NATIONAL CLINICAL GUIDELINES

THE MANAGEMENT OF INFERTILITY

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المبادئ الإرشادية السريرية لدولة قطر
NATIONAL CLINICAL GUIDELINES FOR QATAR

وزارة الصحـــــة العامـــــة
Ministry of Public Health
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Version History

Version	Status	Date	Editor	Description
1.0	Final	22nd September 2020	Guidelines Team	Final version for Publication

Citation

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Abbreviations

The abbreviations used in this guideline are as follows:

BMI	Body Mass Index
CCCT	Clomiphene Citrate Challenge Test
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator Gene
DHEA	Dehydroepiandrosterone
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HSG	Hysterosalpingogram
FISH	Fluorescence *in situ* Hybridisation
FSH	Follicle-Stimulating Hormone
GnRH	Gonadotropin-Releasing Hormone
ICSI	Intracytoplasmic Sperm Injection
hCG	Human Chorionic Gonadotrophin
hMG	Human Menopausal Gonadotrophin
HP-FSH	Highly-Purified Follicle-Stimulating Hormone
HP-hMG	Highly-Purified Human Menopausal Gonadotrophin
IUI	Intrauterine Insemination
IVF	In Vitro Fertilisation
LH	Luteinising Hormone
MAR	Mixed Antiglobulin Reaction
MDT	Multidisciplinary Team

MRI	Magnetic Resonance Imaging
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OAT	Oligo-Astheno-Teratozoospermia
OHSS	Ovarian Hyperstimulation Syndrome
ORT	Ovarian Reserve Test
PCOS	Polycystic Ovary Syndrome
PID	Pelvic Inflammatory Disease
ROB	Robertsonian translocations
Rec-hCG	Recombinant Human Chorionic Gonadotrophin
Rec-hFSH	Recombinant Follicle-Stimulating Hormone
Rec-hLH	Recombinant Human Luteinising Hormone
SIS	Saline-Infusion Sonohysterography
SSRIs	Selective Serotonin Re-Uptake Inhibitors
STI	Sexually Transmitted Infections
TGCT	Testicular Germ Cell Tumour
TRUS	Transrectal Ultrasound
U-hCG	Urinary Human Chorionic Gonadotrophin

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1 Information about this Guideline

1.1 Objective and Purpose of the Guideline

The purpose of this guideline is to define the appropriate diagnosis and management of infertility in both men and women. The objective is to guide the appropriate investigation, treatment and referral of patients presenting to provider organisations in Qatar. It is intended that the guideline will be used primarily by healthcare professionals in primary, secondary, and tertiary care levels [**R-GDG**].

1.2 Scope of the Guideline

This guideline covers the following aspects of care:

- The diagnosis, assessment, and management of infertility in adults of reproductive age groups, including:
  - Risk stratification.
  - Investigations.
  - Lifestyle advice and behavioural interventions.
- Referral indications to specialised infertility services.
- Differential diagnosis of male and female infertility.
- Pharmacological treatment options.
- Surgical treatment options.
- Assisted conception.
- Cryopreservation of sperm, oocytes, and embryos.

Aspects of care not covered in this guideline are:

- Pre-marital screening.
- Detailed medical management of related medical conditions.

1.3 Editorial Approach

This guideline document has been developed and issued by the Ministry of Public Health of Qatar (MOPH), through a process which aligns with international best practice in guideline development and localisation. The guideline will be reviewed on a regular basis and updated to incorporate comments and feedback from stakeholders across Qatar.

The editorial methodology, used to develop this guideline, has involved the following critical steps:

- Extensive literature search for well-reputed, published evidence relating to the topic.
- Critical appraisal of the literature.
- Development of a draft summary guideline.
- Review of the summary guideline with a Guideline Development Group, comprised of practising healthcare professionals, subject matter experts and patient representatives, from across Qatar.
- Independent review of the guideline by the National Clinical Guidelines & Pathways Committee, appointed by the MOPH, from amongst stakeholder organisations across Qatar.

Whilst the MOPH has sponsored the development of the guideline, the MOPH does not influence the specific recommendations made within it.

1.4 Sources of Evidence

The professional literature published in the English language has been systematically queried using specially developed, customised, and tested search strings. Search strategies are developed to allow efficient yet comprehensive analysis of relevant publications for a given topic and to maximise retrieval of articles with certain desired characteristics pertinent to a guideline.

For each guideline, all retrieved publications have been individually reviewed by a clinical editor and assessed in terms of quality, utility, and relevance. Preference is given to publications that:

1. Are designed with rigorous scientific methodology.
2. Are published in higher-quality journals (i.e. journals that are read and cited most often within their field).
3. Address an aspect of specific importance to the guideline in question.

Further information about the literature search and appraisal process is included in the appendix.

1.5 Evidence Grading and Recommendations

Recommendations made within this guideline are supported by evidence from the medical literature and where possible the most authoritative sources have been used in the development of this guideline. To provide insight into the evidence basis for each recommendation, the following evidence hierarchy has been used to grade the level of authoritativeness of the evidence used, where recommendations have been made within this guideline.

Where the recommendations of international guidelines have been adopted, the evidence grading is assigned to the underlying evidence used by the international guideline. Where more than one source has been cited, the evidence grading relates to the highest level of evidence cited:

- **Level 1 (L1):**
  - Meta-analyses.
  - Randomised controlled trials with meta-analysis.
  - Randomised controlled trials.
  - Systematic reviews.

- **Level 2 (L2):**
  - Observational studies, examples include:
    - Cohort studies with statistical adjustment for potential confounders.
    - Cohort studies without adjustment.
    - Case series with historical or literature controls.
    - Uncontrolled case series.
  - Statements in published articles or textbooks.

- **Level 3 (L3):**
  - Expert opinion.
  - Unpublished data, examples include:
    - Large database analyses.
    - Written protocols or outcomes reports from large practices.

To give additional insight into the reasoning underlying certain recommendations and the strength of recommendation, the following recommendation grading has been used, where recommendations are made:

- **Recommendation Grade A (RGA):** Evidence demonstrates at least moderate certainty of at least moderate net benefit.
- **Recommendation Grade B (RGB):** Evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended.
- **Recommendation Grade C (RGC):** Evidence demonstrates potential harm that outweighs benefit; additional research is recommended.
- **Recommendation of the GDG (R-GDG):** Recommended best practice on the basis of the clinical experience of the Guideline Development Group members.

1.6 Guideline Development Group Members

The following table lists members of the Guideline Development Group (GDG) nominated by their respective organisations and the Clinical Governance Group. The GDG members have reviewed and provided feedback on the draft guideline relating to the topic. Each member has completed a declaration of conflicts of interest, which has been reviewed and retained by the MOPH.

Guideline Development Group Members		
Name	**Title**	**Organisation**
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Ms Muneera Abualulla	Dietitian	Primary Health Care Corp
Prof Badreldeen Ahmed	Professor of Obstetrics, Weill Cornell Medicine – Qatar and Qatar University Director of Feto-Maternal Centre	Feto-Maternal Centre,
Ms Zeina Alhadidi	Pharmacist	Ministry of Interior Clinics
Dr Zaynab Al-Lami	Consultant Family Medicine	Primary Health Care Corp
Dr Ahmad Hassan Al-Malki	Consultant Urology, Andrology & Male Infertility	Hamad Medical Corporation
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Guideline Development Group Members		
Name	**Title**	**Organisation**
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Ms Maria Onoufriou	Senior Clinical Embryologist	Sidra Medicine
Ms Elena Ortiz Rubis	General Nurse Practitioner	Al-Ahli Hospital
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1.7 National Clinical Guidelines & Pathways Committee Members

The following table lists members of the National Clinical Guidelines & Pathways Committee (NCGPC), appointed by the MOPH. The NCGPC members have reviewed and provided their feedback and approval of the guideline document. Each member has completed a declaration of conflicts of interest, which has been reviewed and retained by the MOPH.

National Clinical Guidelines & Pathways Committee (NCGPC) Members		
Name	**Title**	**Organisation**
Ms Huda Amer Al-Katheeri	Chair of the NCGPC, Director- Strategic Planning & Performance Department	Ministry of Public Health
Shk Dr Mohammed Hamad J. Al Thani	Co-Chair of NCGPC, Director of Public Health	Ministry of Public Health
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Dr Basil Bashqawi	Accreditation Coordinator, Dept of Health Professions	Ministry of Public Health
Dr Abi Khalil Charbel	Associate Professor of Medicine Consultant Cardiology	Weill Cornell Medicine - Qatar
Dr Paul Dijkstra	Director of Medical Education	Aspetar
Dr Mohamed Elrishi	Consultant Endocrinology and Internal Medicine	Al Ahli Hospital

National Clinical Guidelines & Pathways Committee (NCGPC) Members		
Name	**Title**	**Organisation**
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Dr Ghassan Youseph Hommos	Consultant Endocrinology	Al Emadi Hospital
Dr Hani Benhassen Kilani	Senior Consultant, Executive Director for Corporate Clinical Policy and Guidelines	Hamad Medical Corporation
Dr Egon Toft	VP and Dean	College of Medicine, Qatar University

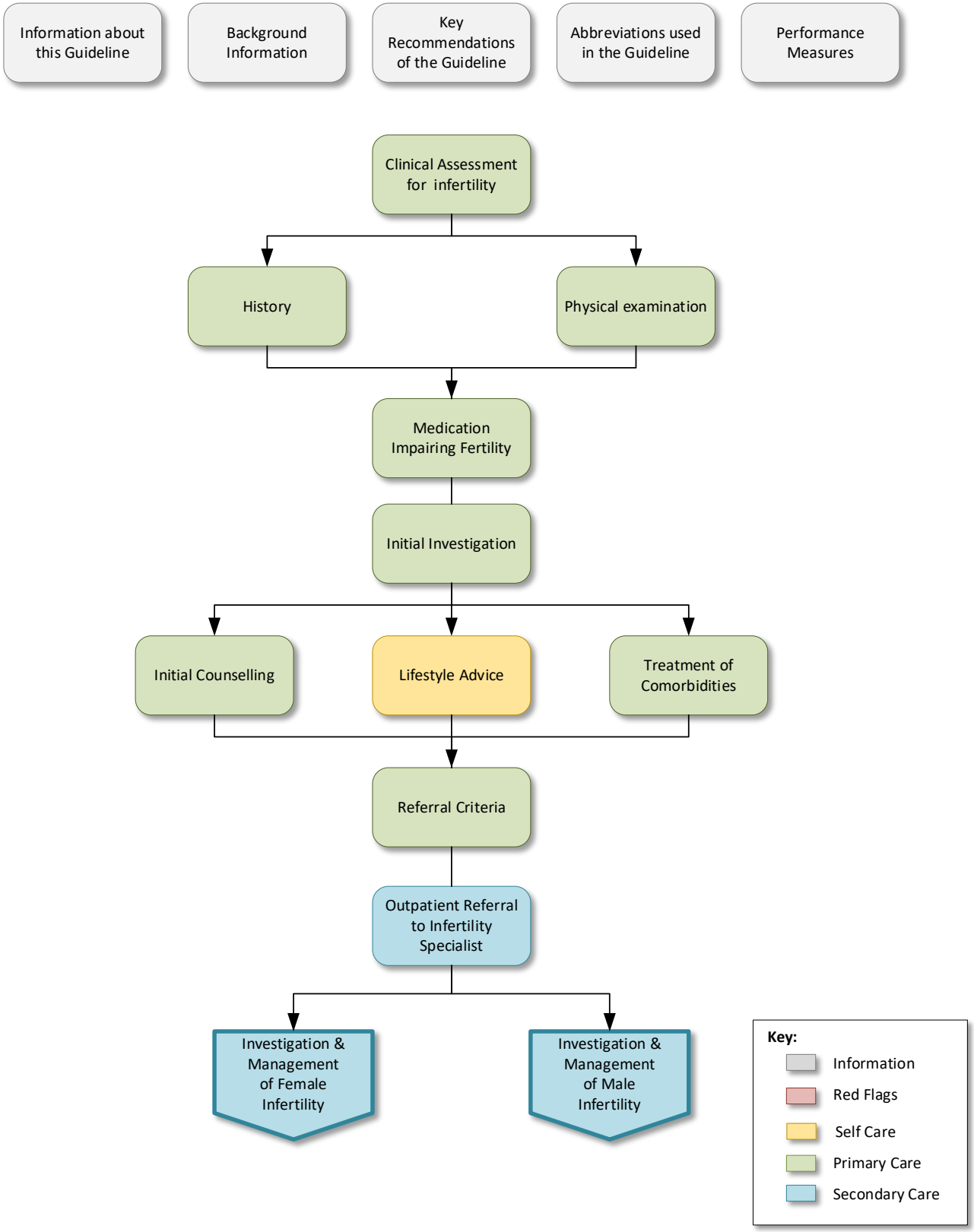
1.8 Responsibilities of Healthcare Professionals

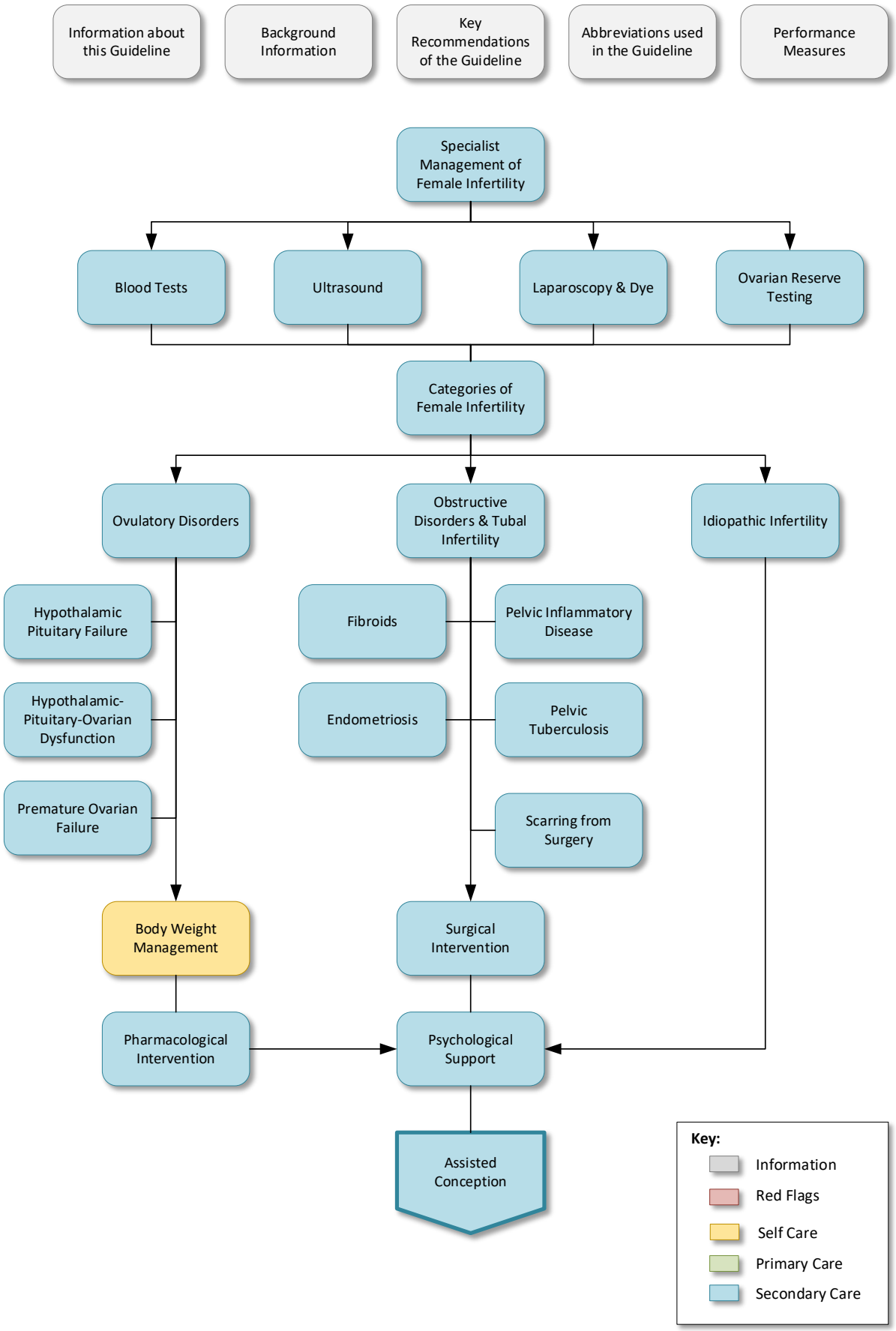
This guideline has been issued by the MOPH to define how care should be provided in Qatar. It is based upon a comprehensive assessment of the evidence as well as its applicability to the national context of Qatar. Healthcare professionals are expected to take this guidance into account when exercising their clinical judgement in the care of patients presenting to them.

The guidance does not override individual professional responsibility to take decisions which are appropriate to the circumstances of the patient concerned. Such decisions should be made in consultation with the patient, their guardians, or carers and should consider the individual risks and benefits of any intervention that is contemplated in the patient's care.

2 Infertility Pathway

Click on a box below to see the relevant page of the Pathway.

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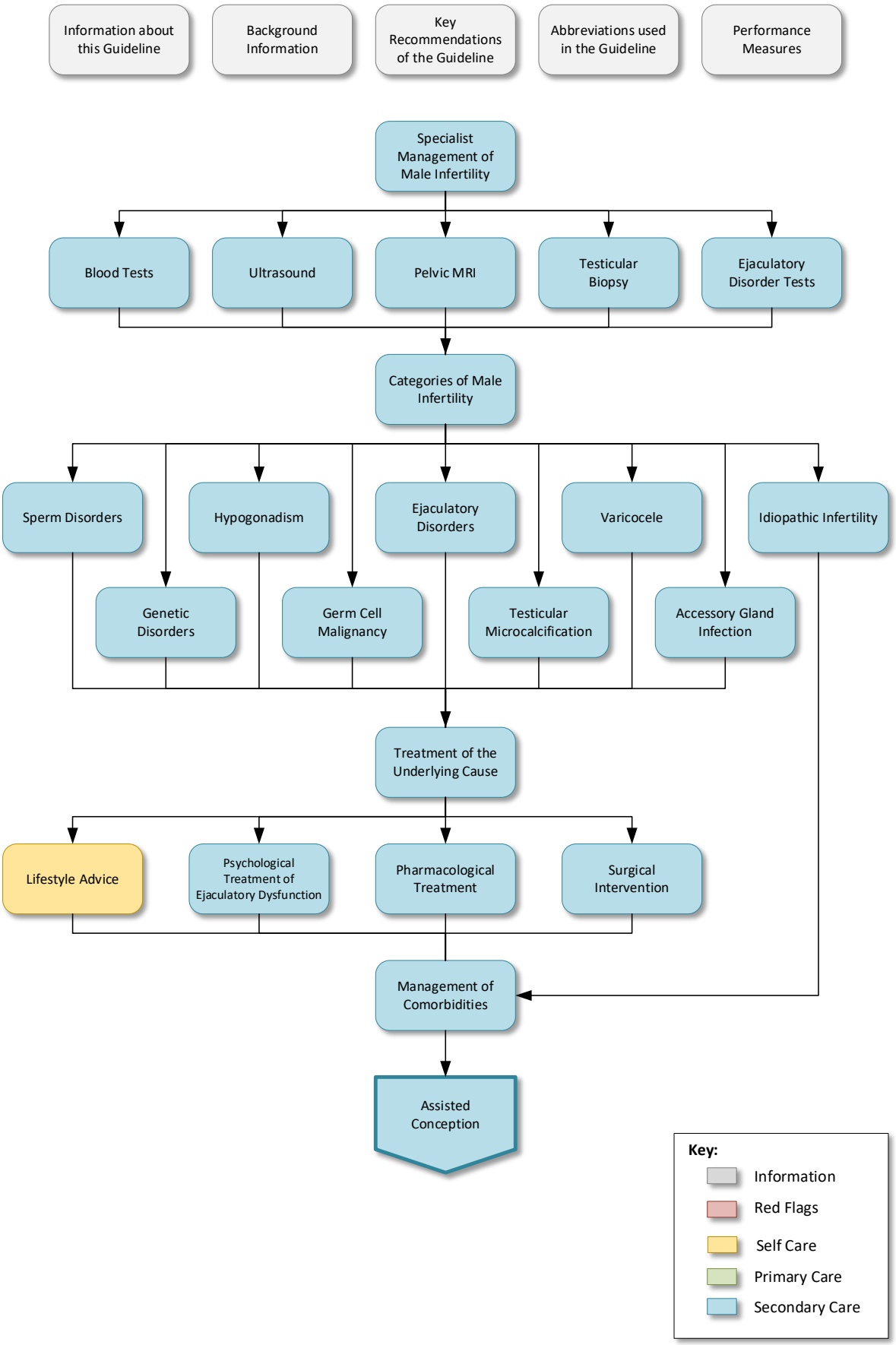
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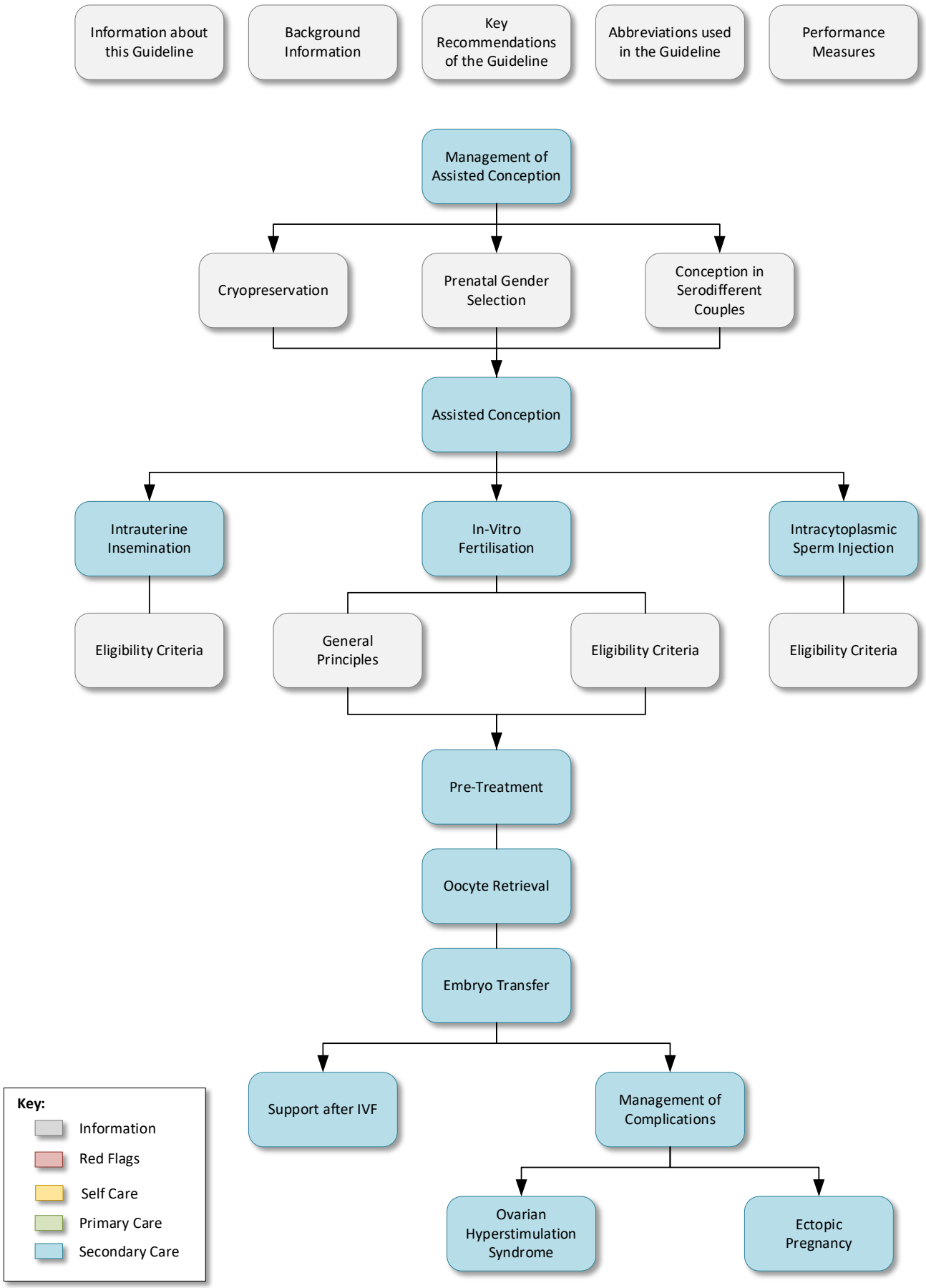
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3 Key Recommendations of the Guideline

The key recommendations of this guideline are as follows:

Clinical Assessment in Primary Care (*Section 5*):

- Couples who are concerned about delays in conception should be offered an assessment and should initially be seen together[1] [**L1**].
- A diagnostic assessment for infertility is warranted for couples who fail to achieve a successful pregnancy after 12 months or more of regular unprotected sexual intercourse[2,3].

Initial Investigation of Female Infertility in Primary Care (*Section 5.4.1*):

- Initial investigation of infertility in women is as follows[1,2,4] [**L1, RGA**]:
    - Basic haematology screen, chlamydia and gonorrhoea tests, HIV, HBsAg, HBsAb, HCV-Ab, Rubella, and Syphilis serology.
    - Evaluation of ovulatory function using one of the following:
        - Mid-luteal phase serum progesterone.
        - Serum gonadotrophins (only for women with irregular menstruation).
        - Day 3 cycle of: Follicle-stimulating hormone (FSH), Oestradiol (E2), Luteinising hormone (LH), Serum anti-Mullerian hormone (AMH), Prolactin, Thyroid hormones.

Initial Investigation of Male Infertility in Primary Care (*Section 5.4.2*):

- Initial investigation in infertility in men should include[4,1,2,5]:
    - Chlamydia and Gonorrhoea tests.
    - Semen analysis.
- If oligozoospermia or azoospermia are present on semen analysis, consider the following tests [15,6]:
    - FSH, LH, serum and free testosterone.
    - Consider prolactin and oestradiol if azoospermia, low libido, and/or impotence are present.
- If the semen analyses are abnormal on two tests with or without laboratory evidence of potential hypogonadism, the patient should be referred for further andrological investigation[5] [**L1**].

Management of Infertility in Primary Care (*Section 6*):

- The initial management of infertility in primary care should involve pre-treatment counselling and lifestyle advice tailored toward improving the couple's chances of conception[1,2] [**L1, RGA**].
- Patients with long term conditions such as diabetes mellitus and hypothyroidism, should be reviewed by an appropriate specialist to ensure optimisation of long term condition management [**R-GDG**].

Referral Criteria to Specialist Care (*Section 7*):

- Consider referral to Specialist Care if any of the following apply [1,4,5][**L1**]:
    - There is a known cause for the infertility:
        - The couple should be referred for specialist assessment, regardless of the period of trying to achieve conception.
    - The couple cannot conceive after 12 months of regular unprotected sexual intercourse.
    - Primary amenorrhoea in the female partner.
- Consider referral to a male fertility specialist or urologist if [1,4,5][**L1]** :
    - Semen analysis is abnormal.

- An anatomical abnormality or obstruction is suspected or detected on examination e.g. varicocele.
- An endocrine disorder such as hyperprolactinemia, is diagnosed.
- Testicular microcalcification or germ cell malignancy is suspected.
- Idiopathic infertility is suspected.

Investigation of Female Infertility in Specialist Care (*Section 8.1*):

- Offer blood tests including HIV, HBsAg, HBsAb, HCV-Ab, Rubella, and Syphilis serology, if these tests have not been performed previously[1] [**L1**].
- Basal FSH, LH, and oestradiol levels measured on day 3 of the menstrual cycle, anti-Müllerian hormone and total antral follicle count, may also be considered[1,7].
- Transabdominal or transvaginal ultrasound[1,4,8] [**L1, RGA**].
- Contrast investigations e.g. hysterosalpingogram, or sonohysterogram are useful for assessing fallopian tubes and uterine cavity[1,4,8] [**L1, RGA**].
- Laparoscopy and dye can be used to examine women with comorbidities such as a history of PID, previous ectopic pregnancy or endometriosis[1,4,8][**L1, RGA**].

Investigation of Male Infertility in Specialist Care (*Section 8.2*):

- Offer blood tests including HIV, HBsAg, HBsAb, HCV-Ab, Rubella, and Syphilis serology, if these tests have not been performed previously[1] [**L1**].
- Consider the following tests[5,9] [**L1, RGA**]:
  - Scrotal ultrasound.
  - Transrectal ultrasound (TRUS), should only be used in men with a low seminal volume and in whom distal obstruction is suspected:
- Consider Pelvic MRI and testicular biopsy in selected cases (see Section 8.2).
- Tests for ejaculatory disorders, genetic abnormalities and other disorders may also be necessary in selected cases.

Management of Female Infertility in Specialist Care (*Section 10*):
The management of female infertility depends upon the underlying cause[1,23,48]:

- Hypothalamic pituitary failure (WHO Group I Ovulation Disorders):
  - Optimise body weight and provide professional advice on body weight management[1,3,61] [**L1, RGA**].
  - If behavioural interventions are not effective, offer GnRH by pulsatile infusion pump or gonadotrophins with LH activity to induce ovulation[1] [**L1, RGA**].
- Hypothalamic-pituitary-ovarian dysfunction (WHO Group II Ovulation Disorders).
  - Optimise body weight and provide professional advice on body weight management[1,3,61] [**L1, RGA**].
  - If behavioural interventions are not effective, offer Clomiphene citrate or Metformin either alone, or in combination[1,10,11] [**L1, RGA**].
  - All women offered ovulation induction with gonadotrophins[1] [**L1**].
- Hyperprolactinaemia:
  - Women with ovulatory disorders due to idiopathic hyperprolactinaemia should be reviewed by an endocrinologist and offered treatment with dopamine agonists (e.g. bromocriptine or cabergoline)[1] [**L1, RGA**].
- Fibroids:
  - Consider pharmacological treatment to shrink fibroids using GnRH analogues (e.g. goserelin acetate) or ulipristal acetate[12] [**L1, RGA**].

    - If treatment with medication is ineffective, consider surgical removal of the fibroids[12] [**L1, RGA**].
- See *Section 10.4* for surgical interventions to treat underlying cause of infertility that are unresponsive or not amenable to pharmacological treatment.

- Unexplained Female Infertility:
    - Consider the following treatments options in women with idiopathic infertility[13] [**L1, RGA**]:
        - Intrauterine insemination (IUI).
        - In-Vitro Fertilisation (IVF) - (If 3 cycles of IUI with ovarian stimulation have been unsuccessful).

Management of Male Infertility in Specialist Care (*Section 12*):
The management of male infertility should be directed to the underlying cause, where this is identifiable[4].

- Ejaculatory Dysfunction:
    - Behavioural Therapy, Couples Therapy and Sex Therapy, may help to manage ejaculatory problems[5,14] [**L1, RGB**]:
    - SSRIs, dapoxetine, phosphodiesterase-5 inhibitors (e.g. sildenafil) and topical anaesthetics (e.g. lidocaine or prilocaine) may also be used in men with premature ejaculation[5,14,15] [**L1**].
- Sperm Disorders:
    - Gonadotrophin hormones should be considered in men with oligo- and azoospermia to stimulate the production of sperm[1,16] [**L1, RGA**].
    - Clomiphene citrate, tamoxifen, gonadotrophins (HMG/rFSH/hpFSH) and oral antioxidants may be considered in men with idiopathic OAT syndrome[5][**L1, RGB**].
- Hypogonadotropic Hypogonadism:
    - Gonadotrophin hormones, anti-oestrogens and aromatase inhibitors may be used to treat hypogonadotropic hypogonadism[1,5] [**L1, RGA**].
- Surgical Interventions:
    - Microsurgical vasovasostomy or vasoepididymostomy should be considered in patients with azoospermia caused by vasal or epididymal obstruction[5] [**L1, RGA**].
    - Varicocelectomy, antegrade or retrograde sclerotherapy, retrograde embolisation may be considered in patients with a varicocele[5,17] [**L1, RGA**].
- Unexplained Male Infertility
    - Offer lifestyle modification advice to patients who are diagnosed with idiopathic male infertility [**R-GDG**].

Intrauterine Insemination (*Section 13.1*):
- Indications for IUI are[1,18] [**L1, RGA**]::
    - Unable to have vaginal intercourse (e.g. due to physical disability or a psychosexual problem).
    - Unexplained infertility.
    - Mild male factor infertility.
    - Mild endometriosis.
    - Require specific consideration in relation to methods of conception (e.g. after sperm washing if man is HIV positive).
- NB: 3-6 cycles of IUI should be offered to couples without a clear fertility dysfunction before IVF is considered[1] [**L1**].

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In-Vitro Fertilisation (*Section 13.2*):

- IVF (with or without ICSI) can be offered to women 18-45 years old who have not conceived after 1 year of regular unprotected intercourse if all of the following conditions have been met [**R-GDG**]:
    - The patient's BMI is <30.
    - The patient's HBA_{1C} level is <6.5%.
    - The patient's TSH level is within normal limits.
    - The patient has had 3 or fewer caesarean sections.
    - If the patient is aged over 40 years, pregenetic screening has been completed.
- IVF should be offered after 3 unsuccessful IUIs [**R-GDG**].
- IVF is not recommended for women >45 years old due to low chances of successful pregnancy[1,19] [**L1, RGB**].

4 Background Information

4.1 Definitions

Infertility is defined as failure to achieve a successful pregnancy after at least 12 months of regular unprotected intercourse[20].

Primary infertility is the failure to conceive or have a live birth[20].

Secondary infertility is the failure to conceive a child or have a live birth, after having one or more pregnancies in the past[20].

4.2 Prevalence

The prevalence of infertility in women is not available for the Qatari population. The worldwide prevalence of primary infertility amongst women was estimated to be 1.9% in 2010. The prevalence of secondary infertility amongst women was estimated to be 10.5%[21].

4.3 Aetiology

In women, the common causes of infertility include[4]:

- Ovulatory dysfunction, classified as:
  - WHO Group I: Hypothalamic Pituitary Failure.
  - WHO Group II: Hypothalamic-Pituitary-Ovarian Dysfunction.
  - WHO Group III: Ovarian Failure.
  - Other Endocrine Disorder.
- Tubal factors.
- Unexplained infertility.

In men, common cause of infertility include[4,5]:

- Idiopathic.
- Varicocele.
- Sperm disorders:
  - Oligozoospermia or azoospermia.
  - Asthenozoospermia.
  - Teratozoospermia.
  - Other unexplained factors.
- Testicular problems:
  - Injury.
  - Infection.
  - Testicular surgery.
  - Testicular tumours.
  - Maldescended testicles.
  - Congenital defects.
- Urogenital tract infection.
- Sexual dysfunction (Ejaculatory dysfunction, reduced sexual desire, erectile dysfunction).
- Hypogonadism.
  - Primary (hypergonadotropic) hypogonadism of unknown cause.
  - Secondary (hypogonadotropic) hypogonadism.

    - Idiopathic hypogonadotropic hypogonadism.
    - Late-onset hypogonadism.
- Immunological factors (Sperm autoantibodies).
- Sterilisation.
- Medications and drugs lowering fertility potentials.
- Smoking.

4.4 Risk Factors

Factors that can affect fertility in both men and women include[1,4,22]:

- Age.
- Weight.
- Sexually transmitted infections (STIs).
- Smoking (including passive smoking).
- Environmental factors (e.g. exposure to pesticides, solvents, heavy metals).
- Stress.
- Diabetes.

5 Clinical Assessment in Primary Care

Couples who are concerned about delays in conception should be offered an assessment and should initially be seen together[1] [**L1**].

5.1 History

5.1.1 Women with Suspected Infertility

A diagnostic assessment for infertility is warranted for couples who fail to achieve a successful pregnancy after 12 months or more of regular unprotected sexual intercourse[2,3].

Essential components in the history should include[1,2,4,23]:

- Age of the patient.
- Duration of infertility and history of any previous evaluation and treatment.
- Menstrual history including:
    - Age at menarche.
    - Cycle length and characteristics.
    - Presence or absence of dysmenorrhea, onset and severity.
- Previous pregnancy (whether achieved through natural conception or via assisted reproductive technology) and delivery history including:
    - Gravidity and parity.
    - Pregnancy outcome, and any associated obstetric complications.
- History of previous contraception.
- Sexual history, including:
    - Frequency, timing, and difficulties with sexual intercourse.
    - The level of libido.
- Past surgical history (indications, surgical procedures, and outcomes).
- Past medical history including:
    - Previous hospitalisations,
    - Systemic diseases (e.g. Diabetes, thyroid disease).
    - Pelvic inflammatory disease and sexually transmitted infections.
- Previous abnormal cervical smear reports and any treatment undertaken.
- Current medications and allergies.
- Family history of any congenital abnormalities, developmental delay, early menopause, or reproductive problems.
- Details of general health and lifestyle, including:
    - Level of stress.
    - Smoking.
    - Illicit drugs.
- History of immunisations.
- Occupational history and exposure to hazards that could affect fertility (e.g. environmental toxins, radiation or cytotoxic agents).
- Use of prescription, over the counter, and recreational drugs that may impair fertility (see *Section 5.2*).

5.1.2 Men with Suspected Infertility

Components of the history in the male partners are the same as that of the female partner mentioned above (except for gynaecological and obstetric histories) [**R-GDG**].

Other clinical features that should be queried include [**R-GDG**]:

- Testicular exposure to heat.
- Presence of symptoms of urogenital infections (including STIs).
- History of mumps and testicular problems.
- Symptoms or history of ejaculatory dysfunction (listed in *Section 11.3*).
- Erectile function.

5.2 Medications Impairing Fertility

Some medication can affect fertility in women. These include[4]:

- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (e.g. long-term use or a high dosage of ibuprofen or aspirin).
- Chemotherapy medications.
- Antipsychotics.
- Spironolactone.

Medications and substances that can affect fertility in men include[4]:

- Selective Serotonin Reuptake Inhibitors
- Alpha adrenergic receptor blockers can affect ejaculate volume
- Sulfasalazine.
- Chemotherapy medications.
- Anabolic steroids.
- Herbal remedies (e.g. root extracts of the Chinese herb Tripterygium wilfordii).

Illegal drugs (including marijuana and cocaine) can cause infertility in both men and women[4,22].

5.3 Physical Examination

5.3.1 Women with Suspected Infertility

A review of systems and physical examination of the gynaecological and endocrine systems should be performed. Physical examination should include[2,4]:

- Weight and height measurements.
- Calculation of the Body Mass Index (BMI).
- Blood pressure and pulse.
- Looking for external factors suggestive of excess androgens or ovulatory dysfunction:
    - Hirsutism.
    - Acne.
    - Galactorrhoea.
- Examination of the thyroid gland:
    - Enlargement.
    - Nodules.
    - Tenderness.
- Examination of breast secretions and their character.
- Pelvic examination for signs of infection (e.g. adnexal masses, tenderness, or nodularity).

5.3.2 Men with Suspected Infertility

Physical examination should include[2,4,5]:

- Weight and height measurements and calculation of BMI.
- Blood pressure and pulse.
- Scrotum and testicles:
  - Size, tenderness, and consistency.
  - Presence of any abnormal masses (e.g. cysts, varicocele, hernia).
  - Check for the presence of testes in the scrotum.
- Penis:
  - Whether circumcised.
  - Presence of plaques.
  - Position of the urethral meatus.
  - Structural abnormalities (e.g. meatal stenosis, Peyronie's disease, phimosis and ulceration).
- Prostate gland examination (optional):
  - Size.
  - Shape (nodularity, irregularity).
  - Tenderness.
- Vas deferens:
  - Examine for presence or absence of vas deferens which raises the suspicion of an underlying congenital abnormality.

5.4 Initial Investigation

5.4.1 Women with Suspected Infertility

Following detailed history and physical examination, subsequent assessment should be conducted in a systematic and cost-effective manner to identify all relevant factors. The initial emphasis should be on the least invasive techniques for detection of the most common causes of infertility [**R-GDG**].

The pace and extent of evaluation should consider the couple's preferences, patient age, the duration of infertility, and unique features of the clinical history and examination [**R-GDG**]

Initial investigation of infertility in women is as follows[1,2,4] [**L1, RGA**]:

- Preconception Screening Tests:
  - Basic haematology screen.
  - Chlamydia and Gonorrhoea test.
  - Rubella and Syphilis serology.
  - HIV serology.
  - Hepatitis B surface antigen and Hepatitis C serology.
- Initial Tests for Ovulatory Function:
  - Ovulatory dysfunction accounts for approximately 15% of all infertile couples and accounts for up to 40% of infertility in women [**R-GDG**].
  - Initial methods for evaluating ovulatory function may include any of the following:
    - Serum progesterone determinations:
      - Should be obtained at the appropriate time in the cycle, preferably approximately one week before the expected onset of the next menses, rather than on any one specific cycle day [**R-GDG**].
      - Progesterone concentration >30 nmol/L provides presumptive but reliable evidence of recent ovulation.

- Serum gonadotrophins (only for women with irregular menstruation):
- Day 3 cycle of:
    - Follicle-stimulating hormone (FSH).
    - Oestradiol (E2)
    - Luteinising hormone (LH).
    - Serum anti-Mullerian hormone (AMH).
    - Prolactin.
    - Thyroid hormones.

5.4.2 Men with Suspected Infertility

Initial investigation of infertility in men involves laboratory evaluation starting with semen analysis[1,23,29].

Initial investigation in infertility in men should include:

- Chlamydia and Gonorrhoea tests[4].
- Semen analysis[1,2,5].
    - Instructions for sample collection should include abstinence from ejaculation for 48-72 hours[1,23,29].
    - Acceptable normal laboratory limits include[2,5]:
        - Semen volume (≥1.5 ml).
        - Semen pH (>7.2).
        - Peroxidase-positive leukocytes (<1 x10^6/mL).
        - Sperm concentration (≥15 x10^6 spermatozoa/mL).
        - Total sperm number (≥39 x10^6 spermatozoa/ejaculate).
        - Total motility (≥40% motile).
        - Progressive motility (≥32%).
        - Vitality (≥58% live spermatozoa).
        - Sperm morphology (≥4% of normal forms).
    - Screening for anti-sperm antibodies is not recommended as part of routine male fertility evaluation[10] [**L1, RGB**].
- Optional semen analysis[5]:
    - Mixed antiglobulin reaction (MAR) test (<50% motile spermatozoa with bound particles per ejaculate).
    - Immunobead test (<50% motile spermatozoa with bound beads/ejaculate).
    - Seminal zinc (≥2.4 µmol/ejaculate).
    - Seminal fructose (≥13 µmol/ejaculate).
    - Seminal neutral glucosidase (≤20 mU/ejaculate).
    - Sperm DNA Fragmentation Index.

Semen analysis should be standardised by the guidelines of the *WHO Laboratory Manual for the Examination and Processing of Human Semen (5th Edition)*[5,24].

Frequency of semen analysis:

- If the results of the first semen analysis are normal, one test is sufficient[5] [**L1**].
- If the results of the first semen analysis are abnormal the test should be repeated[1,5] [**L1**]:
    - The confirmatory tests should be undertaken 3 months after the initial analysis.
    - If azoospermia or severe oligozoospermia is suspected, the confirmatory tests should be performed as soon as possible.

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The presence of oligozoospermia or azoospermia on semen analysis should raise the index of suspicion for hypogonadism. The following hormonal tests should then be considered[15,6]:

- FSH.
    - Morning levels of total testosterone and FSH can help differentiate between primary and secondary disorders. [15] [**L1**]:
- LH.
- Serum and free testosterone:
    - A low testosterone level with an elevated FSH level suggests primary hypogonadism. A low testosterone level with a low FSH level signals a secondary cause.
- Consider prolactin and oestradiol if azoospermia, low libido, and/or impotence are present.

NB: If the semen analyses are abnormal on two tests with or without laboratory evidence of potential hypogonadism, the patient should be referred for further andrological investigation[5] [**L1**] (see *Section 8.2*).

6 Management of Infertility in Primary Care

The initial management of infertility in primary care should involve pre-treatment counselling and lifestyle advice tailored toward improving the couple's chances of conception[1,2] [**L1, RGA**].

6.1 Initial Counselling

Discuss the probability of conception with couples who are concerned about delays and provide the following information[1,4,22]:

- Fertility varies among populations and individuals.
- For women with BMI ≥30, it may take longer to conceive.
- Over 80-84% of couples in the general population will conceive within one year if:
    - The woman is aged <40 years; and
    - The couple have regular unprotected sexual intercourse.
- Of those who do not conceive in the first year, approximately 50% will do so in the second year.
- For couples who have not been able to conceive for more than 3 years, the chance of getting pregnant naturally within the next year is ≤25%[4].

Couples who are concerned about their fertility should be provided with general education on the effects of the following factors on fertility:[1,22,25]

- Stress and other indirect sources of stress such as pressure of family and society for not having children can affect couple's relationship.
- Frequency of intercourse can contribute to the fertility problems.
- Fertility support groups may help them to cope with the problem.

People experiencing delays in conception should be offered counselling and psychological support by a specialist provider with experience in the area of infertility [1] [**L1, RGA**]:

- To reduce psychological stress from fertility problems themselves, investigations, and treatment of fertility problems.
- Provided by a health care specialist not directly involved in the management of the couple's fertility problems.
- Provided before, during, and after investigation and treatment.
- Irrespective of the outcome of the treatment.

6.2 Lifestyle Advice

Couples experiencing delays in conception should be informed that following a healthy eating and lifestyle may improve fertility. The advice should be given in a written and verbal forms[26] [**L1**]. Couples should be referred to specialised clinics and services to receive appropriate lifestyle advice [**R-GDG**].

6.2.1 Smoking Cessation

To increase the likelihood of conception, both partners should be referred to specialised smoking cessation program or clinics for appropriate advice and counselling on smoking cessation[1,4,27,28] [**L1, RGA**]:

6.2.2 Alcohol Intake

The *WHO Global Status Report on Alcohol Consumption 2016* showed that the prevalence of heavy drinking in men (aged 15 years and above) and women (aged 15 years and above) in Qatar was 28.8% and 5.3% respectively[29].

Couples who drink alcohol, should be informed of the negative effects of alcohol consumption on male fertility and pregnancy and advised to stop [**R-GDG**].

6.2.3 Body Weight Management

Obese men and women (BMI ≥30) should be referred to the dietitian for counselling on weight reduction[1,22] [**L1, RGA**]. Women with BMI <19 and irregular menses (or amenorrhoea) should be referred to the dietitian for counselling on weight gain[1] [**L1, RGA**].

6.2.4 Nutrition

Couples should be referred to the dietitian for counselling on healthy eating patterns including consumption of a balanced diet which has a variety of whole grains breads, meat, dairy products, fruit, vegetables, and legumes according to *Qatar Dietary Guideline* recommendations [**R-GDG**]:

- Women attempting to become pregnant should be given folic acid to reduce the risk of neural tube defects in a future foetus[1,22] [**L1, RGA**].

6.2.5 Optimising Sexual Intercourse

To optimise natural fertility, inform the couple that:

- Coitus every 2-3 days optimises the chance of pregnancy[1,22] [**L1**].
- The probability of pregnancy increases after intercourse, within the 3-days immediately prior to ovulation[22,30] [**L2**].

6.3 Treatment of Comorbidities

Patients with long term conditions such as diabetes mellitus and hypothyroidism, should be reviewed by an appropriate specialist to ensure optimisation of long term condition management [**R-GDG**].

Patients with a positive STI test, and their sexual partners, should be referred to the STI specialist for appropriate treatment and contact tracing[1] [**L1, RGA**].

View Pathway

7 Referral Criteria to Specialist Care

Consider referral to Specialist Care if any of the following apply [1,4,5][**L1**]:

- There is a known cause for the infertility:
    - The couple should be referred for specialist assessment, regardless of the period of trying to achieve conception.
- The couple cannot conceive after 12 months of regular unprotected sexual intercourse.
- Primary amenorrhoea in the female partner.

Consider referral to a male fertility specialist or urologist if [1,4,5][**L1]** :

- Semen analysis is abnormal.
- An anatomical abnormality or obstruction is suspected or detected on examination e.g. varicocele.
- An endocrine disorder such as hyperprolactinemia, is diagnosed.
- Testicular microcalcification or germ cell malignancy is suspected.
- Idiopathic infertility is suspected.

View Pathway

8 Clinical Assessment in Specialist Care

8.1 Further Investigation in Women

8.1.1 Blood Tests

Offer blood tests including HIV, HBsAg, HBsAb, HCV-Ab, Rubella, and Syphilis serology if these tests have not been performed previously. Provide Rubella vaccination if indicated[1] [**L1**]. Advise the patient not to become pregnant for at least 1 month following Rubella vaccination[1,23] [**L1, RGC**].

Ovarian Reserve Tests (ORTs) provide an indirect estimate of a woman's remaining follicular pool[7]. ORTs are recommended for women prior to IVF[1,7] [**L1, RGA**].

The following tests may be considered[1,7]:

- Basal FSH, LH, and oestradiol levels measured on day 3 of the menstrual cycle.
- Anti-Müllerian hormone.
- Total antral follicle count.

Ovarian volume, ovarian blood flow, and oestradiol E2 should not be used to predict any outcome of fertility treatment[1] [**L1, RGB**].

8.1.2 Imaging Investigations

An ultrasound scan can be used to check ovaries, uterus, and fallopian tubes. The following options should be considered[1,4,8] [**L1, RGA**]:

- Transabdominal or transvaginal ultrasound to evaluate:
    - Ovarian size, function, and reserve.
    - Lesions within uterine cavity.
    - Endometriosis.
    - PCOS.
    - Antral follicle count and development.
- Contrast investigations e.g. hysterosalpingogram, or sonohysterogram are useful for assessing fallopian tubes and uterine cavity.

8.1.3 Laparoscopy and Dye

Laparoscopy and dye can be used to examine women with comorbidities such as a history of PID, previous ectopic pregnancy or endometriosis[1,4,8][**L1, RGA**].

8.2 Further Investigation in Men

8.2.1 Blood Tests

Offer blood tests including HIV, HBsAg, HBsAb, HCV-Ab, Rubella, and Syphilis serology if these tests have not been performed previously[1] [**L1**].

8.2.2 Ultrasound Scans

Consider the following tests[5,9] [**L1, RGA**]:

- Scrotal ultrasound to detect:
  - Obstructions (e.g. dilatation of rete testis, enlarged epididymis with cystic lesions, or an absent vas deferens).
  - Varicocele especially in patients with difficult examination due to obesity, thickened scrotal wall, or a contracted scrotum[31].
  - Testicular dysgenesis (e.g. non-homogeneous testicular architecture and microcalcifications)[32].
  - Testicular tumours.
- Transrectal ultrasound (TRUS), should only be used in men with a low seminal volume and in whom distal obstruction is suspected:
  - Visualisation of the distal genital tract (including the prostate, vas ampulla, seminal vesicles, and ejaculatory ducts).
  - Evaluation of azoospermia, especially in defining an obstructive versus non-obstructive azoospermia.

8.2.3 Magnetic Resonance Imaging

Consider magnetic resonance imaging (MRI) for evaluating the vas ampulla, seminal vesicles, ejaculatory ducts and intra-abdominal segment of the vas deferens[9,33] [**L2, RGA**].

8.2.4 Testicular Biopsy

A routine diagnostic testicular biopsy is not recommended[5,6,34][**L2, RGB**]. Consider testicular biopsy, under either local or general anaesthesia[35] [**L2, RGA**]:

- If obstructive azoospermia is suspected[34]:
  - To confirm the presence of normal spermatogenesis before surgical correction of the obstruction.
- If non-obstructive azoospermia is suspected[5,34]:
  - For spermatozoa extraction for further intracytoplasmic sperm injection (ICSI) treatment.
- If testicular malignancy is suspected[5,34]:
  - Biopsy +/- orchiectomy if malignancy is confirmed in the same setting [**R-GDG**].

8.2.5 Ejaculatory Disorder Tests

If ejaculatory disorders are suspected, consider the following tests[5]:

- Post-ejaculatory urinalysis of centrifuged urine to check for partial retrograde ejaculation.
- TRUS – if suspecting prostatic or ejaculatory duct cysts.
- Microbiological examination, including:
  - Urine tests.
  - Culture of prostatic secretion.
  - Semen culture.
  - Biochemical infection marker tests.

Additional diagnostic work-up should be guided by the history and physical examination findings such as the presence of an abnormal bulbocavernosus reflex, sphincter tone dysfunction, nocturnal emissions, pre- and existent psychological traumas.

8.2.6 Karyotype Testing

Spermatozoa of infertile men show an increased rate of chromosomal abnormalities and DNA damage. The frequency of chromosomal abnormalities increases along with the testicular deficiency[5].

Karyotype analysis is indicated in men with[5]:

- Azoospermia.
- Severe oligozoospermia (<5 x10^6 spermatozoa/mL), who are seeking fertility treatment[5,6].
- Positive family history of recurrent spontaneous abortions, malformations, or mental retardation, irrespective of the sperm concentration [**R-GDG**].

Consider fluorescence in situ hybridisation (FISH) or multicolour FISH studies to confirm chromosomal abnormalities[5] [**L1, RGA**].

Common chromosome abnormalities and genetic defects that may be reviewed before fertility treatment is offered to the couple[5]:

- Klinefelter's syndrome and its variants:
    - Presence of small firm testicles in men with features of androgen deficiency (female hair distribution, scant hair, long arms and legs) should raise the index of suspicion for this condition
    - FISH may be needed to confirm the diagnosis.
- Sperm chromosomal abnormalities such as aneuploidy in sperm, particularly in patients with macrocephaly:
    - Multicolour FISH may be needed to confirm the diagnosis.
- Kallmann syndrome:
    - Presence of hypogonadotropic hypogonadism and anosmia, in a man with other congenital anomalies (facial asymmetry, colour blindness, deafness and maldescended testes) should raise an index of suspicion for this condition.
    - Clinicians should advise genetic screening prior to therapy.
- Mild androgen insensitivity syndrome:
    - Clinical features vary from predominantly female phenotype through ambiguous genitalia, to male phenotype with small penile shaft, perineal hypospadias, and cryptorchidism.
- Microdeletions on the Y-chromosome:
    - AZF deletion screening is required in men with azoospermia and severe oligozoospermia.
    - Testing is not required in men with obstructive azoospermia.
- Cystic fibrosis mutations:
    - Typically seen in Caucasian men with congenital bilateral absence of the vas deferens.
    - CFTR gene mutation screening is indicated in men with unilateral or bilateral absence of the vas deferens with normal kidneys.

Couples with genetic abnormalities and who carry inheritable disease should be offered genetic counselling (see *Section 11.5*)[5] [**L1,RGA**].

9 Categories of Female Infertility

9.1 Ovulatory Disorders

Problems with ovulation are the most common cause of infertility in women[4]. If hormone levels are abnormal, ovulation disorders should be considered[1]:

- WHO Group I: Hypothalamic Pituitary Failure.
- WHO Group II: Hypothalamic-Pituitary-Ovarian Dysfunction.
- WHO Group III: Ovarian Failure.

9.1.1 WHO Group I: Hypothalamic Pituitary Failure

This category of ovulatory disorders includes primary and secondary hypothalamic amenorrhea[1,36].

Hypothalamic amenorrhoea is characterised by[1,36,37]:

- Low gonadotrophins and low oestrogen levels.
- Consequent impairment of follicular development and ovulatory function.

Hypothalamic amenorrhoea may develop as a result of[36–38]:

- Psychological stress.
- Low body mass index.
- Morbid obesity.
- Excessive physical exercise.
- Use of some medications (e.g. antipsychotics, antidepressants).
- Alcohol and illegal drug consumption.
- Hypogonadotropic hypogonadism (e.g. Kallmann's syndrome).

Hypothalamic amenorrhoea may be diagnosed[37] [**L2, RGA**]:

- In women whose menstrual cycle interval is persistently longer than 45 days.
- In women with amenorrhea lasting for more than 3-month.
- When anatomic or organic causes are excluded.

Psychological status and patient's lifestyle should be carefully evaluated if hypothalamic amenorrhoea is suspected[37] [**L2, RGA**].

9.1.2 WHO Group II: Hypothalamic-Pituitary-Ovarian Dysfunction

This category of ovulation disorders predominantly presents as PCOS[1,36]. Symptoms of PCOS include[10,11,39]:

- Irregular menstruation or no menstruation at all.
- Excessive hair growth (hirsutism) on face, chest or back.
- Weight gain or obesity.
- Thinning hair and hair loss from the head.
- Oily skin or acne.
- Insulin resistance and compensatory hyperinsulinemia.
- Low-grade inflammation.

PCOS can be diagnosed based on the presence of at least two of the criteria listed below[10,36]. All other disorders characterised by androgen excess should be previously excluded:

- Hyperandrogenism determined by the presence of total or free testosterone excess or hirsutism.
- Ovarian dysfunction characterised by oligo-amenorrhea and chronic anovulation.
- Detection of a specific polycystic ovarian morphology by ultrasound.

9.1.3 WHO Group III: Ovarian Failure

Premature ovarian failure is the cessation of ovarian function before 40 years of age[40]. The condition is often accompanied by menopausal symptoms, including[40]:

- Hot flushes.
- Excessive sweating.
- Hair loss.
- Skin and mucous membrane dryness.
- Secondary amenorrhoea.

The following causes of premature ovarian failure may be distinguished[40]:

- Genetic causes (Turner syndrome, fragile X syndrome or pseudohypoparathyroidism type 1a).
- Autoimmune causes (production of anti-ovarian antibodies, thyroiditis, Addison's disease).
- Enzymatic deficiencies (e.g. galactosaemia).
- Oncologic treatment (radio- or chemotherapy).
- Surgical treatment.
- Environmental causes:
    - Viral infections (e.g. mumps virus, *Cytomegalovirus, Varicella* zoster virus).
    - Bacterial and protozoan infections (e.g. tuberculosis, shigella infection and malaria).
    - Smoking.
- Unknown causes.

9.2 Obstructive Disorders and Tubal Infertility

If female hormone levels are within the normal range, consider male infertility (see *Section 11*)[5]. If male fertility is normal, consider a female obstructive disorder[1].

9.2.1 Fibroids

Non-cancerous uterine fibroids (leiomyomas or myomas) can affect reproductive organs in women and decrease fertility, especially submucous uterine fibroids and intramural leiomyomas[4,41].

Fibroids may physically block a fallopian tube or function via other mechanisms[4,41]:

- Alternations in uterine function (e.g. flawed vasculature, increased contractility).
- Changes in the normal uterine anatomy
- Distortions of embryo implantation.
- Local hormonal changes induced by fibroids.
- Early pregnancy losses.

9.2.2 Pelvic Inflammatory Disease

PID is an infection of the upper female genital tract frequently caused by STIs[4,42]. The most frequent pathogens are[42]:

- *Chlamydia trachomatis.*
- *Neisseria gonorrhoea.*
- Anaerobic organisms.

Tubal damage from PID causes inflammation and long-term tubal changes including[42]:

- Fimbrial agglutination.
- Fimbrial phimosis.

- Tubal obstruction.
- Hydrosalpinx.
- Salpingitis isthmica nodosa.

9.2.3 Endometriosis

Endometriosis is a gynaecological condition in which endometrial tissue growth is found outside the uterus[4,42]. Endometriosis can cause infertility[1,4,42] but pathophysiology of the process is not fully understood[42].

Endometriosis results in[4,42]:

- Chronic inflammation produced by the ectopic endometrium.
- Scarring similar to that observed in PID.
- Damage to the ovaries.
- Distal tubal adhesive disease and occlusion.
- Significant pain and avoidance of sexual intercourse.

9.2.4 Pelvic Tuberculosis

Pelvic tuberculosis is uncommon in developed countries but should be considered in expatriates, especially in those with pulmonary tuberculosis[42]. Pelvic tuberculosis usually results into salpingitis of both fallopian tubes and resembles PID in later stages[42]. Large, caseous pyosalpinges are characteristic of tuberculosis infection[42].

9.2.5 Adhesions from Surgery

In some cases, adhesions from abdominal and pelvic surgeries can lead to infertility[42].

Inflammatory bowel diseases (e.g. Crohn's disease or ulcerative colitis) do not affect the chance of conception[42], however, medication adherence to achieve preconception disease control and maintain corticosteroid-free remission, is important throughout pregnancy [**R-GDG**].

9.3 Unexplained Female Infertility

In some cases, no cause of infertility can be identified in the female partner[1,4,13]. Management of unexplained infertility in women is described in *Section 10.5*.

10 Management of Female Infertility in Specialist Care

The management of female infertility depends upon the underlying cause[1,23,48] and is discussed in the sections below.

10.1 Optimisation of Body Weight

Professional advice on body weight management (see *Sections 6.2.3*) should be given to[1,3,61] [**L1, RGA**]:

- Women with hypothalamic pituitary failure (WHO Group I Ovulation Disorders).
- Women with hypothalamic-pituitary-ovarian dysfunction (WHO Group II Ovulation Disorders).

10.2 Psychological Support

Consider referral to a Clinical Psychologist or fertility support groups to help patients to make decisions about alternative parenting options after unsuccessful IVF treatment [19] [**L1, RGA**].

10.3 Pharmacological Intervention

10.3.1 Hypothalamic Pituitary Failure

If behavioural interventions are not effective in women with hypothalamic pituitary failure (WHO Group I Ovulation Disorders), they may be offered GnRH by pulsatile infusion pump or gonadotrophins with LH activity to induce ovulation[1] [**L1, RGA**].

10.3.2 Hypothalamic-Pituitary-Ovarian Dysfunction

If behavioural interventions are not effective in women with hypothalamic-pituitary-ovarian dysfunction (WHO Group II Ovulation Disorders), one of the following treatments should be offered [1,10,11] [**L1, RGA**]:

- Clomiphene citrate:
    - The recommended dose is 50 mg daily for 5 days[43]. The dose should be increased only in those patients who do not ovulate in response to cyclic 50 mg doses. Treatment should not exceed 6 months[1] [**L1, RGC**].
    - Ultrasound monitoring should be performed during at least the first cycle of treatment to ensure that the dose minimises the risk of multiple pregnancy[1] [**L1, RGA**].
    - In patients resistant to clomiphene, consider one of the following[1,11] [**L1, RGA**]:
        - Laparoscopic ovarian electrocauterisation (see *Section 10.4.1*).
        - A combination of clomiphene and metformin.
        - Gonadotrophins.
    - In patients with PCOS who are resistant to clomiphene[1] [**L1, RGB**]:
        - Pulsatile GnRH is not recommended.
        - A combination of adjuvant growth hormone and GnRH agonist and/or human menopausal gonadotrophin is not recommended.
- Metformin:
    - Review side effects (e.g. nausea, vomiting, other gastrointestinal disturbances)[44].
    - Can only be used as a second-line treatment in women with PCOS, after clomiphene citrate and letrozole[45].
- A combination of clomiphene citrate and metformin.

All women offered ovulation induction with gonadotrophins[1] [**L1**]:

- Should be informed about the risk of multiple pregnancy and ovarian hyperstimulation syndrome (OHSS) (see *Section 13.2.9.1*).
- Should undergo ovarian ultrasound monitoring to measure follicular size and number and to reduce the risk of multiple pregnancy and OHSS.

A combination of gonadotrophins and GnRH agonist is not recommended in women with PCOS due to the increased risk of OHSS[1] [**L1, RGC**]. Letrozole[46] can be considered to stimulate ovulation in patients with PCOS[10,11,39,45,47].

10.3.3 Hyperprolactinaemia

Women with ovulatory disorders due to idiopathic hyperprolactinaemia should be offered treatment with dopamine agonists (e.g. bromocriptine and cabergoline)[1] [**L1, RGA**].

10.3.4 Fibroids

Consider pharmacological treatment to shrink fibroids[12] [**L1, RGA**]:

- GnRH analogues (e.g. goserelin acetate):
    - Stops the menstrual cycle during treatment.
    - Makes menstruation less painful.
    - Improves symptoms of frequent urination and constipation.
    - Can cause menopause-like side effects and osteoporosis.
    - Consider using to shrink fibroids prior to surgery.
    - May be prescribed on a short-term basis (max 6 months at a time).
- Ulipristal acetate:
    - Review contradictions before prescribing.
    - Regularly perform blood tests to monitor liver function.

If treatment with medication is ineffective, consider surgical removal of the fibroids (see *Section 10.4.3*)[12] [**L1, RGA**].

10.4 Surgical Intervention

Young patients should be counselled about oocyte cryopreservation prior to ovarian surgeries[48] (see *Section 15*).

10.4.1 Laparoscopic Ovarian Electrocauterisation (Drilling)

Laparoscopic ovarian electrocauterisation (drilling) may be considered as a treatment option in women with PCOS who do not respond to medication[1,11] [**L1, RGA**]:

- General anaesthesia is required [**R-GDG**].
- Testosterone and LH levels decrease after the procedure; FSH levels increase.
- Correction of hormone imbalance can restore the function of the ovaries.

Patient undergoing this procedure should be informed that [**R-GDG**]:

- For some women with PCOS, ovarian drilling may not correct the ovulatory dysfunction or menstrual irregularity.
- There are also risks to fertility, especially if there is excessive damage to the ovary during ovarian drilling, this may lead to premature menopause or even formation of tubal adhesions.

10.4.2 Hysteroscopic Resection

A hysteroscopic resection can be used to remove submucosal fibroids and is suitable for women who want to have children in the future[12,49,50] [**L1, RGA**]:

- No incisions are needed.
- The resection may be carried out under general or local anaesthesia.
- It is unclear whether clinical pregnancy rates improve after the surgery.
- Consider hysteroscopic morcellation in patients with serious complications.

10.4.3 Laparoscopic Surgeries

Laparoscopy can be used to remove or destroy areas of endometriosis tissue and improve fertility in minimal and mild cases[48,51,52] [**L1, RGA**]:

- Ovarian reserve should be considered prior to surgery[48].
- The procedure should be carried out under general anaesthesia[51].
- Consider ovarian cystectomy to remove ovarian cysts (endometriomas) laparoscopically[48,51,52].
- Hormone treatment before and after surgery may be required[51].

Laparoscopic myomectomy is alternative to abdominal myomectomy (see *Section 10.4.4*) to remove fibroids[49] [**L1, RGA**].

Laparoscopic salpingectomy should be considered for women with tubal diseases[1,42] [**L1, RGA**]:

- For mild tubal disease consider tubal surgery as a treatment option.
- Women with proximal tubal obstruction should be offered selective salpingography and tubal catheterisation or hysteroscopic tubal cannulation.
- Women with hydrosalpinges should be offered salpingectomy before IVF treatment.

10.4.4 Abdominal Myomectomy

Abdominal myomectomy may be considered in women with multiple or extremely large fibroids which cannot be removed with endoscopic approaches [12,49] [**L1, RGA**]:

- The number, location, and type of fibroids should be evaluated before the surgery to confirm that myomectomy is suitable.
- Should be carried out under general anaesthesia.

10.4.5 Hysteroscopic Adhesiolysis

Hysteroscopic adhesiolysis should be offered to women with amenorrhoea and intrauterine adhesions as it is likely to restore menstruation and improve fertility[1] [**L1, RGA**].

10.5 Unexplained Female Infertility

Treatment of infertility with unknown causes remains largely empirical[13]. Expectant management is recommended in good-prognosis couples (based on age and duration of infertility)[13] [**L1, RGA**].

Consider the following treatments options in women with idiopathic infertility[13] [**L1, RGA**]:

- IUI (see *Section 13.1*) with:
  - Oral agents (letrozole or clomiphene citrate).
  - Gonadotropin ovarian stimulation.
- IVF (see *Section 13.2*):
  - If 3 cycles of IUI with ovarian stimulation were unsuccessful.
  - ICSI in addition to IVF is not recommended for routine use[13] [**L1, RGB**].

The following treatments are not recommended in women with idiopathic infertility[13] [**L1, RGB**]:

- Laparoscopic surgery in the absence of evidence for tubal or other pelvic pathology.
- Natural-cycle IUI.
- Clomiphene citrate alone.
- Aromatase inhibitors alone.
- Ovarian stimulation with gonadotropin.

10.6 Management of Comorbidities

Obesity in patients trying to conceive should be managed according to the MOPH NCG on *The Management of Obesity in Adults*[53] [**L1, RGA**].

Women with PCOS trying to conceive should be informed about an increased risk of pregnancy complications including hypertension, pre-eclampsia, gestational diabetes, and miscarriage[11] [**L1**].

Women having symptoms caused by fibroids should receive appropriate assessment and treatment to help relieve the symptoms[12] [**L1, RGA**]. If medications are ineffective, surgical interventions may be required[12] [**L1, RGA**] (see *Section 10.4*).

Patients with a positive STI, HIV, hepatitis B, or hepatitis C test, and their sexual partners, should be offered specialist advice and referred for psychological support from therapists or psychologists with experience in these areas and appropriate clinical management[1] [**L1, RGA**].

Inform patients with endometriosis that it is incurable, but there are treatments that can help with symptoms[51]. Offer the following treatments[48,51] [**L1, RGA**]:

- NSAIDs for the pain management.
- Hormone medicines and contraceptives (Note that hormonal treatment will not improve spontaneous pregnancy rates[52]):
  - Combined oral contraceptive pill.
  - Contraceptive patch.
  - Intrauterine contraceptive devices.
  - GnRH.
- Surgery to remove endometriotic tissue (see *Section 10.4*).
- Surgery to remove organs or their parts affected by endometriosis (e.g. hysterectomy).
- Psychological support [**R-GDG**].

11 Categories of Male Infertility

11.1 Sperm Disorders

11.1.1 Oligozoospermia and Azoospermia

Sperm deficiency can be classified into three clinically significant categories based on the number of spermatozoa identified in the centrifuged pellet of two separate semen samples)[1,5,6]:

- Oligozoospermia: <15 x10^6 spermatozoa/mL.
- Severe oligozoospermia: <5 x10^6 spermatozoa/mL.
- Azoospermia: Absence of spermatozoa in the ejaculate[54].
    - Non-obstructive azoospermia (sperm production is impaired):
        - Usually diagnosed in men with significant elevation in FSH (>7.6 mIU/mL) and testicular failure.
        - Primary testicular failure (testicular azoospermia) includes disorders of spermatogenesis intrinsic to the testes; or
        - Secondary testicular failure (pre-testicular azoospermia) includes endocrine abnormalities negatively affecting spermatogenesis.
    - Obstructive azoospermia (sperm are produced but get blocked in the reproductive tract):
        - Usually diagnosed in men with normal size testes and normal serum FSH levels (≤7.6 mIU/mL).
        - Post-testicular azoospermia is associated with ejaculatory dysfunction (see *Section 11.3*) or ductal obstruction that impairs sperm transit.

Refer to the table below to distinguish between different types of azoospermia[6].

Aetiology	Semen Volume	Testosterone	FSH
Pre-Testicular Azoospermia			
Hypogonadotropic Hypogonadism	Normal or decreased	Decreased	Decreased
Exogenous Androgens		Any	
Testicular Azoospermia			
Primary Testicular Failure	Normal	Normal or Decreased	Normal or Increased
Genetic Aetiology			
Varicocele			
Post-Testicular Azoospermia			
Vasectomy	Normal	Normal	Normal
Epididymal Obstruction			
Ejaculatory Duct Obstruction	Decreased	Normal	Normal or increased
Ejaculatory Dysfunction			

Table 11.1: Classification Scheme of Azoospermia Subtypes[6].

Azoospermia and extreme cases of oligozoospermia are usually associated with[5,16] [**L1**]:

- Reduced hormone production (see *Section 11.2*).
- Genital infections (including infection of the prostate gland).
- Genetic abnormalities (e.g. Klinefelter syndrome) (see *Section 11.5*).
- Obstructions and structural problem of the male genital tract.

- Obstructive lesions of the seminal tract.
- Varicocele (see *Section 11.4*).
- Surgery scarring or hernia repairs.
- Overweight or obesity.

Often, oligozoospermia, asthenozoospermia, and teratozoospermia occur simultaneously as oligo-astheno-teratozoospermia (OAT) syndrome[5].

11.1.2 Asthenozoospermia

Asthenozoospermia occurs when sperm have poor motility in at least two semen test[5,55]:

- Total motility <40%.
- Progressive motility <32%.

Complete or severe asthenozoospermia is characterised by total sperm immobility and is usually idiopathic[55].

The main causes of reduced sperm motility include[5,14]:

- Genetic.
- Organic:
    - Leukocytospermia.
    - Varicocele.
    - Genitourinary tract infections.
    - Chronic inflammations.
- Chemical:
    - Chemical pesticides.
    - Air pollution.
    - Oxidative stress.

Reversible causes of asthenozoospermia such as varicocele and infection can be treated. Also, clomiphene citrate has been shown to improve motility in some cases. Assisted conception may be considered (see *Section 13*). Idiopathic causes usually do not respond to treatments [**R-GDG**]

11.1.3 Teratozoospermia

Teratozoospermia is the presence of spermatozoa with abnormal morphology and <4% of normal forms (as per Kruger criteria)[5,56].
Three types of teratozoospermia are recognised[56]:

- Polymorphic teratozoospermia
- Macrozoospermia (macrocephalic sperm head syndrome):
- Globozoospermia (round-headed sperm syndrome):

The main cause of the defect is idiopathic[56]. No treatment is available. Assisted conception may be considered (see *Section 13*).

11.2 Hypogonadism

Hypogonadism is characterised by impaired testicular function and an abnormally low level of testosterone[4,5]. It can be subdivided into three main categories[5]:

- Primary (hypergonadotropic) hypogonadism due to testicular failure results from[5]:
  - Anorchia.
  - Maldescended testes.
  - Genetic and chromosomal anomalies.
  - Trauma.
  - Testicular torsion.
  - Surgery or medications.
  - Exogenous factors (toxins, heat, or occupational hazards).
  - Systemic diseases (liver cirrhosis, or renal failure).
  - Testicular tumours.
  - Varicocele.
- Secondary (hypogonadotropic) hypogonadism caused by insufficient GnRH and/or gonadotropin secretion and results from[4,6]:
  - Hypothalamic disorders (e.g. Kallmann syndrome).
  - Congenital pituitary disorders.
  - Empty sella syndrome.
  - Acquired pituitary disorders:
    - Functional tumours.
    - Non-functional tumours.
  - Illicit anabolic androgenic steroid use.
  - Testicular feminisation.
- Androgen insensitivity (end-organ resistance).

If low gonadotropins and bilateral testicular atrophy is detected, hypogonadotropic hypogonadism should be considered[6] [**L1, RGA**]. If low levels of gonadotropins and sex steroid observed in the absence of anatomical or functional abnormalities of the hypothalamic-pituitary-gonadal axis, idiopathic hypogonadotropic hypogonadism should be considered[6] [**L1, RGA**]. Management of hypogonadotropic hypogonadism is descried in *Section 12.3.3*.

11.3 Ejaculatory Dysfunction

Ejaculatory dysfunction occur when the patient experiences difficulties in releasing semen during sex[4]. Management of ejaculatory dysfunction is described in *Section 12.3*.

11.3.1 Anejaculation

Anejaculation is a complete absence of antegrade or retrograde ejaculation in approximately half of attempts at intercourse[5,14]:

- It is usually associated with a normal orgasmic sensation.
- It is always associated with central or peripheral nervous system dysfunction or with drugs.

The main causes of anejaculation and retrograde ejaculation (see *Section 11.3.1 and 11.3.2*) include[5]:

- Neurogenic:
  - Spinal cord injury.
  - Cauda equina lesions.
  - Multiple sclerosis.
  - Autonomic neuropathy.

    - Retroperitoneal lymphadenectomy.
    - Sympathectomy or aortoiliac surgery.
    - Prostate, colorectal, and anal surgery.
    - Parkinson´s disease.
    - Diabetes mellitus.
    - Psychological issues, depression, or anxiety.
- Pharmacological:
    - α1-adrenoceptor antagonists.
    - Antipsychotics and antidepressants.
    - Alcohol.
    - Antiandrogens.
    - Ganglion blockers.
- Urethral:
    - Ectopic ureterocoele.
    - Urethral stricture.
    - Urethral valves or verumontaneum hyperplasia.
- Endocrine:
    - Hypothyroidism.
    - Hypogonadism (see *Section 11.2*).
    - Hyperprolactinaemia.
- Bladder neck incompetence:
    - Congenital defects or dysfunction of hemitrigone.
    - Bladder neck surgery.
    - Prostatectomy.

11.3.2 Retrograde Ejaculation

Retrograde ejaculation is the total or partial absence of antegrade ejaculation[5]:

- It occurs when semen is passed backwards through the bladder neck into the bladder[5,14].
- It may be associated with a normal or decreased orgasmic sensation[5].
- Symptoms include[14]:
    - Small semen quantity.
    - Cloudy urine after having sex.

11.3.3 Anorgasmia

Anorgasmia is the inability to reach orgasm and, therefore, ejaculate[5].

Delayed ejaculation is a mild form of anorgasmia[5]:

- Ejaculation is usually delayed for 30-60 minutes[14].
- Abnormal stimulation of the erect penis may be required[5].

The main causes of delayed ejaculation include[5,14]:

- Psychological:
    - Depression.
    - Stress.
    - Relationship problems.
    - Anxiety about sexual performance.
    - Strict upbringing and beliefs about sex.
    - Traumatic sexual experience.
    - Fear of causing pain to partner (where partner does experience pain).

- Neurogenic:
    - Type 1 diabetes mellitus.
    - Spinal cord injuries.
    - Multiple sclerosis.
- Organic:
    - Prostatitis-related.
    - Associated with erectile dysfunction.
- Surgery to the bladder or prostate gland.
- Increasing age.
- Pharmacological:
    - Antidepressants (including selective serotonin re-uptake inhibitors – SSRIs).
    - Beta-blockers.
    - Antipsychotics.
    - Muscle relaxants (e.g. baclofen).
    - Powerful analgesics (e.g. methadone).

11.3.4 Asthenic Ejaculation

Asthenic ejaculation an altered propulsive phase, with a normal emission phase[5]:

- It is usually associated with a decreased orgasmic sensation.
- Rhythmical contractions associated with ejaculation are missing.
- Quality of semen is usually unaffected.

11.3.5 Premature Ejaculation

Premature ejaculation always or nearly always occurs prior to, or within approximately one minute, of vaginal penetration[5]:

- The patient is unable to delay ejaculation.
- The patient experiences negative personal consequences:
    - Distress or depression
    - Anxiety.
    - Frustration.
    - Avoidance of sexual intimacy.
- Quality of semen is usually unaffected.

Occasional episodes of premature ejaculation can normally occur and should not cause a concern[14]. Further investigation and assessment are recommended when premature ejaculation occurs in more than half of attempts at intercourse[14] [**L1, RGA**].

The main causes of premature ejaculation include[5,14]:

- Psychological (similar to delayed ejaculation, see *Section 11.3.3*).
- Organic:
    - Incomplete spinal cord lesion.
    - Iatrogenic penile nerve damage.
    - Associated with prostate problems.
    - Thyroid disfunction.
    - Increased sensitivity of the penis.
- Pharmacological:
    - Antihypertensives.
    - Antipsychotics.
    - Recreational drugs.

11.4 Varicocele

Varicocele is abnormal dilation and enlargement of the scrotal venous pampiniform plexus[17]. The following types of varicocele can be distinguished[5]:

- Subclinical
  - Not palpable or visible at rest or during Valsalva manoeuvre.
  - Can be detected by special tests (e.g. Doppler ultrasound studies, usually <3mm in diameter).
- Grade 1:
  - Palpable during Valsalva manoeuvre, but not otherwise.
- Grade 2:
  - Palpable at rest.
  - Not visible.
- Grade 3:
  - Palpable and visible at rest.

The possibility of renal cell carcinoma should always be considered and evaluated in case of right-sided varicocele[17] [**L2, RGA**]. Management and treatment options for varicocele are described in *Section 12.4*.

11.5 Genetic Disorders

Chromosomal abnormalities and genetic disorders that may result in male infertility are listed in *Section 8.2.6*. Couples with a genetic abnormality found on clinical or genetic investigation and in patients who carry a (potential) inheritable disease should be offered appropriate genetic counselling before treatment[5] [**L1, RGA**]. No treatment is available. Assisted conception may be considered (see *Section 13*).

11.6 Male Accessory Gland Infection

Although urethritis and prostatitis are not clearly associated with impaired natural conception, the persistent inflammatory activity in male accessory gland may still reduce fertility[5] [**L1, RGB**]. Inflammation due to orchitis and epididymitis may also negatively affect fertility[5] [**L1, RGB**].

If infection is suspected, repeated semen analysis and semen culture are required to confirm pyospermia and identify pathogenic microorganisms[5]. If infection is caused by *Neisseria gonorrhoea* or *Chlamydia trachomatis*, both partners should undergo treatment[5] [**L1, RGA**]. Treatment options are described in *Section 12.3.4*.

11.7 Germ Cell Malignancy

Testicular germ cell tumour (TGCT) is the most common malignancy in Caucasian men 15-40 years old, especially in those with[5]:

- Reduced fertility.
- Cryptorchidism.
- Hypospadias.
- Dysgenic testes.
- Testicular microcalcification.

View Pathway

11.8 Testicular Microcalcification

Although relationship between testicular microcalcification and infertility is unclear, abnormalities caused by the microcalcification can reduce chances of conception[5].

Testicular microcalcification should be considered premalignant and is also associated with the following clinical conditions[5] [**L1, RGA**]:

- Cryptorchidism.
- Testicular dysgenesis.
- Testicular torsion and atrophy.
- Klinefelter's syndrome.
- Hypogonadism.
- Male pseudohermaphroditism.
- Varicocele.
- Epididymal cysts.
- Pulmonary microcalcification.
- Non-Hodgkin's lymphoma.

11.9 Idiopathic Male Infertility

In some cases, there is no cause of infertility can be identified in either the male partner[1,4,13]. Management of unexplained infertility in men is described in *Section 12.5*.

12 Management of Male Infertility in Specialist Care

The management of male infertility should be directed to the underlying cause, where this is identifiable[4].

12.1 Lifestyle Modification

Provide the following lifestyle modification advice to patients who are diagnosed with idiopathic male infertility [**R-GDG**]:

- Smoking cessation.
- Avoid alcohol consumption.
- Avoid drug abuse.
- Avoid any activity that can trigger an increase in scrotal temperature such as extended driving, hot bath, saunas, and long office hours.
- Regular aerobic exercise.
- Workplaces should be well aerated and strict adherence to safety rules maintained.

12.2 Psychological Treatment of Ejaculatory Dysfunction

Treatment of psychological aspects of ejaculatory failure can restore fertility without the need for invasive methods[1]. The following therapies may help to manage ejaculatory problems[5,14] [**L1, RGB**]:

- Behavioural therapy.
    - Using a thick condom to decrease sensation.
    - Introducing poses with decreased sensitivity.
    - Take breaks during sex.
    - Distraction technique.
    - "Squeeze" and "stop-go" techniques.
- Cognitive behaviour therapy.
- Couples therapy.
- Sex therapy (psychotherapy and structured changes in sex life).

Psychosexual therapy is not recommended for anorgasmia[5] [**L1, RGB**].

12.3 Pharmacological Intervention

12.3.1 Sperm Disorders

Gonadotrophin hormones should be considered in men with oligo- and azoospermia to stimulate the production of sperm[1,16] [**L1, RGA**].

Some natural antioxidants such as vitamins (E, C and carotenoids) have been shown to have beneficial effects in spermatogenesis, a thorough work-up is required to identify patients that need to be supplemented[57,58].

Consider the following treatments options in men with idiopathic OAT syndrome[5][**L1, RGB**]:

- Clomiphene citrate.
- Tamoxifen.
- Gonadotrophins (HMG/rFSH/hpFSH).
- Oral antioxidants.

12.3.2 Ejaculatory Dysfunction

Consider the following medications to manage premature ejaculation[5,14,15] [**L1**]:

- SSRIs:
  - Paroxetine.
  - Sertraline.
  - Fluoxetine.
- Dapoxetine.
- Phosphodiesterase-5 inhibitors (e.g. sildenafil).
- Topical anaesthetics (e.g. lidocaine or prilocaine).

Pseudoephedrine may be used in retrograde ejaculation[14] [**L1, RGB**]. Consider tamsulosin along with antidepressant treatment if ejaculation is associated with pain[5] [**L1, RGA**]. Drug treatment is not recommended for anejaculation caused by lymphadenectomy and neuropathy[5] [**L1, RGB**].

12.3.3 Hypogonadotropic Hypogonadism

Consider the management of hypogonadotropic hypogonadism with the following medications[1,5] [**L1, RGA**]:

- Gonadotrophin hormones:
  - Human chorionic gonadotropin.
  - Human menopausal gonadotropins.
  - Recombinant follicle-stimulating hormone.
  - Highly purified FSH.
- Anti-oestrogens and aromatase inhibitors may help in elevating FSH and LH in obese male with low testosterone level caused by aromatase-mediated conversion of testosterone to oestradiol.

Testosterone suppresses pituitary production of LH and FSH, therefore, replacement therapy is not recommended in patients with hypogonadism who wish to conceive[5] [**L1, RGC**].

12.3.4 Infectious Diseases

Antibiotic treatment should be offered to men with leucocytes in their semen and an identified infection[1] [**L1, RGA**].

12.3.5 Idiopathic Semen Abnormalities

Idiopathic semen abnormalities should **not** be treated with[1] [**L1, RGB**]:

- Androgens.
- Bromocriptine.
- Kinin-enhancing drugs.

12.4 Surgical Intervention

Microsurgical vasovasostomy or vasoepididymostomy should be considered in patients with azoospermia caused by vasal or epididymal obstruction[5] [**L1, RGA**].

The following treatment options may be considered in patients with varicocele[5,17] [**L1, RGA**]. Avoidance of the vas deferens and the testicular artery during surgery is mandatory[17] [**L1, RGC**].

- Varicocelectomy:
  - Microsurgical (the most effective method)
  - Open
  - Laparoscopic
- Antegrade or retrograde sclerotherapy
- Retrograde embolisation

12.5 Idiopathic Male Infertility

Treatment of infertility with unknown causes remains largely empirical and uncertain[5]. Patients should be informed about the high risk of bias and heterogeneity of available recommendations[5][**L1**].

The following treatments are not recommended in men with idiopathic infertility[1,5] [**L1, RGB**]:

- Androgens.
- Bromocriptine.
- α-blockers.
- Systemic corticosteroids.
- Magnesium supplementation.
- Kinin-enhancing drugs.

12.6 Management of Comorbidities

Obesity in patients trying to conceive should be managed in accordance with the MOPH NCG on *The Management of Obesity in Adults*[53] [**L1, RGA**].

Patients with a positive STI, HIV, hepatitis B, or hepatitis C test and their sexual partners should be offered specialist advice and referred for psychological support and appropriate clinical management[1] [**L1, RGA**].

13 Assisted Conception

13.1 Intrauterine Insemination

IUI is a type of artificial insemination that involves the introduction of spermatozoa into a female's uterine cavity to facilitate fertilisation[4].

13.1.1 General Principles

Patients scheduled for artificial insemination should be informed that[1] [**L1**]:

- The procedure should occur around ovulation time.
- Using fresh sperm is associated with higher conception rates than frozen-thawed sperm.
- Intrauterine insemination is associated with higher conception rates than intracervical insemination.

13.1.2 Eligibility Criteria for IUI

Indications for IUI are[1,18] [**L1, RGA**]::

- Unable to have vaginal intercourse (e.g. due to physical disability or a psychosexual problem).
- Unexplained infertility.
- Mild male factor infertility.
- Mild endometriosis.
- Require specific consideration in relation to methods of conception (e.g. after sperm washing if man is HIV positive).

NB: 3-6 cycles of IUI should be offered to couples without a clear fertility dysfunction before IVF is considered[1] [**L1**].

IUI should **not** be routinely offered to couples if [1,18] [**L1, RGB**]:

- Tubal causes of infertility are present in the female partner.
- Severe male factor infertility is present.

13.2 In-Vitro Fertilisation

During IVF, eggs retrieved from the woman's ovaries are fertilised with sperm in a laboratory and the resulting viable embryo is then introduced into the woman's uterus for development[1,4,19].

13.2.1 General Principles

Patients with fertility problems undergoing IVF treatment should be[1,19][**L1, RGA**]:

- Informed of the risks and benefits of IVF.
- Informed that the treatment can be both physically and emotionally demanding.

IVF should be carried out using the patient's eggs and her spouse's sperm[1,19] [**L1**]. Utilisation of donor gametes and embryos is not permitted in Qatar [**R-GDG**].

A full cycle of IVF treatment should comprise one episode of ovarian stimulation and the transfer of any resultant fresh and frozen embryo(s)[1] [**L1**]. When required, patients should be offered psychological support to help them to cope with the stress[19] [**L1, RGA**].

13.2.2 Eligibility Criteria for IVF

IVF (with or without ICSI) can be offered to women 18-45 years old who have not conceived after 1 year of regular unprotected intercourse if all of the following conditions have been met [**R-GDG**]:

- The patient's BMI is <30.
- The patient's HBA_{1C} level is <6.5%.
- The patient's TSH level is within normal limits.
- The patient has had 3 or fewer caesarean sections.
- If the patient is aged over 40 years, pregenetic screening has been completed.

IVF should be offered after 3 unsuccessful IUIs [**R-GDG**]. IVF is not recommended for women >45 years old due to low chances of successful pregnancy[1,19] [**L1, RGB**].

13.2.3 Risks Associated with IVF

Patients undergoing IVF should be informed about the potential risks of the procedure before treatment including[19,42]

- Ovarian hyperstimulation syndrome (OHSS).
- Multiple pregnancy and births.
- Premature delivery and low birth weight.
- Miscarriage.
- Ectopic pregnancy.
- Physical, and emotional stress.
- Complications resulting from the egg retrieval procedure such as bleeding, infection, visceral or blood vessel damage.

13.2.4 Pre-Treatment in IVF

Before IVF treatment, the patient's natural menstrual cycle should be supressed with either oral contraceptives, or progestogen in patients that are not following a long down-regulation protocol[1,19] [**L1, RGA**].

Protocols with GnRH antagonists are effective in preventing a premature surge of LH and induce a shorter and more cost-effective ovarian stimulation compared to the long agonist protocol[59,60].

Once the natural menstrual cycle is suppressed, patients should receive either GnRH agonist down-regulation or GnRH antagonists as part of gonadotrophin-stimulated IVF treatment cycles[1] [**L1, RGA**]. Only patients with low risk of OHSS can receive GnRH agonists for down regulation and follow a long down-regulation protocol[1,19] [**L1, RGA**]. The following medications are recommended for ovarian stimulation[1,19,61] [**L1, RGA]**:

- Urinary gonadotrophins (hMG, HP-hMG, HP-FSH, U-hCG); or
- Recombinant gonadotrophins (rec-hFSH, long acting FSH, rec-hLH, 2 rec-hFSH: 1 rec-hLH, rec-hCG).
- Alternatively, clomiphene citrate in combination with gonadotropin or FSH may be considered in patients with poor ovarian reserve and poor responders[62] [**L2, RGB**].
- Growth hormone can be considered in individual cases but is not routinely recommended as adjuvant treatment[1] [**L1, RGB**].

An individualised starting dose of FSH is recommended[1] [**L1, RGA**]. The dose should not exceed 450 IU/day[1] [**L1, RGC**]. The effect of ovarian stimulation should then be monitored with vaginal ultrasound scans[1,19] [**L1, RGA**]. In some cases, blood tests may be required[19].

13.2.5 Oocyte Retrieval

Transvaginal retrieval of oocytes should be performed under conscious sedation[1,19] [**L1, RGA**]. Women who have developed 3 or more follicles prior to oocyte retrieval should be offered follicle flushing [**R-GDG**]. Assisted hatching can be used if indicated [**R-GDG**]:

- Thick zona pellucida
- Recurrent implantation failure.

13.2.6 Embryo Transfer Strategies

Embryo transfer is the final step of the IVF or ICSI treatment cycles and is often considered the simplest[19] [**L1**]. The embryo transfer:

- May be performed without sedation[19] [**L1**].
- Should be ultrasound-guided[1] [**L1, RGA**].
- Is not recommended if endometrium thickness is <5 mm[1] [**L1, RGB**].
- Should be performed using a soft embryo transfer catheter to improve IVF-embryo transfer pregnancy rates[63][**L1**].

The quality of embryos should be evaluated at both cleavage and blastocyst stages[1] [**L1**].

- The number of embryos transferred should be agreed upon by the physician and the patient before commencement of the treatment [19,64]. Informed consent should be obtained, and the information documented in the clinical record.

The following recommendations should be considered during embryo transfer (*Table 13.2.6*)[64]:

Patients with a good prognosis:

- Transfer of a euploid embryo has the best prognosis in patients of all ages and should be limited to one
- Patients younger than 35 years of age should be advised to receive a single embryo transfer, irrespective of the embryo stage.
- For patients between 35 -37 years of age, a single-embryo transfer should be strongly considered.
- For patients between 38 - 40 years of age, no more than three cleavage-stage embryos or two blastocysts should be transferred.
- In patients where euploid embryos are available, a single-blastocyst embryo transfer should be performed.
- Patients that are 41-42 years old should not receive more than four cleavage-stage embryos or three blastocysts. If euploid embryos are available, then a single blastocyst transfer should be performed.

Good Prognostic Embryos	Age (Years)			
Cleavage-Stage Embryos	**< 35**	**35-37**	**38-40**	**41-42**
Euploid	1	1	1	1
Other Favourable Prognosis*	1	1	≤3	≤4
All Others	≤2	≤3	≤4	≤5
Blastocysts				
Euploid	1	1	1	1
Other Favourable Prognosis*	1	1	≤2	≤3
All Others	≤2	≤2	≤3	≤3

Table 13.2.6: Recommended Limits to the Number of Embryos Transferable [64].

**Other Favourable Prognosis* implies any ONE of the underlisted criteria:*

- Fresh Embryo Transfer Cycle:
  - 1 or more high-quality embryos available for cryopreservation
  - Previous life birth after an IVF cycle.
- Frozen Embryo Transfer Cycle:
  - Availability of vitrified day-5 or-6 blastocysts.
  - Euploid embryos.
  - First frozen embryo transfer cycle.
  - Previous live birth after an IVF cycle.

Other Circumstances[64]:

- Patients who do not meet criteria for a favourable prognosis (See *Section 13.2.8*) in each of the above age groups) may have an additional embryo transferred based on individual circumstances.
- The patient must be counselled regarding the additional risk of twin or higher-order multiple gestation.
- In circumstances in which the number of embryos or blastocysts transferred exceeds recommended limits, both counselling and justifiable reasons for this should be recorded in the patient's medical record.
- Patients with a comorbid condition for which a multiple pregnancy may lead to increased risk of significant morbidity, should not have more than one embryo transferred.
- In females 43 years of age or older, data are currently insufficient to recommend a limit on the number of embryos to transfer when the patient uses her own oocytes. Nevertheless, it is important to take caution, considering that the risk of multiple pregnancy increases with advancing maternal age.
- In frozen-embryo transfer cycles, favourable characteristics should be based on the [82]:
  - Woman's age at the time of freezing the embryos.
  - Presence of high-quality vitrified embryos or euploid embryos.
  - Previous live birth after an IVF cycle.
  - The number of embryos transferred should not exceed the recommended numerical limit transferable for each age group.

Patients should be informed that[1,19]:

- Bed rest >20 minutes after the embryo transfer does not improve the outcome the treatment.
- No more than two embryos may be transferred during one cycle of IVF treatment (for young patients).
- Double embryo transfer is associated with the risks of multiple pregnancy.
- Any extra good-quality embryos may be preserved for future IVF attempts (see *Section 15*).

13.2.7 Support after IVF

For luteal phase support after IVF treatment:

- Progesterone is recommended[1] [**L1, RGA**].
- Human chorionic gonadotrophin is not recommended for routine use[1] [**L1, RGC**].
- Women undergoing IVF treatment should be informed that continuing any form of treatment for luteal phase support beyond 8-10 weeks' gestation has no proven benefit. [**L1, RGB**].

Consider referral for psychological support to a clinical psychologist or fertility support group to help patients with anxiety and stress after unsuccessful IVF treatment[19] [**L1, RGA**].

13.2.8 Predicting IVF Success

The following characteristics have been associated with a favourable prognosis[19,65]:

- Younger age women.
- Expectation of one or more high-quality embryos available for cryopreservation.
- Euploid embryos.
- Previous live birth after an IVF cycle.
- Availability of vitrified, high-quality, day-5, or day-6 blastocysts for transfer

Other factors that may influence success rate of IVF include[19,65]:

- The underlying cause of the infertility.
- The patient's health status (e.g. endometriosis may negatively impact IVF success rates)[48].
- The patient's lifestyle during the procedure such as healthy weight, smoking cessation, avoidance of alcohol, and caffeine may improve the chances of conception[34,19][**L1**].

13.2.9 Management of Complications

13.2.9.1 Ovarian Hyperstimulation Syndrome

Ovarian Hyperstimulation Syndrome (OHSS) is the most common side effect of IVF [**R-GDG**]. It occurs in women who are sensitive to medications used during ovarian stimulation[19,66]. Risk factors for OHSS include[66]:

- Young age.
- Low BMI.
- PCOS.
- History of previous OHSS.
- Individual response to controlled ovarian stimulation.

The Clinician assessing a patient of suspected OHSS should elicit the following history [**R-GDG**]:

- Time of onset of symptoms relative to trigger.
- Medication used for trigger (HCG or GnRH agonist).
- Number of follicles on final monitoring scan.
- Number of eggs collected.
- Were embryos transferred and if so, how many?

Signs and symptoms of OHSS include[19,66]:

- Pain and bloating in the lower abdomen.
- Enlargement of the ovaries.
- Nausea and vomiting.
- Shortness of breath

- Feeling faint.
- Rapid weight gain.

The diagnosis of OHSS should be clinically suspected in women with a history of ovarian stimulation, followed by typical symptoms of abdominal distension, abdominal pain, nausea, and vomiting [**R-GDG**]. A differential diagnosis of ovarian cyst accident, ectopic pregnancy and appendicitis should always be considered [**R-GDG**].

All cases which develop OHSS and present either in the Emergency dept. or in the Clinics should be registered centrally with the IVF Clinic in Women's Hospital [**R-GDG**]

Management of OHSS should be guided by its severity, however clinician should bear in mind that the severity of the patient's condition may change over time [**R-GDG**]:

- Mild cases can be managed as outpatient. They will need to be reviewed every 2 to 3 days. However, urgent clinical review is necessary if the severity of the condition changed.
- Moderate to Severe, and Critical cases should be managed as an inpatient.
- A clinician experienced in the management of OHSS should remain in overall charge of the woman's care.

Patient assessment and clinical examination should include pain, breathlessness, intake and output, body weight, and abdominal girth measurements[67]:

- Pelvic ultrasound should be ordered to measure ovarian size and check for ascites.
- Blood investigation that are helpful in assessing the severity and should be done for all patients and includes full blood count, liver function test and renal function test.
- Management is essentially supportive until the condition resolves spontaneously.
- Symptomatic relief of nausea and pain includes:
    - Anti-emetics such as metoclopramide can be prescribed to improve oral intake.
    - Treat pain with paracetamol and if necessary, opiates.
    - NSAIDs are not recommended.
- Patients should be encouraged to drink to thirst, rather than to excess.
- Strenuous exercise and sexual intercourse should be avoided due to increased risk of ovarian torsion.

Other relevant treatments depending on the patient's presentation may include[66] [**L2, RGA**]:

- Circulatory volume correction.
- Electrolyte replacement.
- Anticoagulant therapy.
- Improvement of renal function.
- Aspiration of the ascitic fluid and pleural effusion (if required).

Surgical treatment and termination of pregnancy may be required in critically severe cases of OHSS but only as a last resort[66] [**L1, RGA**].

13.2.9.2 Ectopic Pregnancy

IVF treatment is associated with an increased risk of ectopic pregnancy[19,68]. Ultrasound scanning is recommended at 2 weeks after positive pregnancy test, to confirm viability and localisation of the pregnancy [**R-GDG**]. Symptoms of ectopic pregnancy include[19,68,69]:

- Pain in the lower abdomen and pelvis.
- Vaginal bleeding.
- Dyspareunia.

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13.3 Intracytoplasmic Sperm Injection

Intracytoplasmic Sperm Injection (ICSI) is an alternative method of fertilisation that involves the injection of a single sperm cell directly into the ooplasm of an oocyte[1,70].

Couples should be informed that[1]:

- ICSI improves fertilisation rates compared to IVF alone (in couples with male factor infertility).
- ICSI does not affect the pregnancy rate.

13.3.1 Eligibility Criteria for ICSI

ICSI should be offered to couples[1,70] [**L1**]:

- Not able to conceive due to:
    - Severe deficits in sperm quality.
    - Obstructive azoospermia.
    - Non-obstructive azoospermia.
- With failed or very poor fertilisation during IVF cycle.
- Women with advance maternal age due to oocyte zona hardening.
- Whose oocytes that were previously cryopreserved.
- At risk for HIV infection.

The following genetic counselling and genetic testing should be considered before performing ICSI in especially in men with a severe deficit of sperm quality or non-obstructive azoospermia[18] [**L1**]:

- Men with Y-chromosome microdeletion and their wives who wish to have ICSI should be informed that microdeletions will be passed to sons, but not to daughters.
- Y-chromosome microdeletions testing of males with azoospermia or severe oligozoospermia.

14 Conception in Couples with Abnormal Serology

14.1 HIV Infection

A multidisciplinary team (MDT) approach is required for counselling and effective treatment of infertility in couples where one or both partners are HIV positive[71]. Any decision about fertility management should be taken in agreement between[1]:

- The couple.
- Fertility specialist.
- HIV specialist.

If the following conditions apply, the risk of HIV transmission from HIV-positive male to HIV-negative female through unprotected sexual intercourse is negligible and further sperm washing is not required (but may be considered)[1] [**L1**]:

- The male partner is compliant with highly active antiretroviral therapy (HAART).
- The male partner has had a plasma viral load <50 copies/ml for >6 months.
- There are no other infections present.
- Unprotected intercourse is limited to the time of ovulation.

Further sperm washing to reduce the risk of HIV transmission is required if[1] [**L1**]:

- The male partner is not compliant with HAART.
- The male partner has had a plasma viral load ≥50 copies/ml.

No pre-exposure prophylaxis for HIV-negative women can be recommended[1] [**L1, RGB**].

HIV-positive couples should not be denied access to assisted reproductive technology (IUI, IVF, ICSI) but[71] [**L3**]:

- Optimum medical status of HIV suppression should be assessed before treatment.
- Couples with high motivation for childbearing and strict adherent to their antiretroviral therapy should be selected for the treatment.
- The most effective treatment with the least risk of transmission of HIV should be applied.
- Surplus embryos from HIV infected patients should only be stored in HIV dedicated tanks. If this is not available, then embryos should not be frozen. Therefore, minimum production of egg should be considered at stimulation [**R-GDG**].

14.2 Viral Hepatitis B and C Infections

Vaccination against hepatitis B should be offered to partners of infected people before starting fertility treatment[1,72] [**L1, RGA**]. Sperm washing is not recommended as part of fertility treatment for men with hepatitis B[1] [**L1, RGB**].

No vaccine for hepatitis C is currently available[72]. Any decision about fertility management in couples where one or both partners have hepatitis C should be taken in agreement between[1]:

- The couple.
- Fertility specialist.
- Hepatitis specialist.

15 Cryopreservation

Cryopreservation is the storage of biological material at sub-zero temperatures, at which the biochemical processes of cell metabolism and biochemical reactions are stopped[5].

Sperm cryopreservation should be offered to men and adolescent boys who[1,5] [**L1, RGA**]:

- Prepare for medical treatment for cancer that is likely to affect their fertility.
- Plan a surgery that might interfere with fertility.
- Plan testicular biopsies for fertility diagnosis.
- Have a progressive decrease in semen quality because of a disease leading to azoospermia.
- Diagnosed with paraplegia or psychogenic anejaculation.
- Diagnosed with hypogonadotropic hypogonadism and had gonadotropin induced medical spermatogenesis.
- Have nonobstructive azoospermia.

Oocyte or embryo cryopreservation should be offered to women of reproductive age who are preparing for medical treatment for cancer that is likely to affect their fertility if[1] [**L1, RGA**]:

- They are well enough to undergo ovarian stimulation and egg collection.
- The ovarian stimulation and egg collection will not worsen patient's condition.
- Enough time is available before the start of their cancer treatment.

When considering cryopreservation to preserve fertility in people diagnosed with cancer[1,73] [**L1**]:

- Evaluate and discuss the impact of the cancer and its treatment on future fertility of the patient.
- The final decision should be made before starting chemotherapy or radiotherapy.
- Do not use a lower age limit for cryopreservation in people diagnosed with cancer.
- Use sperm, embryos or oocytes:
    - Slow – Freeze cryopreservation is the most commonly use method for freezing sperm.
    - Vitrification is the most preferred method for cryopreservation of oocytes and embryos

Any remaining good-quality embryos after IVF should be stored[1] [**L1**]. The cryopreserved material should be stored for an initial period of 10 years[1] with further extension in men who remain at risk of significant infertility[1]. [**L1**].

Medicolegal considerations should be in accordance with the Code of Professional Conduct for the Guidance of Registered Medical Practitioners issued by the MOPH Qatar for consent to surgical procedures including[74]:

- Obtaining written informed consent from patients with respect to cryopreservation and reproductive technology procedure before commencement of such procedures.
- Patients may vary or withdraw their consent at any time in writing provided that the gametes have not already been used in treatment.
- Relevant centres are required to make use of the appropriate sample consent forms.

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16 Prenatal Sex Determination and Gender Selection

16.1 Criteria for Gender Selection in IVF

Parents may request to select the gender of their foetus for the following reasons only [**R-GDG**]:

- Medical reasons related to the baby's health:
  - To avoid genetic diseases carried by the parents which may be inherited by babies of a certain gender and cause illness, or anomalies, leading to death or severe disability Examples of these genetic diseases include:
    - X-linked muscular dystrophy.
    - Haemophilia.
    - Fragile X syndrome.
- Medical reasons related to the maternal health:
  - Chronic or severe maternal health conditions in which further pregnancy would constitute a risk to the life of the mother, including:
    - Congenital heart disease.
    - Advanced or end stage kidney disease.
    - Severe restrictive lung disease with pulmonary hypertension.
  - When mother is advised by clinician to avoid further pregnancy for health preservative reasons and due to increased likely hood of complications. These include conditions such as:
    - Organ transplant.
    - Multiple caesarean sections.
    - Perimenopausal women.
  - Due to infertility related factor or the need to employ pre-implantation genetic testing (PGT) for avoidance of genetically abnormal genes.

NB:

- Prenatal requests for gender selection should not be permitted unless the above criteria are met [**R-GDG**].
- Request for gender selection should not be granted for economic or other preferential reasons (i.e. a personal desire to have a certain gender) [**R-GDG**].
- Gender selection for non-medical reasons may however be permitted in exceptional circumstances [**R-GDG**]:
  - Whether the procedure is to be performed at the HMC Assisted Conception Unit or another private sector hospital - in all cases, prior approval must be sought from the WWRC Ethics Committee before treatment is started.

For further information, please refer to the MOPH policy for Gender Selection during In-Vitro Fertilisation.

16.2 Requirements for Supporting the IVF Gender Selection Process

When gender selection is advised to avoid genetic diseases carried by parents through abnormal genes, the following documents should be provided [**R-GDG**]:

- A medical report by a consultant geneticist and a genetic counsellor to prove that babies of the applicant parents of a certain gender are liable to be inflicted with a certain disease, or disability.
- Such a report should include results of genetic testing for both parents confirming them as carriers of a heritable genetic abnormality.

When gender selection is recommended for the mother's health-related reasons [**R-GDG**]:

- A written letter to this effect must be provided and signed by a committee consisting of the supervising consultant gynaecologist, and a consultant who is specialised in the treatment of the mother's kind of health problem.
- Such letter should state the health reason why it is medically recommended for the mother to have a gender selection to avoid any further pregnancy.

Recommendation for gender selection based on infertility reasons, or the need to use PGT, should be only be made by a consultant on assisted conception or a geneticist respectively [**R-GDG**].

A data registry should be established to document all cases in which gender selection has been requested and the outcome of such requests. These data should be reported to the appropriate regulatory body in the Ministry of Public Health [**R-GDG**].

Frequency of Gender Selection:

- Where gender selection is recommended to avoid genetic diseases to the baby, selection should be allowed as many times as desired by the couples [**R-GDG**].
- When gender selection is advised to avoid risky pregnancy or due to infertility or the use of PGT, selection should only be allowed once, provided that gender selection resulted in a successful delivery of a normal baby of the desired gender [**R-GDG**].
- Additional gender selection may be allowed, only for exceptional reasons, to be recognised by relevant organisation ethical committee [**R-GDG**].

17 Key Considerations for Patient Preferences

Patient preferences refer to patient perspectives, beliefs, expectations, and goals for health and life, and to the steps employed by individuals in assessing the potential benefits, harms, costs, and limitations of the management options in relation to one another. Patients may have preferences when it comes to defining their problems, identifying the range of management options and selecting or ranking the outcomes used to compare these options.

It is important for healthcare professionals to develop an understanding of the patient as an individual and the unique way in which each person experiences a condition and its impact on their life.

The following recommendations are therefore made for physicians and other healthcare professionals regarding general principles of patient care in Qatar:

- **Respect Patients:** Treat patients with respect, kindness, dignity, courtesy and honesty. Ensure that the environment is conducive to discussion and that the patient's privacy is respected, particularly when discussing sensitive, personal issues. Ask the patient how they wish to be addressed and ensure that their choice is respected and used.

- **Maintain Confidentiality:** Respect the patient's right to confidentiality and avoid disclosing or sharing patients' information without their informed consent. In this context, students and anyone not directly involved in the delivery of care should first be introduced to the patient before starting consultations or meetings, and let the patient decide if they want them to stay.

- **Obtain Informed Consent:** Obtain and document informed consent from patients, in accordance with MOPH policy and guidance.

- **Encourage Shared Decision Making:** Ensure that patients are involved in decision making about their own care, or their dependent's care, and that factors that could impact the patient's participation in their own consultation and care including physical or learning disabilities, sight, speech or hearing impairments and problems with understanding, reading or speaking English are addressed.

- **Disclose Medical Errors:** Disclose errors when they occur and show empathy to patients.

- **Ensure Effective Communication:** Explore ways to improve communication including using pictures, symbols or involving an interpreter or family members. Avoid using medical jargon. Use words the patient will understand and confirm understanding by asking questions.

- **Ensure Continuity of Care:** Provide clear and timely sharing of patient information between healthcare professionals especially at the point of any transitions in care.

18 Performance Measures

A list of performance measures is given below in *Table 18.1*.

Ref	Numerator	Denominator
INF01	The number in the denominator who are provided with lifestyle advice.	The number of men referred from primary care for investigation of infertility in the last 12 months.
INF02	The number in the denominator who have had an evaluation of ovulatory function in primary care prior to referral.	The number of women referred from primary care for investigation of infertility in the last 12 months who do not have primary amenorrhoea or a known cause for infertility.

Table 18.1: Performance Measures.

The Performance Measures relating to facilities that offer IVF treatments are as follows[75]:

Name	Measure Description
Multiple Pregnancy Rate / Fresh Transfer	The percentage of transfers with more than one gestational sac seen on ultrasound at 7 weeks.
Percentage of Single Embryo Transfer	The percentage of embryo transfers where a single embryo was transferred (regardless of whether there were one or more embryos on the day of transfer).
Percentage of Single Elective Embryo transfers	The percentage of single embryo transfers where there was surplus to freeze.
Average Embryos Transferred	The average number of embryos transferred over all ages.
<35 Average Embryos Transferred	Average number of embryos transferred for women less than 35 years of age.
Average Embryos Cryopreserved	Average number of embryos cryopreserved.
Productive Index	Total number of clinical pregnancies (US confirmed)/number of transfers (both fresh and frozen).
Percentage of Miscarriages	Percentage of sacs that are lost or without a fetal heart.
Percentage of Biochemical Pregnancies	Percentage of transfers with an elevated hCG measurement but no sac seen on ultrasound.

Table 18.2: Performance Measures for IVF Treatment Centres[75].

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Appendix: Detailed Description of the Literature Search

A systematic search for existing literature on infertility was performed in the period November 24th – December 17th, 2019.

The search for clinical practice guidelines on infertility diagnosis and/or management was performed in the *PubMed* database and websites of relevant organisations and societies including the *American Society for Reproductive Medicine, National Health Service (NHS), World Health Organization (WHO), American College of Obstetricians and Gynecologists (ACOG)*, and other. The present guideline is primarily based on UK NICE and NHS England guidelines and is supplemented with other relevant studies.

Peer-reviewed scientific publications were found in PubMed and via *Google Scholar* Internet search engine. Non-peer reviewed studies were identified in *bioRxiv*. Books were checked on PubMed. Information published on medical websites and drug prescribing information sheets were found via Google search engine.

The included publications were identified using the term "infertility" and specified with the following terms in combinations:

Fertility, prevalence, Qatar, male/female, sperm, semen, oocyte, embryo, management, physical, examination, causes, risk factors, idiopathic, nutrition, diet, referral criteria, pharmacological treatment/pharmacotherapy, alternative, medication, psychotherapy, laparoscopy, fibroid, myoma, malignancy, tuberculosis, endometriosis, ovarian failure/reserve, PCOS, HIV, hepatitis, varicocele, hypogonadism, ejaculation problem/disorder, intrauterine insemination/IUI, in vitro *fertilization/IVF, intracytoplasmic sperm injection/ICSI, ovarian hyperstimulation, ectopic pregnancy, complication(s), cryopreservation.*

Figure A.1 on the next page demonstrates graphically the results of the search and application of exclusion criteria.

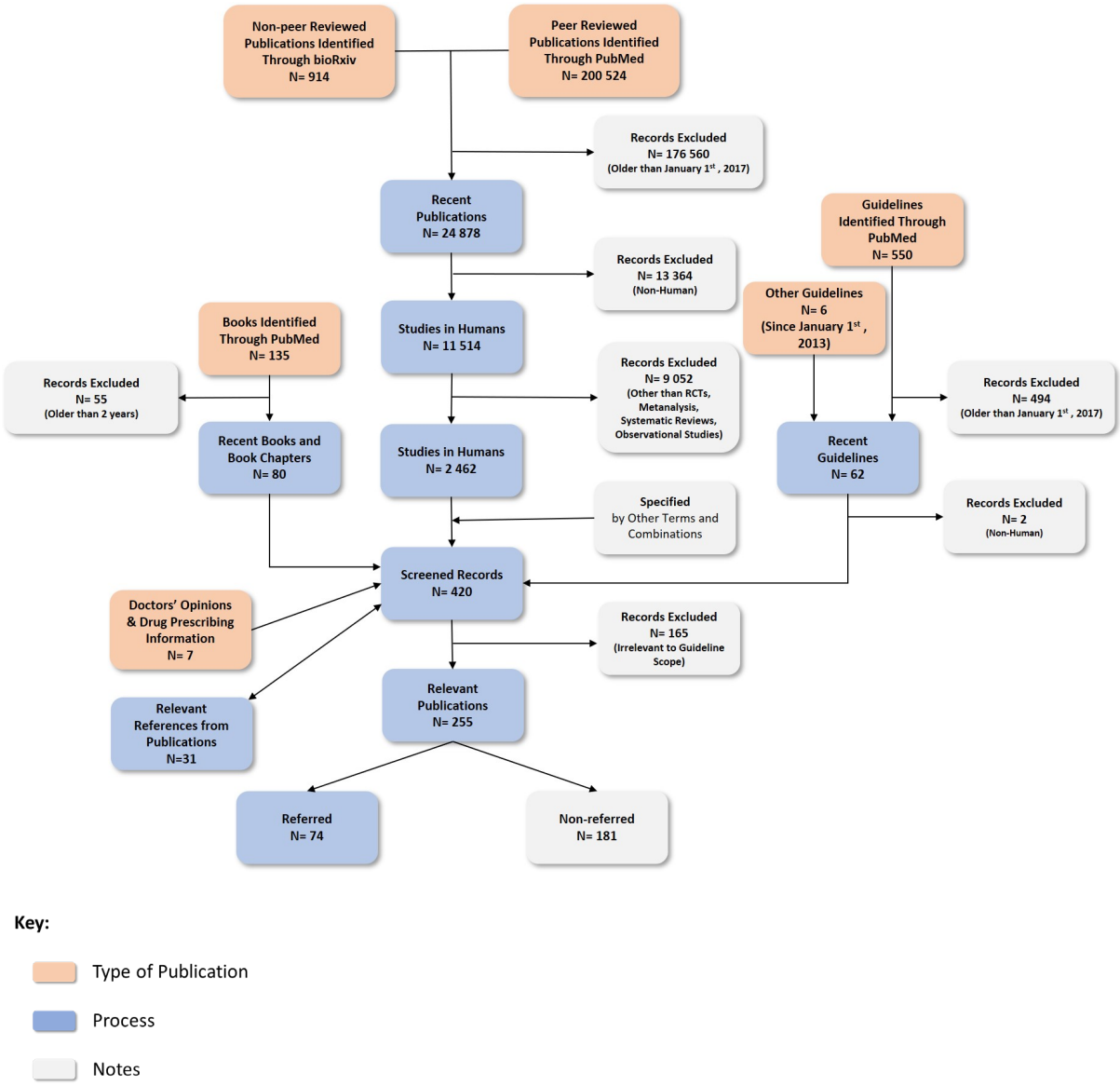

Fig A.1: Literature search results and application of exclusion criteria.

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