



ASSISTED REPRODUCTIVE TECHNOLOGY CLINICAL PRACTICE GUIDELINE

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Document Title:	Clinical Practice Guideline on Assisted Reproductive Technology		
Document Ref. Number:	DOH/HWFP/GD/CPGART/V1/2023	Version:	V 1
New / Revised:	New		
Publication Date:	December 2023		
Effective Date:	December 2023		
Document Control:	DoH Strategy Sector		
Applies To:	- DoH licensed Healthcare Professionals - DoH licensed Healthcare Providers - DoH authorized Health Payers. - All Health Insurance products and schemes.		
Owner:	Healthcare Workforce Sector		
Revision Date:	December 2026		
Revision Period:	3 Years after Publication		
Contact:	HCWS@doh.gov.ae		

Acknowledgment

This document was developed by the Department of Health - Healthcare Workforce Sector in collaboration with a group of local and international Subject Matter Experts. The department would like to acknowledge their contribution and dedication to the quality of the healthcare services and patient safety.

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1. Guideline Purpose and Brief

The purpose of this guideline is to assist healthcare professionals and providers in making informed decisions on the delivery of healthcare interventions in Assisted Reproduction including Assisted Reproductive Technology (ART). This guideline is built on best practices and in consultation with expert practitioners based on international ART guidelines and publications. The guideline consists of evidence-based and best practice recommendations on how healthcare professionals and providers can improve service delivery, quality, patient safety, and patient outcomes in alignment with other DOH regulatory tools.

2. Definitions and Abbreviations

No.	Term / Abbreviation	Definition
2.1	Advanced Maternal Age	Woman $\geq$ 35 years of age.
2.2	American Society for Reproductive Medicine (ASRM)	A nonprofit, multidisciplinary organization based in the United States of America that works on reproductive medicine and the advancement of its science and practice.
2.3	Anejaculation	inability to ejaculate semen
2.4	Antral Follicle Count (AFC)	A measurement of ovarian reserve done with high quality ultrasound equipment.
2.5	Assisted Hatching	An Assisted Reproductive Technology procedure in which the zona pellucida of an embryo is either thinned or perforated by chemical, mechanical or laser methods.
2.6	Assisted Reproductive Technology (ART)	Any intervention that includes the in vitro handling of both human oocytes and sperm or of embryos for the purpose of reproduction.
2.7	Asthenozoospermia	Reduced percentage of motile sperm in the ejaculate $<$ 30% progressive motile spermatozoa.
2.8	Azoospermia	The absence of spermatozoa in the seminal fluid; affects around 1% of the population and 10% of infertile men. Obstructive Azoospermia (OA): absence of spermatozoa and spermatogenic cells in semen because to obstruction. OA is less common than NOA and occurs in 15-20% of men with azoospermia. Non-Obstructive Azoospermia (NOA): when there is a problem with sperm production at testicular level- impaired spermatogenesis.
2.9	Conventional IVF	In Vitro Fertilization achieved by a mixture of recovered oocytes with spermatozoa in a small volume of culture medium.
2.10	Cryopreservation	The process of slow freezing or vitrification to preserve biological material (e.g., gametes, zygotes, cleavage-stage embryos, blastocysts or gonadal tissue) at extreme low temperature.
2.11	Endometriosis	A condition in which tissue like the lining of the uterus grows outside the uterus.
2.12	European Society of Human Reproduction and Embryology (ESHRE)	A nonprofit, multidisciplinary organization based in Europe that provides guidance and accreditations for the practice of reproductive medicine and collaborates with politicians and policy makers throughout Europe.
2.13	Expectant Management	A formal approach that encourages conception through unprotected vaginal intercourse. It involves supportively offering an individual or couple information and advice about the regularity and timing of intercourse and any lifestyle changes which might improve their chances of conceiving. It does not involve active clinical or therapeutic interventions.
2.14	Gamete intrafallopian transfer (GIFT)	The transfer of both gametes (oocytes and spermatozoa) into a Fallopian tube during an ART procedure.

2.15	Healthy Live Birth	The complete expulsion or extraction from the mother of a baby, irrespective of the duration of the pregnancy, which, after such separation, breathes or shows any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of the voluntary muscles, whether the umbilical cord has been cut or the placenta is attached.
2.16	Human Fertilisation and Embryology Authority (HFEA)	An executive non-departmental public body of the Department of Health and Social Care in the United Kingdom.
2.17	Hydrosalpinx / Hydrosalpinges	A distally occluded, dilated, and fluid-filled Fallopian tube secondary to infection, scar tissue, or endometriosis. (Hydrosalpinges is the term used for bilateral fallopian tube occlusion)
2.18	Hypergonadotropic hypogonadism	Gonadal failure associated with reduced gametogenesis, reduced gonadal steroid production, and elevated gonadotropin production.
2.19	Hypogonadotropic hypogonadism	Gonadal failure associated with reduced gametogenesis and reduced gonadal steroid production due to reduced gonadotropin production or action.
2.20	Infertility	Failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse. Primary infertility refers to couples that have never had a child and cannot achieve pregnancy after at least 12 consecutive months having sex without using birth control methods. Secondary infertility refers to couples who have been able to achieve pregnancy at least once before (with the same or different sexual partner). The American Society of Reproductive Medicine has revised the definition of infertility to encourage women over 35 years of age are to seek fertility evaluation if they fail to conceive after six months of trying. Fertility interventions may be initiated in less than 1 year If infertility is diagnosed based on medical, sexual, and reproductive history, age, physical findings, and diagnostic testing (Sub-clause 3.5.3).
2.21	Intracytoplasmic Sperm Injection (ICSI)	Procedure of injecting a spermatozoon into the cytoplasm of a mature oocyte for IVF as part of infertility treatment.
2.22	Intra-Uterine Insemination (IUI)	A procedure in which laboratory processed sperm are placed in the uterus around the time of ovulation to attempt a pregnancy.
2.23	In-vitro fertilization (IVF)	A sequence of procedures that involves extracorporeal fertilization of gametes. It includes conventional in vitro insemination and ICSI.
2.24	Laparoscopic Tubal Ligation	Interruption of the fallopian tubes laparoscopically.
2.25	Low Ovarian Reserve	Literature suggests a low ovarian reserve when the AFC < 5-7 follicles, and/or anti-müllerian hormone (AMH) levels < 0.7-1.3 ng/ml. Experts suggest considering other qualitative measures as well, such as: previous multiple failed cycles, failed fertilization, quality of eggs.
2.26	Male factor infertility	The presence of abnormal semen parameters or sperm functional assays, or the functional inability to adequately deliver semen into the vaginal canal, by the male partner of a couple unable to achieve conception after 1 year of unprotected intercourse. Semen parameters as per the World Health organization (WHO) semen analysis criterion, 6th edition – 2021 (detailed in Sub-clause 3.5.3).
2.27	Medically Assisted Reproduction (MAR)	Any treatment offered to couples experiencing reproductive problems for the purpose of establishing a pregnancy.
2.28	Microdissection testicular sperm extraction (MicroTESE)	A surgical procedure using an operating microscope to identify seminiferous tubules that may contain sperm to be extracted for IVF and/or ICSI.

2.29	Microsurgical epididymal sperm aspiration (MESA)	A surgical procedure performed with the assistance of an operating microscope to retrieve sperm from the epididymis.
2.30	National Institute for Health and Care Excellence (NICE)	An executive non-departmental public body of the Department of Health and Social Care in England that publishes guidelines on the use of health technologies, clinical practice, for health promotion, and for social care services and users.
2.31	Obesity	Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health. A body mass index (BMI) equal to or over 25 is considered overweight, and ≥ 30 is obese. Obesity increases the risk of several common conditions, including type 2 diabetes, dyslipidemia, hypertension, coronary heart disease, cholelithiasis, endometrial and postmenopausal breast cancer, stroke, osteoarthritis, and infertility.
2.32	Oligo-astheno-teratozoospermia (OAT)	When all three anomalies (Oligozoospermia (low sperm number), Asthenozoospermia (low motility), and Teratozoospermia (abnormal shape)) occur simultaneously, which is defined as oligo-astheno-teratozoospermia syndrome.
2.33	Oligozoospermia	Decreased numbers of sperm in the ejaculate (< 16 million sperm/mL), which is further subdivided depending on the number of sperms into mild (10–16 million sperm/mL), moderate (5–10 million sperm/mL), and severe (< 5 million sperm/mL).
2.34	Ovarian Hyper-Stimulation Syndrome (OHSS)	An exaggerated systemic response to ovarian stimulation characterized by a wide spectrum of clinical and laboratory manifestations. It is classified as mild, moderate or severe according to the degree of abdominal distention, ovarian enlargement and respiratory, hemodynamic and metabolic complications. Severe OHSS: A systemic response due to ovarian stimulation interventions that is characterized by severe abdominal discomfort and/or other symptoms of ascites, hemoconcentration (Hct > 45) and/or other serious biochemical abnormalities requiring hospitalization for observation and/or for medical intervention (paracentesis, other). Refer to Humaidan et al. 2016¹ Figure 1 and Table 1 for detailed definition and criteria.
2.35	Ovarian Reserve	A term generally used to indicate the number and/or quality of oocytes, reflecting the ability to reproduce. Ovarian reserve can be assessed by any of several means: female age; number of antral follicles on ultrasound; Anti-Mullerian hormone levels; follicle stimulating hormone (FSH) and estradiol levels; response to gonadotropin stimulation, and oocyte and/or embryo assessment during an ART procedure, based on number, morphology, or genetic assessment of the oocytes and/or embryos.
2.36	Ovarian Insufficiency	Depletion or dysfunction of ovarian follicles with cessation of menses before age 40 years (previously referred to as premature menopause or primary ovarian failure). It can be caused by a primary disorder in the ovary, or it can occur due to secondary causes (e.g., Fragile X syndrome, turner syndrome or mosaic turner syndrome, Female Parental consanguinity, Vitamin D deficiency).
2.37	Ovarian stimulation (OS)	Pharmacological treatment with the intention of inducing the development of ovarian follicles. It can be used for two purposes: 1) for timed intercourse or insemination; 2) in ART, to obtain multi follicular recruitment at follicular aspiration.
2.38	Ovulation Induction (OI)	A pharmacological treatment of women with anovulation or oligo-ovulation with the intention of inducing normal ovulatory cycles.
2.39	Percutaneous epididymal sperm aspiration (PESA)	The collection of sperm through a fine needle inserted directly from the epididymis, where sperm is stored, after it is formed in the testes.

¹ Humaidan et al. 2016. Ovarian hyperstimulation syndrome: review and new classification criteria for reporting in clinical trials. *Human Reproduction*, 31(9), pp.1997-2004.

2.40	Polycystic ovary syndrome (PCOS)	A chronic metabolic and hormonal condition, which can impact on physical health and emotional wellbeing. Recommendations from the International <i>Evidence-Based Guideline for the Assessment and Management of Polycystic Ovary Syndrome</i>
2.41	Poor Ovarian Responder	A woman treated with ovarian stimulation for ART, in which at least two of the following features are present (Bologna criteria): • Woman with advanced maternal age or presenting other risk factors such as previous ovarian surgery, genetic defects, chemotherapy, radiotherapy, and autoimmune disorders. • A previous poor ovarian response • An abnormal ovarian reserve test
2.42	Poor Ovarian Response	≤ 3 oocytes developed/obtained following ovarian stimulation aimed at obtaining >3 oocytes.
2.43	Preimplantation genetic testing (PGT)	A test to analyze the DNA from oocytes (polar bodies) or embryos (cleavage stage or blastocyst) for Human leukocyte antigen (HLA) typing or for determining genetic abnormalities. These include: PGT for aneuploidies (PGT-A); PGT for monogenic/single gene defects (PGT-M); and PGT for chromosomal structural rearrangements (PGT-SR).
2.44	Preimplantation Genetic Testing for Aneuploidy (PGT-A)	A test to analyze polar bodies, blastomeres or trophectoderm from oocytes, zygotes, or embryos for the detection of aneuploidy, mutation and/or DNA rearrangement.
2.45	Preimplantation Genetic Testing for Monogenic disorders (PGT-M)	A test to analyze polar bodies, blastomeres or trophectoderm from oocytes, zygotes, or embryos for the detection of specific genetic, structural and/or chromosomal alterations.
2.46	Preimplantation Genetic Testing for Structural Chromosomal Rearrangements (PGT-SR)	Genetic test performed on embryos created through IVF to screen for chromosomal structural rearrangements normally caused by balanced translocations and inversions.
2.47	Salpingectomy	The surgical removal of an entire Fallopian tube.
2.48	Semen Analysis	A description of the ejaculate to assess the function of the male reproductive tract. Characteristic parameters include volume, pH, concentration, motility, vitality, morphology of spermatozoa and presence of other cells.
2.49	Sperm Motility	The percentage of moving spermatozoa relative to the total number of spermatozoa.
2.50	Surgical Sperm Retrieval	A surgical procedure involving one or more testicular biopsies or needle aspirations to obtain sperm for use in IVF and includes: Percutaneous epididymal sperm aspiration (PESA) Testicular Sperm Aspiration (TESA) Testicular Sperm Extraction (TESE; Open TESE and Micro-TESE)
2.51	Teratozoospermia	A reduced percentage of morphologically normal sperm in the ejaculate < 4% normal forms.
2.52	Testicular sperm aspiration (TESA)	A surgical procedure involving one or more testicular needle aspirations to obtain sperm for use in IVF.
2.53	Testicular sperm extraction (TESE)	The collection of sperm from a biopsy or several biopsies from the testicular tissue after making an incision in the scrotal skin.
2.54	Unexplained Infertility	The diagnosis of infertility in couples with normal ovarian function, Fallopian tubes, uterus, cervix, and pelvis; and with adequate coital frequency, normal testicular function, genitourinary anatomy, and a normal ejaculate.
2.55	Zygote intrafallopian transfer (ZIFT)	The transfer of one or more zygotes into the Fallopian tube during an ART procedure.

3. Guideline Content

3.1 Counseling:²

- 3.1.1 It is recommended to offer initial fertility counselling to married couples concerned about fertility; or who are unable to/ find it difficult to have vaginal intercourse; or have delays in conception.
- 3.1.2 Offer initial advice for all couples concerned about their fertility on chances of conception, frequency and timing of sexual intercourse (regular intercourse 2-3 times/week), effects of alcohol intake and limits (no more than 1-2 units of alcohol/week), first- and second-hand smoking effects (smoking cessation), obesity and weight loss (follow a supervised weight loss program if BMI > 30), underweight and weight gain, occupational exposure to hazards, effects of medications and recreational drug use (not to use any addictive drugs), dietary supplements such as folic acid and vitamin B12, especially for those diagnosed with BMI>30, diabetes or are on anti-epileptic medications (Folic acid 5mg should be provide as a daily supplement to prevent neural tube defect), vaccinations (Rubella vaccination if seronegative & avoid pregnancy for one month), and psychosexual counselling (treat any psychosexual problem if present).
- 3.1.3 Genetics counseling to be done by certified genetic counselor.

3.2 ART Indications³

- 3.2.1 Couple seeking **Fertility** where:
 - 3.2.1.1. The woman is of reproductive age and the couple have not conceived after 12 months for women aged <35 or after 6 months for woman aged ≥35 of unprotected vaginal sexual intercourse and in the absence of any known cause of infertility, or history of unsuccessful infertility treatments.
 - 3.2.1.2. Infertility may be diagnosed earlier than 6 months, i.e. there are features or findings indicative of subfertility in one of or both couple such as advanced maternal age, very advanced maternal age (≥40 years of age), low ovarian reserve, male factor infertility, endometriosis, or tubal obstruction (further detailed in sub-clause 3.5.3).
- 3.2.2 Couple or single individuals seeking **Fertility Preservation** in the following conditions:
 - 3.2.2.1. When either the male or female is considering gonadotoxic therapy or surgery, which have predictable negative impact on fertility, or has risk of decreased ovarian reserve for female patients, including but not limited to:
 - (a) Pre-Cancer treatment - Clinicians should inform patients receiving potentially gonadotoxic therapies about options for fertility preservation and future reproduction prior to the initiation of such treatment. A collaborative multidisciplinary team approach is encouraged.
 - (b) Autoimmune diseases treatment, such as high dose corticosteroids.
 - (c) Endometriosis
 - (d) Benign ovarian masses requiring radical surgery.
 - (e) Prior to Bariatric Surgery as some studies suggested association with decreased ovarian reserve.
 - (f) Women carrying Breast Cancer 1 (BRCA1) gene or Breast Cancer 2 (BRCA2) gene genetic mutation and have an increased risk of developing ovarian cancer or are at high risk of breast cancer before definitive treatment (some studies suggest a likelihood of accelerated ovarian aging and ovarian reserve loss after cancer treatments).
 - 3.2.2.2. Reduced ovarian reserve at young age.
 - 3.2.2.3. To protect against future infertility due to reproductive aging or other causes.

3.3 Contraindications to ART and Pregnancy:

- 3.3.1 It is strongly recommended to conduct a full assessment and counseling for any couple seeking assisted reproduction prior to any fertility treatment. It is recommended to assess for any contraindication to pregnancy in general, any contraindication to any form of Medical Assisted Reproduction (ART); and any maternal risks associated with pregnancy or delivery. Such would include certain maternal conditions or systemic illnesses such as diabetes or cardiopulmonary conditions (pulmonary hypertension, heart failure, certain cerebrovascular conditions).

For further information refer to:

²American Society for Reproductive Medicine (ASRM) 2022, *Optimizing natural fertility: a committee opinion.*

³ESHRE Guideline Group on Female Fertility Preservation et al. 2020, *Guideline Group on Female Fertility Preservation; ASRM 2018, Fertility preservation and reproduction in patients facing gonadotoxic therapies: an Ethics Committee opinion.*

3.4 Pre-ART Considerations for Female Patients:

3.4.1 Age:

- 3.4.1.1. The suggested ideal age for women undergoing ART treatments is between 18-45 years of age, with special attention given to women aged ≥ 40 years age.
- 3.4.1.2. For women aged between 45-47 years of age, international bodies (ESHRE, HFEA, and ASRM) recommend to consider ART for normal cycling women with adequate ovarian reserve along with clinical judgment that is based on ovarian reserve indicators and previous fertility outcomes (if any) (for detailed ovarian reserve tests– refer to sub-clause 3.6.5.5).
- 3.4.1.3. It is strongly recommended to counsel women of advanced maternal age about the associated risks and the success rate of ART for women of advanced maternal age.
- 3.4.1.4. ART treatments are strongly discouraged in women over age 47.

3.4.2 Body Mass Index (BMI):

- 3.4.2.1. It is recommended to consider BMI along with other patient factors during assessment. Anovulatory infertility risk is higher in underweight (BMI < 18.5 kg/m²) and obese (BMI ≥ 30 kg/m²) women.
- 3.4.2.2. The preferred BMI range for women undergoing assisted reproduction is from 19-35 kg/m² while taking into consideration obstetric and anesthetic risks. However, this is not a cut-off threshold to deny ART treatment.
- 3.4.2.3. **For women with a BMI < 18.5 kg/m²,** pregnancy rates are lower compared with normal-weight women, in parallel with increased time-to-pregnancy periods and adverse pregnancy outcomes. Therefore, it is recommended to offer underweight women counselling and a multidisciplinary approach including a referral to a dietitian (and psychological counseling when clinically indicated) to rule out and manage medical and psychiatrist illness related to underweight. This may run in parallel with fertility treatment.
- 3.4.2.4. **For women with a BMI 35-40 kg/m²,** Studies suggested obese women responded poorly to ovulation induction and in some circumstances had lower pregnancy rates and confirmed obese women to have lower success rate (single live birth) following IVF in contrast to normal-weight patients. Therefore, for obese women, it is recommended to consider additional criteria such as actual weight, neck/abdomen/waist circumference, waste to hip ratio, per centage of body fat, presence of other comorbidities, and the available clinical setting.
 - (a) It is recommended to refer women with BMI of ≥ 35 kg/m² to a dietitian first with aims to reduce weight by 0.5 - 1 kg/week (loss of around 5% of total body weight within one month). While further research is required, some studies argue that weight loss goals are often not achieved, time to achieve pregnancy is prolonged, and the live birth rates are either equivalent or lower in women undergoing pretreatment lifestyle weight loss intervention vs. immediate infertility treatment. On the other hand, weight loss may still improve the chance of unassisted conception. Therefore, a parallel weight loss program while undergoing fertility treatment may also be offered.
 - (b) There are significant safety concerns (including anesthetic and procedural safety concerns) that must be acknowledged with increasing BMI, particularly in the case of IVF. It is recommended to discuss with obese women seeking assisted reproduction these concerns, the associated increased risk of fertility treatment failure, and the resulting risks to both pregnancy and the child; and offer these women a shared decision-making process. When an appropriate clinical setting is available to accommodate these associated risks and concerns, it is recommended not to delay infertility treatment.

3.5 Infertility Assessment prior to ART:

- 3.5.1 It is recommended to evaluate the reproductive history for both male and female couples in parallel and in an environment where they can discuss sensitive issues.
- 3.5.2 A multidisciplinary team approach is suggested when indicated, and includes referral to:
 - 3.5.2.1. A family medicine at the primary healthcare (mainly for weight loss candidate).
 - 3.5.2.2. A psychologist.
 - 3.5.2.3. An obstetrician/maternal medicine for preconceptual counselling for pregnancy care, follow-up, and delivery after completing the ART treatment.
 - 3.5.2.4. A urologist and/or andrologist to evaluate male factors.

3.5.3 Indications for Fertility Assessment:

- 3.5.3.1. Women < 35 years of age, having unprotected intercourse trying to conceive for at least 12 months without success; this is while keeping in mind that up to 40-50% of young, healthy couples who have regular intercourse and fail to conceive in the first 12 months will conceive in the subsequent 12 months with no specific treatment.
- 3.5.3.2. Women ≥ 35 years of age after 6 months of failed attempts to conceive or earlier, if clinically indicated based on medical, sexual, and reproductive history, age, physical findings and diagnostic testing (sub-clauses 3.4).

3.5.3.3. It is recommended to initiate diagnostic testing for infertility without delay on presentation when a condition known to cause infertility/ sub-fertility is present. Such may include:

(a) **Female features/ findings:**

- .(i) Advanced maternal age
- .(ii) Ovulatory dysfunction such as Oligo- or amenorrhea
 - Polycystic ovarian syndrome
 - Thyroid dysfunction
 - Obesity
 - Endocrine abnormalities (Pituitary, Thyroid, or prolactin) & eating disorders such as anorexia nervosa.
 - Premature ovarian failure (women <40 years of age)
- .(iii) Known or suspected uterine/tubal/peritoneal disease, previous history of tubal ligation or endometriosis:
 - History indicating an increased risk of Fallopian Tube Occlusion (i.e., previous pelvic infection or pelvic surgery), Hydrosalpinx, absence of tubal patency on Hysterosalpingography or Hysterosalpingo-Contrast Sonography (HyCosy), or previous ectopic pregnancy.
 - History of Myomectomy (Fibroid surgery), previous dilation and curettage, or Asherman Syndrome-intrauterine adhesions.
 - History of Ovarian surgery (oophorectomy, cystectomy)
- .(iv) Low ovarian reserve (based on the 2011 Bologna Criteria⁴) / genetic or acquired conditions that predispose to low ovarian reserve (e.g., Female parental consanguinity, Vit D deficiency, chemotherapy, radiation exposure, FMR1 premutation).

(b) **Male features/ findings**

- .(i) Male Infertility factor – Abnormal sperm parameters (sub-clause 3.6.6) caused by testicular defects in spermatogenesis or Sperm transport disorders, or that are idiopathic.
- .(ii) Advanced paternal age (≥40 years)
- .(iii) Testosterone Deficiency
- .(iv) Hypogonadotrophic Hypogonadism
- .(v) Other reproductive problems such as Sexual dysfunction (Erectile and Ejaculatory Dysfunction) and their causes (such as Long-term Diabetes and use of Psychotic Medicines leading to decrease libido).
- .(vi) Other Acquired disorders such testicular tumor, other cancers, spinal cord injury, trauma, or history of vasectomy.

(c) **Miscellaneous infertility features/ findings in either or both couple:**

- .(i) History of Gonadotoxic treatment in either partner
- .(ii) Genital tract Infections
- .(iii) Chronic viral infection (e.g., Human Immunodeficiency Virus (HIV), Hepatitis B or Hepatitis C)
- .(iv) Familial and hereditary condition
- .(v) History of consanguinity
- .(vi) Other medical conditions such Coeliac Disease, inflammatory conditions, other autoimmune disease...etc.
- .(vii) Medication side effect, cytotoxic drugs and/or pelvic irradiation (e.g., immune modulators)
- .(viii) Other lifestyle risk factors (smoking, alcohol consumption, illicit drug use, and obesity)

3.5.3.4. **Early Infertility evaluation:** indicated to conditions optimize ART treatments in some couples who do not have the above conditions, such conditions may include:

- (a) History of pregnancy loss
- (b) family history of birth defects, developmental delay, early menopause, or reproductive problems
- (c) Known genetic/chromosomal disorders or when preimplantation genetic testing is indicated.
 - .(i) Known chromosomal disorders in the patient, or family member.
 - .(ii) Any genetic condition in the patient or family member.
 - .(iii) Carrier of genetic condition or mutation.
 - .(iv) Family history of genetic conditions.
 - .(v) Abnormal pre-marital screening result or whole exome sequencing result.
 - .(vi) Previous child or pregnancy with any genetic abnormality.

For further information refer to:

⁴ Ferraretti A et al. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: The Bologna criteria. *Human reproduction*. 2011 ;26(7):1616-24.

3.6 Infertility Diagnostic Evaluation Pre-ART treatment:

- 3.6.1 All patients undergoing infertility assessment and/or being considered for assisted reproduction are recommended to undergo an appropriate diagnostic evaluation, both to establish a diagnosis and to enable informed discussion about the implications of treatment. Such diagnostic evaluation is strongly recommended to be conducted in a systematic, expeditious, and cost-effective manner to identify all relevant factors, with an initial emphasis on the least invasive methods for the detection of the most common causes of infertility.
- 3.6.2 **History:** A comprehensive and detailed history should be obtained from both partners, and should include present history, contraceptive history, sexual history, past medical history, social history, lifestyle, family history, and history of consanguinity from both partners; and menstrual and obstetric history from the female partner to identify couple who are less likely to conceive. Couples should be interviewed separately and together, to bring out key facts that one partner might not wish to disclose to the other.
- 3.6.3 **Physical Examination:** A full clinical examination of all relevant systems for both partners is recommended.⁵
- 3.6.4 Both male and female patients are recommended to undergo screening for Sexual Transmitted Infections (HIV, hepatitis B, Hepatitis C, and Syphilis).
- 3.6.5 **Female-specific investigations:**^{6,7}
- 3.6.5.1. **Menstrual History**
- 3.6.5.2. **Serum progesterone** is recommended for female patients undergoing investigation for infertility.
- (a) A progesterone concentration >3 ng/mL provides presumptive and sufficient evidence of recent ovulation. Levels can fluctuate sevenfold over a few hours; therefore, a single value may be used to confirm ovulation, but not to assess the quality of the luteal phase.
- 3.6.5.3. **Serum gonadotropins:** Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH), and Estradiol level measurements are recommended for women with irregular menstrual cycles⁰.
- (a) In women with normal FSH and Estradiol levels in the setting of oligomenorrhea or anovulation, evaluation for PCOS is recommended. Additional screening for 21-hydroxylase deficient non-classic adrenal hyperplasia is recommended for those with clinical signs of androgen excess.⁸
- 3.6.5.4. **Serum Prolactin:** recommended in the setting of galactorrhea, oligomenorrhea, or amenorrhea.
- 3.6.5.5. **Ovarian reserve testing** is recommended to predict high and poor response to ovarian stimulation during ART treatment. These tests use quantitative outcomes such as oocyte yield and ovarian responsiveness to measure the ovarian reserve either by hormone levels (Anti-Müllerian hormone – AMH, FSH) or ultrasound imaging of the ovaries (Antral Follicle Count -AFC). Low ovarian reserve results may be used to counsel patients on suboptimal response and yield, however, it is strongly recommended not to use such results to refuse treatment.
- (a) Studies suggest that AFC is more reliable than AMH to predict ovarian response in IVF. Moreover, literature stated that AMH has significant inter cycle and intra cycle variability.
- 3.6.5.6. **Thyroid function tests:** Serum thyroid-stimulating hormone can identify thyroid disorders which may require further investigation and impair fertility when untreated. Therefore, it is recommended to offer thyroid function assessment along with thyroid antibodies to women with symptoms and signs of thyroid disease and/or suspected/confirmed ovulatory dysfunction.
- 3.6.5.7. **Uterine Imaging for Detecting Uterine Abnormalities:**
- (a) Ultrasonography is the best imaging modality available to assess uterine anatomy.
- (b) Transvaginal ultrasound allows for visualization of most uterine pathologies, such as leiomyomas, endometrial polyps, adenomyosis, and pelvic endometriosis.
- (c) Hysterosalpingography (HSG) defines the size and shape of the uterine cavity. It can reveal potential developmental anomalies or other acquired abnormalities (endometrial polyps, submucous myomas, synechiae) that may impact reproduction. However, HSG has relatively a low sensitivity (50%) and positive predictive value (PPV) (30%) for the diagnosis of endometrial polyps and submucous myomas in asymptomatic infertile women.

For further information refer to:

⁵ TABLE 2. Penzias et al 2021, *Fertility evaluation of infertile women: a committee opinion Fertility and sterility*, 116(5), pp.1255-1265.

⁶ American Society for Reproductive Medicine 2021, *Fertility Evaluation of Infertile Women: a committee opinion; American College of Obstetricians and Gynecologists 2019, Infertility Workup for the Women's Health Specialist: ACOG Committee Opinion, Number 781.*

⁷ Figure. Carson and Kallen 2021, *Diagnosis and management of infertility: a review. JAMA.* 2021 Jul 6;326(1):65-76.

⁸ O- Teede et al. 2018. *International evidence-based guideline for the assessment and management of polycystic ovary syndrome. Human reproduction*, 33(9):1602-1618.

- (d) Hysterosalpingograms are used to detect potential developmental uterine anomalies, Asherman's syndrome and tubal patency. Yet, HSG is not sensitive for endometrial polyps or intrauterine masses unless they are large, and which are usually diagnosed on ultrasound.
- (e) Sonohysterography (SHG) is a transvaginal ultrasonography after the introduction of saline into the uterine cavity. It better defines the size and shape of the uterine cavity and has a high (>90%) PPV and negative predictive value for the detection of intrauterine pathologies (endometrial polyps, submucous myomas, synechiae).
- (f) Other imaging modalities such as Three-Dimensional Ultrasound and pelvic Magnetic Resonance Imaging (MRI) may be used to further evaluate the uterus, often to further characterize findings of an initial study such as a pelvic ultrasound or HSG. These radiological studies have the advantage of assessing for intramural fibroids and adnexal pathology that are undetectable on hysterosalpingogram or hysteroscopy.
- (g) Hysteroscopy is the definitive method for the diagnosis and treatment of intrauterine pathologies. While some international experts recommend further evidence for routine use of hysteroscopy, local data⁹ from a randomized control trial suggests that more than 10% of asymptomatic patients with assumed normal uterus on ultrasound, will have an abnormality detected with hysteroscopy. Moreover, other literature suggested that performing hysteroscopy prior embryo transfer significantly increases the chance of implantation¹⁰.

3.6.5.8. Imaging for Assessing Tubal Patency

- (a) HSG is recommended for tubal patency and architectural detailed assessment where it can detect proximal or distal tubal occlusion, salpingitis, Hydrosalpinx, Asherman Syndrome and may suggest the presence of adhesions. Catheter position and/or transient tubal/myometrial contractions may cause an artifact during an HSG study, and therefore further evaluation is recommended to exclude such artifacts when findings suggest bilateral proximal tubal obstruction.
- (b) Hysterosalpingo-Contrast Sonography (HyCosy) uses a contrast medium to determine tubal patency. Its accuracy may be more operator-dependent than a standard HSG. The HyCosy sensitivity of to determine tubal patency ranges from 76%–96%, and the specificity ranges from 67%–100%. Therefore, it is recommended to offer HyCoSy where appropriate expertise is available as for women who are not known to have comorbidities.
- (c) Tubal patency may also be assessed by direct observation through Hysteroscopy. However, a meta-analysis of six published trials demonstrated that utilizing hysteroscopy to predict tubal patency had a sensitivity of 88% and specificity of 85%.
- (d) Laparoscopy is not recommended as a routine method for assessing tubal patency.
 - .(i) It is recommended to offer HyCosy or HSG initially for women not known to have gynecological comorbidities (such as pelvic inflammatory disease, previous ectopic pregnancy or endometriosis) to screen for tubal occlusion given high reliability in ruling out tubal occlusion, less invasive, and more cost-effective when compared to laparoscopy.
 - .(ii) On the other hand, laparoscopy is recommended for women suspected to have gynecological comorbidities (such as endometriosis) to assess tubal and other pelvic pathologies and allow for possible correction when indicated at the same time such as for assessment and management of endometriosis.

3.6.5.9. Imaging for peritoneal diseases assessment

- (a) While Transvaginal US may reveal pelvic pathologies such as endometriomas that are otherwise unrecognized, Laparoscopy is currently the only available method for specific diagnosis of peritoneal factors such as endometriosis and pelvic/ adnexal adhesions that may impair fertility. However, the ASRM does not recommend laparoscopy for routine evaluation of infertile women without a suspected pelvic pathology (risk factors in history or abnormal HSG) or another indication that requires surgical evaluation (such as severe dysmenorrhea).
- (b) **Endometrial Biopsy** is no longer recommended in the initial assessment unless there is clinical suspicion of endometritis, then an endometrial biopsy is recommended.

⁹ Ghasemi M et al 2022. Uterine Cavity Irrigation with Office Hysteroscopy During Ovarian Stimulation for IVF: A Randomized Controlled Trial. *Frontiers in Endocrinology*, 13, p.4.

¹⁰ Smit et al 2013 The international agreement study on the diagnosis of the septate uterus at office hysteroscopy in infertile patients. *Fertility and sterility*, 99(7), pp.2108-2113.

3.6.6 Male Infertility Assessment:¹¹

- 3.6.6.1. Male factor infertility is indicated by abnormality in ≥ 1 of the following semen Analysis (as recommended by Schlegel et al. 2020 in the American Urology Association Male Infertility guideline):

Semen Analysis	Abnormal Value*
Semen volume (mL)	<1.4
Sperm concentration (million/ml)	<16
Total sperm number (million/ejaculate)	<39
Total motility (%)	<42
Progressive motility (%)	<30
Non-progressive motility (%)	<1
Immotile sperm (%)	<20
Vitality (%)	<54
Normal forms (%)	<4

**Higher values are considered within the normal range.*

- (a) It is suggested that the results of the semen analysis be used to guide management of the patient. In general, results are of greatest clinical significance when multiple abnormalities are present.
- (b) If the results of the first semen analysis are abnormal, a repeat confirmatory test is recommended at least a month apart while ensuring an abstinence period of 3-5 days prior to testing. While retrospective literature suggests timing to be individualized depending on the results of the initial analysis, the quality of the semen analysis laboratory, and other relevant patient factors, further prospective studies are required.
- (c) However, if a gross spermatozoa deficiency (azoospermia or severe oligozoospermia) is detected, it is recommended to repeat the test as soon as possible and offer sperm cryopreservation.
- 3.6.6.2. AUA expert opinion suggests evaluating azoospermic men with semen volume, physical exam, and FSH levels to differentiate genital tract obstruction from impaired sperm production.
- 3.6.6.3. It is strongly recommended to evaluate patients with pyospermia for infection.
- 3.6.6.4. Hormonal evaluation including FSH, and testosterone is suggested by experts for infertile men with impaired libido, erectile dysfunction, oligozoospermia or azoospermia, atrophic testes, or evidence of hormonal abnormality on physical evaluation.
- 3.6.6.5. Sperm DNA fragmentation may affect male fertility, either by reversible causes (e.g., Anti-depressant use, genitourinary infection) or other causes. Although it is not indicated routinely, it is essential to treat it in cases of unexplained or idiopathic infertility, varicocele with normal semen analysis, repeated abortions, and failed ART.
- 3.6.6.6. Recent studies suggest that karyotyping and Y-chromosome microdeletion analysis are essential for male patients with azoospermia, severe oligozoospermia, hypergonadotropic hypogonadism, or in couple with recurrent pregnancy loss.
- 3.6.6.7. Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) mutation carrier testing (including assessment of the 5T allele) is suggested by experts for men with vasal agenesis or idiopathic obstructive azoospermia. Genetic evaluation of the female partner is suggested by experts in couple where that man harbors a CFTR mutation.
- 3.6.6.8. Anti-sperm antibody (ASA) testing is not recommended by experts in the initial evaluation of male infertility.
- 3.6.6.9. Experts suggest not to preform scrotal ultrasound routinely in the initial male evaluation.
- 3.6.6.10. Experts suggest not to perform transrectal ultrasonography (TRUS) as part of the initial evaluation. Rather, it is suggested to recommend TRUS for men with semen analysis suggestive of ejaculatory duct obstruction (i.e., acidic, azoospermic, semen volume <1.5mL, with normal serum T, palpable vas deferens).
- 3.6.6.11. Experts suggest not to routinely perform abdominal imaging for the sole indication of an isolated small or moderate right varicocele.
- 3.6.6.12. Recommend further reference to "The Diagnosis and Treatment of Infertility in Men: AUA/ ASRM Guideline, 2020" for further guidance.

¹¹ Refer to **Male Infertility Algorithm**. Schlegel et al 2020. *Diagnosis and treatment of infertility in men: AUA/ASRM guideline*. Linthicum (MD): American Urology Association.

3.6.7 Genetic Screening

3.6.7.1. Where a specific genetic defect associated with infertility is known or suspected, it is recommended to offer couples appropriate genetic testing and counselling before pregnancy (**refer to Circular No (2022/297)**)

Indications include:

- (a) Known chromosomal disorders in the patient, or family member.
- (b) Any genetic condition in the patient or family member
- (c) Carrier of genetic condition or mutation
- (d) Family history of genetic conditions
- (e) Abnormal pre-marital screening result or whole exome/genome sequencing result
- (f) Previous child or pregnancy with any genetic abnormality
- (g) In men with history of genetic disorders in family- whole exome or whole genome sequencing is advised.
- (h) Karyotyping indicated as mentioned above in male assessment.

3.6.7.2. Genetics counselling is recommended to interpret the results and may be useful for:

- (a) Patients undergoing karyotype testing.
- (b) patients with a genetic abnormality found on clinical or genetic investigation.
- (c) patients who carry a (potential) inheritable disease.
- (d) Patients who have a child with genetic condition
- (e) Discussing genetic results and helping couples understand abnormal genetic testing results.
- (f) Evaluating whole exome / whole genome sequencing results.

3.7 General Infertility Treatment Considerations Pre-ART:

3.7.1 It is recommended to optimize and control other medical comorbidity(s).

3.7.2 It is recommended to offer Rubella screening and vaccination to susceptible women. It is strongly recommended to advised female patients not to become pregnant for at least one month following vaccination.

3.7.3 Androgen therapy is not recommended for the treatment of male infertility. Gonadotrophic hormones treatment on the other hand is indicated in infertile men with hypogonadotrophic hypogonadism.

3.7.4 Lifestyle modifications and add-on treatments¹² may be recommended to improve fertility. While further randomized control trials are needed, early studies suggest these treatments may improve fertility by reducing oxidative stress (especially among obese and male patients). Such treatments are recommended to be individualized after discussion with patients and include:

3.7.4.1. Healthy diet, antioxidants, and nutritional treatment and supplements (when indicated).

3.7.4.2. Correction of nutritional deficiencies.

3.7.4.3. Weight loss and regular exercise.

3.7.4.4. Smoking and alcohol cessation, avoid illicit drugs.

3.7.4.5. Reduce other stress factors (while stress is associated with recurrent pregnancy loss, there is no current evidence that stress is a direct cause of pregnancy loss).

¹² ESHRE 2014, *The responsible use of treatment add-ons in fertility services: a consensus statement - or its most updated version when published.*

3.7.5 Table 1: A Summarized Diagnostic approach and Treatment Considerations Pre-ART.

Infertility Causes	Causes & Diagnostic Approach	Treatment approach considerations
Ovulatory Dysfunction and Anovulation¹³	• Polycystic Ovary Syndrome (PCOS) • Elevated androgens from Adrenal Hyperplasia or Adrenal Tumor • Idiopathic Chronic Anovulation • Functional Hypothalamic Amenorrhea • Obesity • Thyroid Disease • Pituitary Disease Diagnostic Approach: Postovulatory serum progesterone level, Gonadotropins, Androgen levels, Pelvic Transvaginal Ultrasound.	Women with anovulatory infertility due to hypothalamic pituitary failure can improve their chance of regular ovulation, conception, and uncomplicated pregnancy by: • Increasing the body weight if BMI < 18 • moderating exercise levels if undertaking high levels of exercise.
Tubal Infertility The severity of tubal abnormalities helps determine the most effective treatment.	• Blocked fallopian tubes. • Pelvic adhesions Secondary to history of sexually transmitted infection, cervical dysplasia, abdominal surgery, or previous intraabdominal infection. Diagnostic Approach • HycoSy • HSG • Sonohysterography (SHG) • Laparoscopy with Chromopertubation (Gold Standard) • Hydrosalpinx requires diagnostic laparoscopy	Offer operative Laparoscopy for patients with hydrosalpinx. Patients with unilateral proximal tubal blockage have similar pregnancy rates after ovarian stimulation with intrauterine insemination, compared to woman with unexplained infertility and bilateral patent tubes. When bilateral tubal obstruction exists, surgery to restore tubal patency or ovarian stimulation with IVF can be considered. It is recommended to consider Laparoscopic tubal ligation or salpingectomy prior to IVF in women with Hydrosalpinges. This approach increases the clinical pregnancy rate and chances of live birth.
Endometriosis	Anatomic distortion: adhesions blocking the fallopian tubes or impairing tubal patency, or ovarian masses (e.g., endometriomas) occurring between the tube and site of ovulation can impair tubal patency, oocyte quality, and retrieval of oocytes by tubal fimbria. For diagnosis consider diagnostic Laparoscopy and pelvic MRI.	Data are conflicting regarding whether endometriosis can affect endometrial receptivity. Although laparoscopic surgery for endometriosis improves spontaneous pregnancy rates, it is not recommended as part of a routine fertility evaluation in women without endometriosis symptoms.
Low Ovarian Reserve	• Age • History of ovarian surgery, chemotherapy, radiation therapy with exposure to the ovaries, • Family history of premature menopause, or a fragile X (FMR1) pre-mutation. • Female parental history of consanguinity • Vitamin D deficiency Diagnostic Approach: serum ovarian reserve markers such as AMH, FSH or ultrasound - AFC.	While ASRM recommends that extremely low ovarian reserve tests' results may be used to counsel these women regarding suboptimal response and yield, ASRM strongly recommended not to use such results to refuse treatment.

For further information refer to:

¹³ Teede et al 2018, Recommendations from the International Evidence-Based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. Human Reproduction. 33(9):1602-1618 ASRM 2015, Subclinical Hypothyroidism in the Infertile Female Population: A Guideline.

Infertility Causes	Causes & Diagnostic Approach	Treatment approach considerations
Uterine Factors	• Endometrial Polyps, • Leiomyomas, • Intrauterine Synechiae, • Congenital uterine malformations • Fibroids • Endometritis • Intrauterine adhesions/ Ashermann syndrome • Adenomyosis Diagnostic approach: • SHG has high sensitivity and specificity to detect polyps or leiomyomas and is superior to HSG and transvaginal ultrasound for evaluating the uterine cavity (Sub-clause 3.6.5.7(d)). • Diagnosis of polyps, fibroids, adenomyosis, and adhesions requires 3-dimensional ultrasound and/ diagnostic Hysteroscopy. • If a congenital malformation is suspected, further evaluation with pelvic MRI, 3D ultrasound, or diagnostic Hysteroscopy is warranted. • Endometritis may require Diagnostic Hysteroscopy, and/ or endometrial biopsy.	While surgery to correct uterine cavity defects is commonly performed to improve reproductive outcomes, it is not certain from the literature whether surgery should be offered routinely to women with a congenital uterine anomaly, unless they have a history of failed IVF or pregnancy loss. It is recommended to offer women with amenorrhea who are found to have intrauterine adhesions hysteroscopic adhesiolysis because this is likely to restore menstruation and improve the chance of pregnancy. Limited studies suggest surgery consideration for infertile women with cavity-distorting defects, especially if other symptoms (eg, abnormal uterine bleeding) are present. Operative hysteroscopy is required for treatment of congenital uterine abnormalities, Endometrial Polyp, fibroids, Intrauterine adhesions/ Ashermann syndrome, and adenomyosis (adenomyosis may otherwise require laparoscopic surgery). Fibroids and Intrauterine adhesions/ Ashermann syndrome may otherwise require laparoscopic/open myomectomy. Endometritis would require antibiotics for treatment.
Cervical Factors Infertility	• Anatomical abnormality - Congenital anomalies • Postsurgical scarring - cervical stenosis, • Decreased cervical mucous. The use of the postcoital test is not recommended.	Studies regarding the effect of cervical surgery on fertility are limited by small sample size, short follow-up, and insufficient detail regarding the extent of surgery.
Male Factor Infertility¹⁴	• Disorders of male physiology (low testosterone concentrations or low sperm count) • Azoospermia It is recommended to evaluate for male factor infertility concurrently with the female evaluation. In addition to a reproductive history, examination of the testes for size and varicocele and semen analysis should be performed to determine semen volume and sperm production. Sperm DNA fragmentation*, Hormonal evaluation, and chromosomal evaluation may be indicated in specific cases.	Congenital bilateral absence of the vas deferens should prompt evaluation for a mutation in the cystic fibrosis transmembrane conductance regulator, as the protein is absent in patients with cystic fibrosis. *While Sperm DNA fragmentation test may also be indicated for specific cases, it is strongly recommended to inform these patients that treatments which effectively reduce sperm DNA fragmentation are limited.

¹⁴ For further information refer to: Schlegel et al 2020, *Diagnosis and Treatment of Infertility in Men: American Urological Association / American Society for Reproductive Medicine Guidelines*. (Refer to Reference # 11)

3.8 Assisted Reproduction and Assisted Reproductive Technology (ART):

- 3.8.1 Medical Assisted Reproduction treatment includes reproduction brought to treat different forms of fertility impairment and infertility. These include ovulation induction, ovarian stimulation, ovulation triggering, all ART procedures, and intra-uterine insemination. These treatments are recommended to be carried out by Reproductive Medicine physicians to lower risks of multiple pregnancies.
- 3.8.2 ART treatments include In-Vitro Fertilization (IVF) with or without Intracytoplasmic Sperm Injection.
 - 3.8.2.1. It is recommended not to delay ART treatments in couples with features / findings of sub-fertility.
- 3.8.3 Therapeutic approaches are recommended to be individualized considering patient's age and duration of infertility, and to emphasize strategies most likely to result in a healthy live birth.
- 3.8.4 It is strongly recommended to refer candidates known to have chronic viral infection (e.g., HIV, Hepatitis B or Hepatitis C) to specialized infectious diseases services to provide further investigations and specialized treatment.
- 3.8.5 The most effective and least risk-associated treatment is recommended as a first line option.
 - 3.8.5.1. While ovulation induction and/or ovarian stimulation with Intrauterine Insemination (IUI) are considered initial cost-effective treatments in certain clinical indications, recent literature¹⁵ however, argues that there is a concern for other prognostic factors such as age and risk of multiple pregnancy rates that might affect its outcome and success. Furthermore, accelerated aging of the ovaries leading to more aneuploid oocytes is reported in the local population in women <35 years of age and IUI may not be the best approach. Therefore, a shared decision-making approach along with clinical judgment is recommended.
- 3.8.6 No more than 6 ovarian stimulation per 1 year for assisted reproduction and in-vitro fertilization¹⁶.
- 3.8.7 Limit the use of ovulation induction or ovarian stimulation agents to the lowest effective dose and duration of use.¹⁷
- 3.8.8 **Ovulation Induction**
 - 3.8.8.1. May be considered with either timed intercourse or IUI to achieve fertilization at the time of ovulation. However, clinical judgment and a shared clinical decision approach is recommended as best practice approach will depend on other factors such as maternal age and ovarian reserve.
 - 3.8.8.2. For women presenting with ovulatory disorders, ovulation induction with timed intercourse may be recommended as an initial treatment before considering ART.
 - 3.8.8.3. For women with PCOS, it is recommended to refer to Teede et al 2018¹⁸, Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome.
 - 3.8.8.4. Women with functional hypothalamic amenorrhea are hypoestrogenemic and are therefore unlikely to respond to clomiphene citrate. Gonadotropin-releasing hormone (GnRH) is recommended to be considered as first-line therapy where available. If unavailable, gonadotropin therapy is recommended, with both LH and FSH.
 - (a) Recommend having strict attention to follicle numbers to avoid multiple gestation and ovarian hyperstimulation.
 - 3.8.8.5. Both clomiphene citrate and aromatase inhibitors have similar ovarian hyperstimulation rates, miscarriage rates, and multiple pregnancy rates.
 - 3.8.8.6. Gonadotropins ovulation induction without ultrasound monitoring is not recommended.
 - 3.8.8.7. Experts recommend no more than 3 unsuccessful cycles of ovulation induction as success rate falls in subsequent cycles. Such patients need to move to more advanced treatments.
- 3.8.9 **Ovarian Stimulation**¹⁹
 - 3.8.9.1. May be combined with IUI to treat unexplained infertility or IVF; live birth rates depend on the diagnosis, sperm viability, and ovarian response.

¹⁵ Lawrenz, B., Melado, L. and Fatemi, H.M., 2023. Ovulation induction in anovulatory infertility is obsolete. *Reproductive BioMedicine Online*, 46(2), pp.221-224.

¹⁶ As per Article 5 of Cabinet Resolution No. (64) of 2020 concerning the Executive Regulations of Federal Law No. 7 / 2019 concerning Medically Assisted Reproduction.

¹⁷ For available Medications may refer to **Table 4**. Carson and Kallen 2021, *Diagnosis and management of infertility: a review*. JAMA. 2021 Jul 6;326(1):65-76.

¹⁸ Teede et al 2018, *Recommendations from the International Evidence-Based Guideline for the Assessment and Management of Polycystic Ovary Syndrome*; ASRM 2015, *Subclinical Hypothyroidism in the Infertile Female Population: A Guideline*.

¹⁹ For further information refer to: Bosch et al 2020, *Guideline: Ovarian Stimulation for IVF/ICSI*; Penzias et al 2020, *Evidence-based treatments for couples with unexplained infertility: A Guideline*.

- 3.8.9.2. Clomiphene Citrate alone for women with unexplained infertility does not increase the chances of pregnancy or live birth.
 - (a) Treatment with clomiphene citrate for longer than 6 months is not recommended.
 - (b) Ultrasound monitoring is recommended to ensure that prescribed dose is one which minimizes the risk of multiple pregnancies.
- 3.8.9.3. Gonadotropins result in a higher live birth rate than continued clomiphene citrate after 3 ovulatory cycles for women with PCOS; however, high multiple pregnancy rates have been also reported with the use of gonadotropins. Therefore, clinical judgment and available resources are recommended to be considered in a shared decision-making approach.
 - (a) Experts recommend offering tubal and hormonal evaluations along with a sperm analysis for the husband before starting low dose gonadotropin injections.
 - (b) Ovarian ultrasound monitoring is recommended during gonadotropin therapy.
- 3.8.9.4. Women with ovulatory disorders due to hyperprolactinemia are recommended be offered treatment with dopamine agonists such as cabergoline.²⁰

3.8.10 Intrauterine Insemination (IUI)

- 3.8.10.1. Placing sperm into the uterus 24 to 36 hours after an endogenous LH surge or an exogenous ovulation trigger.
- 3.8.10.2. IUI may be considered for achieving pregnancy in couples with severe sexual dysfunction, in patients with cervical factor infertility as long as at least one fallopian tube is patent, and initially for infertility caused by mild male sub-fertility (considering sub-clause 3.8.5.1 during decision making).
- 3.8.10.3. In patients with unexplained infertility, IUI combined with Ovarian Stimulation may be offered instead of IUI alone as an initial treatment. IUI alone does not increase pregnancy rates in this population.
 - (a) While recent studies and the ASRM guideline for unexplained infertility suggest IUI combined with Ovarian Stimulation may be offered initially to patients with unexplained infertility, there are concerns based on local studies²¹ to be considered as outlined in sub-clause 3.8.5.1
- 3.8.10.4. IUI may be considered as a treatment option in the following married couple groups as an alternative to vaginal sexual intercourse:
 - (a) Married couples who are unable to, or would find it very difficult to, have vaginal intercourse because of a clinically diagnosed physical disability or psychosexual problem.
 - (b) Married couple with conditions that require specific consideration in relation to methods of conception (for example, after sperm washing where the husband is HIV positive and is not on antiviral therapy).
- 3.8.10.5. IUI is not recommended for married couple who are having regular unprotected sexual intercourse in normal cycling women as evidence suggests no difference between IUI and timed intercourse.

3.9 Surgical Sperm Retrieval (SSR) For ART:

- 3.9.1.1. sperms are used for ART in patient's wife depending on clinical indications:
 - (a) Azoospermia (obstructive, or non-obstructive)
 - (b) Anejaculation
 - (c) Erectile dysfunction resistant to medical treatment
 - (d) Complete Asthenozoospermia, when clinically indicated (no response to Hypoosmotic Swelling Test, laser activation, etc.)
- 3.9.1.2. While SSR was previously indicated on for Severe Oligo-astheno-teratozoospermia (OAT), recent studies demonstrated that patients with male factor infertility and oligozoospermia did not have improved ICSI outcomes with the use of TESE samples compared with ejaculated sperm.
- 3.9.1.3. SSR includes the following procedures:
 - (a) Percutaneous Epididymal Sperm Aspiration (PESA)
 - (b) Needle Aspiration Biopsy (NAB)
 - (c) Open Fine Needle Aspiration (OFNA)
 - (d) Testicular Sperm Aspiration (TESA)
 - (e) Testicular Sperm Extraction (TESE)

²⁰ Table 4. Carson and Kallen 2021, *Diagnosis and management of infertility: a review. JAMA. 2021 Jul 6;326(1):65-76.*

²¹ Lawrenz, B., Melado, L. and Fatemi, H.M., 2023. Ovulation induction in anovulatory infertility is obsolete. *Reproductive BioMedicine Online*, 46(2), pp.221-224.

- (f) Micro-surgical Testicular Sperm Extraction (Micro-TESE)
- (g) Micro-Surgical Epididymal Sperm Aspiration (MESA)

3.9.1.4. The simplest and least invasive technique is recommended to be used first while considering clinical judgment and available resources / expertise are crucial factors to consider as well in decision making to ensure optimal outcomes.

- (a) When operative sperm retrieval is required for men with failure to ejaculate, a NAB biopsy may provide adequate number of sperms.

3.10 Pre-implantation Genetic Investigations and Counselling during ART:

3.10.1 May be used to identify embryos with a single gene disorder or to screen for euploid embryos.

3.10.2 It is recommended to involve specialists in maternal-fetal medicine or those with expertise in the woman's particular medical condition during such counselling.

3.10.3 Though ASRM states that physicians and patients should be aware that long-term effects of embryo biopsy on a developing fetus still require further studies, recent studies failed to demonstrate that blastocyst biopsy is harming the embryo and confirmed the clinical use of embryo biopsy if done correctly.

3.10.4 Large, prospective, well-controlled studies evaluating the combination of multiple approaches for enhanced embryo selection applicable in a more inclusive IVF population are needed to determine not only the effectiveness, but also the safety and potential risks of these technologies.

3.10.5 Preimplantation Genetic investigations include Preimplantation Genetic Testing for Aneuploidy (PGT-A), Pre-implantation Genetic Diagnosis (PGT-M) and Pre-implantation Genetic Testing for Structural Chromosomal Rearrangements and Translocations (PGT-SR).

3.10.6 PGT-A test may be considered for the following clinical indications:

- Advanced Maternal age
- Advanced paternal age (≥ 50 years old)
- Low ovarian reserve
- Male factor infertility
- Recurrent miscarriages: ≥ 2 pregnancy losses before 24 weeks of gestation
- Recurrent IVF implantation failure: ≥ 2 or more failed embryo transfers without PGT-A
- Family history of chromosome problems (e.g., Down's syndrome)
- Carrier of genetic disorder / History of child affected with genetic disorder /family history of genetic disorder.

3.10.7 PGT-M may be considered for:

- Patients are diagnosed with an autosomal dominant or X-linked genetic disorder.
- Couples who were both diagnosed as carriers of the same autosomal recessive disorder.
- Patients diagnosed with mitochondrial disorders caused by mitochondrial DNA (mtDNA)
- Consanguine marriage or history of single gene disorders
- Patients who are compound heterozygous.
- History of children with single gene disorder or family history of single gene disorder.

3.10.8 PGT-SR may be considered for Carriers of structural chromosomal rearrangements.

3.10.9 PGT-M, PGT-SR work up with genetic laboratory, and genetic counselling are recommended by experts prior to an ART cycle. During the ART cycle, embryo biopsy is obtained after ICSI for genetic laboratory testing.

3.10.10 International guidelines recommend offering women prenatal screening and testing for genetic disorders along with education and pretest counseling aimed at helping them to understand and weigh the benefits, risks and limitations of various testing modalities, and then make an autonomous decision that is most consistent with individual values and preferences.

3.11 In-Vitro Fertilization

3.11.1 Involves various steps including controlled ovarian stimulation, follicular tracking with ultrasound, oocyte retrieval surgically (transabdominal, transvaginal, transurethral or transrectal route), fertilization, embryo culture, and embryo transfer. Additionally, preimplantation genetic testing and intracytoplasmic sperm injection may also be included in the process. Cryopreservation with vitrification may then be used to freeze excess embryos for fertility preservation.

3.11.2 Pre-IVF Specific Assessment and Counselling:

- 3.11.2.1. Recommended to discuss the risks and benefits of IVF, and associated success rate with advanced maternal age, BMI > 35kg/m², history of previous pregnancy and history of treatment and number of previous cycles.
- 3.11.2.2. Expert opinion suggests discussing lifestyle factors and counsel couples on life-style modifications such as weight loss for women with obesity, avoiding maternal and paternal smoking as it may adversely affect ART success rates, and reducing caffeine consumption. May also refer to sub-clause 3.7.4 for general considerations on lifestyle modifications and treatments for patients with infertility.

3.11.3 Approach to IVF²²

- 3.11.3.1. It is recommended to refer women directly to IVF when investigations show there no chance of pregnancy with expectant management and/or where IVF is the only effective treatment.
- 3.11.3.2. It is recommended to consider the outcome of previous IVF treatment when assessing the likely effectiveness and safety of any further IVF treatment.
- 3.11.3.3. A fresh cycle starts with one or more episodes of ovarian stimulation resulting in a fresh embryo transfer, including consultation, investigation, monitoring, collection of oocytes, fertilization, and oocytes and embryos cryopreservation as required.
- 3.11.3.4. Down regulation and other regimens to avoid premature LH surges in gonadotrophin-stimulated IVF treatment cycles are recommended.
 - (a) It is recommended to use either gonadotrophin-releasing hormone agonist down-regulation or gonadotrophin-releasing hormone antagonists as part of gonadotrophin-stimulated IVF treatment cycles.
 - (b) Gonadotrophin-releasing hormone agonists is recommended for women who have a low risk of ovarian hyperstimulation syndrome.
- 3.11.3.5. Local experts suggest²³ conventional IVF may be used in cycles with PGT-A, as both IVF and ICSI may generate equal numbers of euploid blastocysts.
- 3.11.3.6. Controlled ovarian stimulation in IVF is recommended while limiting drugs used to the lowest effective dose and duration.
 - (a) When using gonadotropins for ovarian stimulation in IVF treatment, NICE guidelines recommend using an individualized starting dose of FSH based on stress predicting factors such as Age, BMI, Presence of polycystic ovaries, and Ovarian Reserve status.
 - (b) Recommended to offer women Human Chorionic Gonadotropin (hCG; urinary or recombinant) or GnRh Agonist trigger only in antagonist treatment cycles to trigger ovulation during IVF treatment.
 - (c) Ultrasound monitoring (with or without estradiol levels) for efficacy and safety throughout ovarian stimulation is strongly recommended.
 - (d) Clinics providing ovarian stimulation with gonadotropins are recommended to have protocols in place for preventing, diagnosing and managing ovarian hyperstimulation syndrome.

3.11.4 Oocyte and Sperm Retrieval in IVF

- 3.11.4.1. Oocyte retrieval can be done through transvaginal ultrasound (TVUS), transabdominal ultrasound (TAUS), or transvesical ultrasound (TVUSS) depending on several factors, such as ovary location, patient body habitus, and the presence of pre-existing conditions such as endometriosis, ovary transposition, hysterectomy or Mullerian agenesis. Large, randomized control trials on the safety of transrectal ultrasound (TRUS) on humans for oocyte retrieval are needed.
- 3.11.4.2. Ultrasound guided transvaginal oocyte retrieval is a widely performed procedure, with a low complication rate. Transabdominal-guided oocyte retrieval continues to be used at some centers for rare patients who have ovaries inaccessible by transvaginal US.
- 3.11.4.3. Laparoscopic oocyte retrieval & transabdominal oocyte retrieval can also be offered to patients who are Virgo Intacta. Ultrasound guided transrectal oocyte retrieval procedure is an alternative where expertise is available.
- 3.11.4.4. Women undergoing transvaginal retrieval of oocytes may be offered sedation.

²² For further information refer to Bosch et al 2020, ESHRE guideline: Ovarian Stimulation for IVF/ICSI.

²³ De Munck, et al., 2020. Intracytoplasmic sperm injection is not superior to conventional IVF in couples with non-male factor infertility and preimplantation genetic testing for aneuploidies (PGT-A). *Human Reproduction*, 35(2), pp.317-327

- 3.11.4.5. Women who have developed at least 3 follicles before oocyte retrieval are not recommended to be offered follicle flushing routinely because this procedure does not increase the numbers of oocytes retrieved or pregnancy rates, and it increases the duration of oocyte retrieval and associated pain.
- 3.11.4.6. Surgical sperm recovery before ICSI may be performed using several different techniques depending on the pathology and wishes of the man.
- 3.11.4.7. Assisted hatching is not routinely recommended as it has not been shown to improve live births, however it may increase pregnancy rates. Therefore, consideration is recommended be alongside clinical judgment.

3.11.5 Embryo transfer strategies in IVF²⁴

- 3.11.5.1. For patients undergoing an embryo transfer procedure, single embryo transfer is recommended to be the preferred choice. However, depending on the quality of the embryos and the clinical judgement, double embryo transfer may be an alternative, if deemed necessary to improve the chance of a pregnancy while considering contraindications outlined in 5.1
- 3.11.5.2. It is recommended to evaluate embryo quality, at both cleavage and blastocyst stages. Where a top-quality blastocyst is available, use single embryo transfer.
 - (a) For women aged under 35 years it is recommended to use single embryo transfer.
 - (b) For women of advanced maternal age, it is recommended to use a single embryo transfer if the embryo was genetically tested. Double embryo transfer is not recommended when the embryo is genetically normal, or if there are 1 or more top-quality embryos. Consider double embryo transfer if there are no top-quality embryos or if maternal age is > 40.
- 3.11.5.3. No more than 2 embryos should be transferred during an embryo transfer procedure²⁵. (Refer to 5.1 Appendix 1: Possible contraindications for dual embryo transfer)
- 3.11.5.4. When considering double embryo transfer, it is recommended to advise patients of associated risks.
- 3.11.5.5. It is strongly recommended that women undergoing IVF treatment be offered ultrasound-guided embryo transfer because this improves pregnancy rates.
- 3.11.5.6. Recent studies (including local data) recommend not to deny patients treatment based on endometrium thickness as it is not a reliable predictive factor; in contrast to earlier studies and guidelines stating that endometrium thickness may be a predictive factor for IVF success.
- 3.11.5.7. Suitable endometrial preparation is essential to obtain successful pregnancy rates.
 - (a) Natural cycle IVF may be considered for women of advanced age and who are identified as poor responder according to 2011 Bologna criteria, with outcomes comparable to conventional IVF.
 - (b) Local studies suggest natural cycle to have higher birth rates and highlighted possible maternal risks associated with hormonal replacement therapy cycle. In contrast, other studies suggest that for women with regular ovulatory cycle, the likelihood of a live birth after replacement of frozen–thawed embryos are similar for embryos replaced during natural cycles and hormone-supplemented cycles. Therefore, patient factors and available expertise are recommended to be considered alongside clinical judgment as further randomized control trails are still required.

3.11.6 Luteal phase support after IVF

- 3.11.6.1. It is recommended to offer women to support the luteal phase defect during the early pregnancy.
- 3.11.6.2. Luteal phase support after IVF treatment is not recommended routinely because it is not more effective than progesterone and has an increased likelihood of ovarian hyperstimulation syndrome.
- 3.11.6.3. The optimum route and duration of supplementation has not been established; treatment duration in best practice recommendations has ranged from obtaining a positive or negative pregnancy test to the end of the first trimester among different clinical trials.

3.11.7 Intracytoplasmic Sperm Injection – ICSI is indicated for couples with men having suboptimal semen parameters or who experienced no or low fertilization rates after conventional insemination. The recognized indications for treatment by ICSI include:

²⁴ For further information refer to: Penzias et al 2017, *Performing the Embryo Transfer: A Guideline*, ASRM.

²⁵ As per Article 5 of Cabinet Resolution No. (64) of 2020 concerning the Executive Regulations of Federal Law No. 7 / 2019 concerning Medically Assisted Reproduction.

- 3.11.7.1. Abnormal semen parameters (refer to sub-clause 3.6.6)
- 3.11.7.2. obstructive azoospermia
- 3.11.7.3. non-obstructive azoospermia.
- 3.11.7.4. couples in whom a previous conventional IVF treatment cycle has resulted in failed or poor fertilization.

3.12 Gamete Intrafallopian Transfer (GIFT) and Zygote Intrafallopian Transfer (ZIFT)

- 3.12.1 There is insufficient evidence to recommend the use of gamete intrafallopian transfer or zygote intrafallopian transfer in preference to IVF in couples with unexplained fertility problems or male factor fertility problems.
- 3.12.2 In addition to similar risks associated with other ART treatments, there are other risks of complications from the laparoscopic surgery, such as infection, organ perforation, and/or anesthesia related side effects that need to be considered.

3.13 Gamete and Embryo Pooling, Cryopreservation:

- 3.13.1.1 In presenting the option of oocyte cryopreservation, it is strongly recommended for physicians to explain their practice's own experience with oocyte cryopreservation, including pregnancy rates.
- 3.13.1.2 Embryo pooling is intended to increase the number of embryos available for future use, thus to maximize chances of successful outcome (Indications outlined in sub-clause 3.2.2). Other indications include:
 - (A) Patients with a previous poor ovarian response, or patients with an abnormal ovarian reserve test, or patients with two cycles with poor ovarian response after maximum stimulation in the absence of the poor ovarian responder and abnormal ovarian reserve criteria.
 - (B) Patients with poor embryo quality, defined as slow dividing embryos.
 - (C) When genetic testing is indicated. (Refer to sub-clause 3.6.7) and/or Genetic conditions such as Fragile X Premutation and Mosaicism for Monosomy X (refer to sub-clause 3.6.7)
 - (D) History of Ovarian surgery (oophorectomy, cystectomy) or History of Myomectomy (Fibroid surgery)
 - (E) Recurrent implantation failure
 - (F) family history of premature menopause or early menopause
 - (G) Male factor infertility
 - .(i) Erectile dysfunction
 - .(ii) Retrograde ejaculation
 - .(iii) Sperm back up freeze due to unavailability during treatment due to occupation and travel commitments.
 - .(iv) patient with cancer and potential future chemo and/or radiotherapy.

3.13.2 Fertility Preservation²⁶

- 3.13.2.1. Using sperm, embryos, or oocytes' cryopreservation to preserve fertility. (As outlined in sub-clause 3.2.2)
- 3.13.2.2. Fertility preservation for Oncology patients
 - (a) When preserving fertility for oncology patients, it is recommended to discuss at diagnosis, the impact of the cancer and its treatment on future fertility with the patient through a multi-disciplinary approach that includes the cancer-treating team.
 - (b) It is recommended to consider the following factors when deciding to offer fertility preservation to oncology patients: diagnosis, treatment plan, expected outcome of subsequent fertility treatment, prognosis of the cancer treatment, and viability of stored or post-thawed material.
 - (c) For cancer-related fertility preservation, it is recommended not to use a lower age limit for cryopreservation for fertility preservation.
 - .(i) It is recommended to offer sperm cryopreservation to men and adolescent boys who are preparing for medical treatment for cancer that is likely to make them infertile.
 - .(ii) Oocyte or embryo cryopreservation is recommended for women of reproductive age (including adolescent girls respectively) who are preparing for medical treatment for cancer that is likely to make them infertile if

For further information refer to:

³ ESHRE Guideline Group on Female Fertility Preservation et al. 2020, ESHRE Guideline: Female Fertility Preservation. (Please refer to reference #3 if you refer to the same source)

they are well enough to undergo ovarian stimulation and egg collection, and this will not worsen their condition, and enough time is available before the start of their cancer treatment.

3.13.2.3. Fertility preservation may be recommended for single individuals of advanced maternal age to protect against infertility.

3.14 Risks Associated with ART

3.14.1 Morbidity and mortality rates related to IVF are low. Complications may arise due to hormonal stimulation and egg retrieval. Such includes Ovarian Hyperstimulation Syndrome (OHSS)^{27,28}, thromboembolism, infection, abdominal bleeding, adnexal torsion, allergic reaction, and anesthetic complications. Data on long term follow-up for cryopreservation is limited.

3.15 Multidisciplinary Team Approach

3.15.1 Experts suggest a multidisciplinary team approach during infertility treatment to provide patients with adequate services and achieve optimal treatment outcomes. This team may include Gynecologists, Embryologists, and the other professionals who may aid in providing successful infertility treatment where required.

3.15.1.1. Obstetricians would have better insight when managing antenatal care post IVF and may aid in approaching patients in early pregnancy / or with high-risk pregnancies.²⁹

3.15.1.2. Urologists may aid as members of the fertility team to provide men with presumed fertility problems individualized care, and support in the overall diagnosis and counselling process where required.

3.16 Recommendations for Further Research

3.16.1 Experts recommend further data is needed on infertility and ART treatments within the UAE population.

3.16.1.1. There are many individuals facing potential fertility loss with no other options supported by large randomized clinical trials. Experts suggest that non-conventional (functional medicine) and adjuvant treatment options may be considered as potential add-on treatments to this population who have failed to achieve success with conventional treatments, especially that such are limited treatment options.³⁰

3.16.1.2. Therefore, experts suggest the need for properly well-designed research studies including double blinded randomized clinical trials tailored to the UAE population to assess potential adjuvant treatments and other areas that include international uncertainties within infertility and ART treatments.

²⁷ Pfeifer et al 2016, ASRM Prevention and Treatment of Moderate and Severe Ovarian Hyperstimulation Syndrome: A Guideline - or its most updated version when published.

²⁸ Figure 1 and Table 1. Humaidan et al. 2016. Ovarian hyperstimulation syndrome: review and new classification criteria for reporting in clinical trials. *Human Reproduction*, 31(9), pp.1997-2004.

²⁹ 4.13 - DOH 2022, Antenatal Ultrasound Guideline - for further reference regarding early pregnancy diagnosis

³⁰ ESHRE 2014, The responsible use of treatment add-ons in fertility services: a consensus statement - or its most updated version when published.

4. Relevant Reference Documents

No.	Reference Date	Reference Name	Relation Explanation / Coding / Publication Links
1	February 2023	United Arab Emirates. Federal Law No. (7) of 2019 Concerning Medically Assisted Reproduction.	Arabic version https://www.doh.gov.ae/ar/about/law-and-legislations English version https://mohap.gov.ae/en/about-us/legal-references
2	February 2023	United Arab Emirates. Cabinet Resolution No. (64) of 2020 Concerning the Implementing Regulation of Federal Law No. (7) of 2019 Concerning Medically Assisted Reproduction.	Arabic version https://www.doh.gov.ae/ar/about/law-and-legislations English version https://mohap.gov.ae/en/about-us/legal-references
3	February 2023	<i>ESHRE Guideline Group on Female Fertility Preservation et al.</i> 2020. ESHRE guideline: female fertility preservation. Human Reproduction Open,	https://doi.org/10.1093/hropen/hoaa052
4	February 2023	American Society for Reproductive Medicine, 2018a. Fertility preservation and reproduction in patients facing gonadotoxic therapies: an Ethics Committee opinion. Fertility and sterility, 110(3), pp.380-386.	https://doi.org/10.1016/j.fertnstert.2018.05.034
5	February 2023	<i>Teede et al.</i> 2018. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Human reproduction, 33(9), pp.1602-	https://doi.org/10.1093/humrep/dey256
6	February 2023	<i>American Society for Reproductive Medicine</i> , 2015. Subclinical hypothyroidism in the infertile female population: a guideline. Fertility and sterility, 104(3), pp.545-553.	https://doi.org/10.1016/j.fertnstert.2015.05.028
7	February 2023	<i>Schlegel et al.</i> 2020. Diagnosis and treatment of infertility in men: AUA/ASRM guideline. Linthicum (MD): American Urology Association.	https://doi.org/10.1097/JU.0000000000001521
8	February 2023	<i>Penzias et al.</i> 2017. Performing the embryo transfer: a guideline. Fertility and sterility, 107(4), pp.882-896.	https://doi.org/10.1016/j.fertnstert.2017.01.025
9	February 2023	<i>Pfeifer et al.</i> 2016. Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. Fertility and sterility, 106(7), pp.1634-1647.	https://doi.org/10.1016/j.fertnstert.2016.08.048
10	February 2023	<i>Penzias et al.</i> 2020. Evidence-based treatments for couples with unexplained infertility: a guideline. Fertility and sterility, 113(2), pp.305-322	https://doi.org/10.1016/j.fertnstert.2019.10.014
11	May 2023	<i>Department of Health Abu Dhabi</i> 2022. Antenatal Ultrasound Guideline. DOH/Guideline/Antenatal Ultrasound.	https://www.doh.gov.ae/en/resources/guidelines

12	March 2023	ESHRE 2014. The responsible use of treatment add-ons in fertility services: a consensus statement.	https://www.eshre.eu/Guidelines-and-Legal/Position-statements/Treatment-
13	February 2023	<i>National Institute for Health and Care Excellence. Fertility: assessment and treatment for people with fertility problems.</i> CG156. London: NICE, 2013.	http://www.nice.org.uk/CG156
14	February 2023	<i>Becker CM et al. ESHRE guideline: endometriosis.</i> Human reproduction open. 2022;2022(2):hoac009.	https://doi.org/10.1093/hropen/hoac009
15	February 2023	<i>American Society for Reproductive Medicine, 2022. Optimizing natural fertility: a committee opinion.</i> Fertility and Sterility, 117(1), pp.53-63.	https://doi.org/10.1016/j.fertnstert.2021.10.007
16	February 2023	<i>Ferraretti A et al. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: The Bologna criteria.</i> Human reproduction. 2011 Jul 1;26(7):1616-24.	https://doi.org/10.1093/humrep/der092
17	February 2023	<i>Carson SA, Kallen AN. Diagnosis and management of infertility: a review.</i> JAMA. 2021 Jul 6;326(1):65-76.	https://doi.org/10.1001/jama.2021.4788
18	February 2023	<i>ESHRE Guideline Group on Female Fertility Preservation, Anderson RA et al. ESHRE guideline: female fertility preservation.</i> Human reproduction open. 2020;2020(4):hoaa052.	https://doi.org/10.1093/hropen/hoaa052
19	February 2023	<i>ESHRE Guideline Group on Ovarian Stimulation, Bosch E et al. ESHRE guideline: ovarian stimulation for IVF/ICSI.</i> Human reproduction open. 2020;2020(2):hoaa009.	https://doi.org/10.1093/hropen/hoaa009
20	February 2023	<i>Zegers-Hochschild F et al. The international glossary on infertility and fertility care,</i> 2017. Human reproduction. 2017 Sep 1;32(9):1786-801.	https://doi.org/10.1093/humrep/dex234
21	February 2023	<i>Diemer T, et al. EAU (European Association of Urology) Guidelines on Male Infertility 2019.</i> Eur Urol. 2021 Nov;80(5): 603-620. doi:	https://doi.org/10.1016/j.eururo.2021.08.014
22	December 2022	Circular: Updates on Procedures of requesting Genetic Testing for Thiqa Members	https://www.doh.gov.ae/-/media/B6A906DE0BCB497B9E611ADDE8807F6D.ashx

5. Appendix

5.1 Appendix 1: Possible contraindications for dual embryo transfer

5.1.1 The treating clinician can consider these conditions and decide after complete clinical assessment including medical history, family history and investigations.

- BMI < 18 or > 35
- Short stature i.e., less than 150 cm
- Small pelvis
- Previous IVF success
- Systemic diseases such as:
 - Hypertension
 - Diabetes
 - Sickle cell
 - Type 1 Diabetes Mellitus (DM),
 - Uncontrolled Type II DM,
 - DM with end organ damage
 - Chronic kidney disease
 - Cardiopathy,
 - Autoimmune diseases
- History of mid-trimester miscarriage and recurrent miscarriages
- High risk of developing deep vein thrombosis (DVT) like APS or ATIII deficiency or a personal history of unprovoked DVT
- Previous history of twins
- History of spontaneous preterm delivery
- History of premature rupture of membranes
- History of abnormal placentation such as placenta accreta, increta, percreta or previa
- History of obstetrical complications or outcomes (intrauterine growth restriction, abruptio placentae, postpartum bleeding, intrauterine fetal death etc)
- Two or more previous C-sections
- Uterine/Mullerian anomalies such as septum, double uterus, etc.
- Intramural fibroids >4 cm in diameter
- Previous myomectomy of an intramural fibroid 4cm or larger
- Patients having history for uterine surgery with opening of endometrial cavity /adenomyiosis.

Adopted from Department of Health, 2023, DOH Policy on THIQA Coverage for ART Services. DOH/STR/CPL/3/2023.

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