, are AZFc deletions which lead to a variable phenotype. Most men with AZFa (0.5–4%), AZFb (1–5%) or AZFbc (1–3%) deletions have Sertoli cell-only syndrome. The probability that testicular biopsy will be able to retrieve sperm from these patients is extremely low [20].

Consensus-based recommendation 3.12.E87	
Expert consensus	**Strength of consensus +++**
After excluding other causes, cases with non-obstructive azoospermia must and of cases with severe oligozoospermia (< 5 million/ml) should be analyzed for AZF microdeletions (AZFa, b, c).	

ii. Chromosomal changes

In addition to maldistribution of sex chromosomes, balanced chromosome translocations may also result in disordered spermatogenesis. This increases the percentage of men with chromosomal changes who only have a fertility disorder and are otherwise healthy.

The probability that men undergoing fertility treatment have chromosomal abnormalities increases with decreasing sperm counts (▶ **Table 7**); compared to normal populations, the probability is higher, even for men with normal sperm counts. It is considered a subfertility factor.

Consensus-based recommendation 3.12.E88	
Expert consensus	**Strength of consensus +++**
Chromosome analysis should be carried out in cases with non-obstructive azoospermia or severe oligozoospermia (< 5 million/ml) after excluding other causes.	

▶ **Table 7** Percentage of men with abnormal chromosome findings according to sperm analysis results [14].

Sperm analysis results	Percentage of patients with chromosomal abnormalities (confidence interval)
Azoospermia (n = 1599)	15.4 (13.6–17.2%)
Oligozoospermia < 1 million/ml (n = 539)	3.0 (1.5–4.4%)
Oligozoospermia > 1–5 million/ml (n = 475)	2.1 (0.8–3.4%)
Oligozoospermia > 5–10 million/ml (n = 879)	3.5 (2.3–4.7%)
Oligozoospermia > 10–20 million/ml (n = 808)	1.1 (0.4–1.8%)
Normozoospermia > 20 million/ml (n = 729)	2.9 (1.7–4.1%)
Normal sperm count	0.3–0.5%

iii. Monogenic causes of disorders of spermatogenesis

As the causes of non-obstructive disorders of spermatogenesis in more than 80% of affected men are still unknown, an intensive search for new candidate genes is underway. Given the number of available genetic analyses of monogenic disorders of spermatogenesis, it is important to take into account that confirmed disorders currently do not influence the procedure or outcome of ART. This assessment may change in future if, depending on the genetic cause, targeted treatments become available. Further scientific studies are necessary to better understand the importance of individual genetic mutations for spermiogenesis.

Consensus-based recommendation 3.12.E89	
Expert consensus	**Strength of consensus +++**
Genetic analysis may be offered if there is a suspicion of a rare monogenic cause of disordered spermatogenesis.	

iv. Obstructive azoospermia

The basis for this diagnosis is intact spermatogenesis in the testicular tissue, a finding which offers good chances of success for ART with TESE/ICSI. Around 2% of men with azoospermia have anomalies of Wolffian duct derivatives, usually in the form of a CBAVD, more rarely taking the form of a CUAVD or bilateral epididymal obstruction. At least one *CFTR* mutation is found in around 80% of patients with CBAVD and the cause is assumed to be CF-associated disease.

Consensus-based recommendation 3.12.E90	
Expert consensus	**Strength of consensus +++**
After excluding other causes, the CTFR gene must be analyzed if there is a suspicion of obstructive azoospermia. The analysis must cover all relevant pathogenic mutations, including TG-T repeats in CFTR intron 8; complete sequencing must be carried out if only a heterozygous mutation is identified.	

Consensus-based recommendation 3.12.E91	
Expert consensus	**Strength of consensus +++**
If the findings of *CFTR* analysis in a patient with obstructive azoospermia are normal, the *ADGRG2* gene should be analyzed.	

b. Endocrine disorders

If endocrine abnormalities are present, differentiating between hypo- or hypergonadotropic hypogonadism will be important for the genetics.

i. Hypergonadotropic hypogonadism

Primary testicular functional failure is found primarily in men with Klinefelter syndrome; it is the most common genetic cause of male infertility in men with azoospermia, occurring in about 14% of men with azoospermia. Around 80% have a 47,XXY karyotype, while about 20% have higher grade aneuploidies, mosaicism (46,XX/47XXY) or structurally changed X chromosomes [33].

Consensus-based recommendation 3.12.E92	
Expert consensus	**Strength of consensus +++**
After other causes have been excluded, chromosome analysis must be carried out in men with hypergonadotropic hypogonadism.	

ii. Hypogonadotropic hypogonadism

The incidence of congenital hypogonadotropic hypogonadism (CHH) is around 1 in 4000–10 000 men, making it about 3 to 5 times more common in men than in women [10]. Numerous genes have been identified as possible causes of CHH, accounting for 40–50% of cases [8]; the X chromosome KAL1 gene is the most important of these genes and accounts for around 10% of cases.

Consensus-based recommendation 3.12.E93	
Expert consensus	**Strength of consensus +++**
After excluding exogenous causes, genetic analysis of CHH genes may be carried out in men with congenital hypogonadotropic hypogonadism (CHH).	

1.4.1.2 Female genetic factors

Ovulatory dysfunction

Oligorrhea or amenorrhea (ovulatory dysfunction) is present in around 40% of women with fertility disorders [24]. The decisive factor is maternal age, and maternal age also determines the success of ART with the patient's own oocytes, while primarily genetic causes are comparatively rare. Above the age of 40–45 years, the overwhelming majority of oocytes are aneuploid, meaning that only a small percentage will successfully develop into a blastocyst and implant [1, 15].

a. Hypergonadotropic hypogonadism

Around 10–13% of affected women have gonosomal aberrations such as a 45,X or 47,XXX cell line or a structurally changed X chromosome, meaning that chromosome analysis is indicated if other causes of infertility have been ruled out [27].

Consensus-based recommendation 3.12.E94	
Expert consensus	**Strength of consensus +++**
After excluding other causes, chromosome analysis must be carried out in women with hypergonadotropic hypogonadism.	

Premutations in the *FMR1* gene (CGG repeats of 55–200) often lead to primary or secondary ovarian insufficiency; if they are passed on to children, they have a high probability of expanding into a full mutation. Full mutations of *FMR1* (CGG repeats of more than 200) can result in mental disability (fragile X syndrome, fra [X] syndrome), particularly in males; the mutations are not associated with ovarian insufficiency. Around 2% of Caucasian women with primary ovarian insufficiency and no familial aggregation and 10–15% of Caucasian women with familial aggregation have a premutation of the *FMR1* gene [25]; given the associated risk of a child with fragile X syndrome, this finding may have a significant impact on subsequent family planning.

Consensus-based recommendation 3.12.E95	
Expert consensus	**Strength of consensus +++**
Genetic analysis of CGC repeats in the *FMR1* gene must be carried out in women with primary or premature ovarian insufficiency after other causes of infertility have been excluded.	

b. Hypogonadotropic hypogonadism

The incidence of congenital hypogonadotropic hypogonadism (CHH) is about 1 in every 30 000–40 000 women, making it a very rare entity. While Kallmann syndrome (KS), in which the sense of smell is diminished or absent, is formally differentiated from normosmic hypogonadotropic hypogonadism (nHH), in practice the transition is fluid. At present, 35–40% of the molecular causes of congenital hypogonadotropic hypogonadism are known and can be traced back to mutations in at least 20 genes [21]. The exogenous administration of sex hormones, gonadotropins or GnRH analogs represents the only treatment option for all known disorders [8].

Consensus-based recommendation 3.12.E96	
Expert consensus	**Strength of consensus +++**
After excluding exogenous causes, genetic analysis of CHH genes may be carried out in women with congenital hypogonadotropic hypogonadism (CHH).	

c. Hyperandrogenism

AGS is the most important underlying genetic disease leading to hyperandrogenism. The most common form is a 21-hydroxylase deficiency caused by autosomal recessive mutations in the *CYP21A2* gene. Endocrine treatment is guided by the underlying enzyme defect and the pathogenicity of confirmed mutations. Prenatal treatment to prevent virilization in female fetuses with a risk of AGS due to 21-hydroxylase deficiency was still classified as an experimental therapy at the time of compiling the guideline, and the benefits and risks of this treatment should therefore be carefully weighed up in each individual case [2].

Consensus-based recommendation 3.12.E97	
Expert consensus	**Strength of consensus ++**
A genetic workup must be carried out if there is a suspicion of adrenogenital syndrome.	

Balanced chromosome changes

Structural chromosome aberrations are also a relevant cause of infertility in women, even if these abnormalities are not apparent during gynecological examinations. A French study reported that the female partners of infertile men had an increased percentage of balanced translocations (factor 4,5) or inversions (factor 16) which was comparable to that of their investigated male partners (n = 3208 patients) [16]. The percentage of women with chromosome changes was inversely correlated with their partner's sperm pathology.

Consensus-based recommendation 3.12.E98	
Expert consensus	**Strength of consensus +**
After excluding other causes of infertility, a chromosome analysis of both partners should be carried out.	

1.4.2 Treatment of genetic factors

Consensus-based recommendation 3.12.E99	
Expert consensus	**Strength of consensus +++**
If structural chromosome changes are confirmed in one of the partners, the couple must be informed about the options for polar body diagnosis and preimplantation genetic diagnosis as well as about prenatal diagnostic examinations (invasive and non-invasive prenatal options for a diagnostic workup).	

Conflict of Interest

The authors' conflicts of interest are listed in the long version of the guideline.

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